Heterogeneous Catalysts for the One-Pot Synthesis of Chemicals and Fine Chemicals

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1. Introduction

The search for alternative cleaner, safer, and environmentally friendly technologies is one of the priorities in chemistry. With this objective, the reduction of wastes together with the use of renewable feedstocks, environmentally friendly reagents and catalysts are important parameters to achieve more sustainable processes.[1,2] In addition to those, catalysis can improve sustainability of chemical processes by means of process intensification. In this sense, one-pot procedures involving multiple catalytic events allows the decrease of energy consuming steps such as separation and purification of intermediates. These transformations known as tandem, domino, or cascade reactions[3,4] have become an important area of research in organic chemistry[5−10] since they improve atom economy and lower *E* factors ($kg_{subproduct}/kg_{product}$), energy and raw materials consumption. By means of coupled reactions, nature performs many biochemical processes in living organisms using two essential tools: site-isolation and substrate selectivity. Taking into account this model, challenges for one-pot transformations are centered on the design of highly selective catalysts with well-optimized isolated active sites. In this sense, heterogeneous catalysts are promising candidates to perform multistep processes,[11−15] particularly when different and incompatible active sites are required. They allow the generation of robust site-isolated and well-defined[16] multisite catalysts in which the active sites can act both in a cooperative way (for instance acid−base) or in different steps of a given cascade process.[13,17]

The success of a given multistep sequential or multicomponent process requires a balance of equilibria and a suitable sequence of reversible and irreversible steps. The simplest way to perform a multistep synthesis is to perform the consecutive steps not only in the same vessel but also under the same reaction conditions. However, when this is not possible, the one-pot reaction is carried out in two or more stages under different optimized reaction conditions in order to reach the maximum selectivity to the target product.

In this review, we report a variety of one-pot processes which are carried out on solid catalysts, emphasizing the particular design of the active sites. Then, we have separated

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the different processes according to the catalyst type: those bearing a single active site able to catalyze two or more consecutive steps, and multisite catalysts in which a different active site is required for each reaction step.

2. Multistep Sequential Processes

2.1. Multistep Sequential Processes with Single-Site Acid Catalysts

2.1.1. Solid Bronsted Acid Sites

There are a large number of reactions that are catalyzed by organic and inorganic liquid Bronsted acid catalysts. Common catalysts of this type are, for instance, sulfuric, hydrochloric, phosphoric, hydrofluoric, perchloric, *p*-toluenesulfonic, and fluoroalkyl sulfonic acids. They have been, and still are, very successful catalysts for the production of chemicals, fine chemicals, and even oil refining processes.[18]

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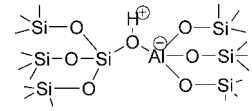
However, the tendency is to substitute those mineral liquid acids as well as the liquid organic acids by solid catalysts that can be reused and do not require a neutralization step at the end of the reaction, with the corresponding formation of waste products. In the case of liquid organic catalysts based on sulfonic groups, the solid alternative has been straightforward by preparing organic polymers that contain sulfonic groups in their backbone structure.[19−21] Sulfonic groups within alkyl chains or aromatic molecules have been supported or interlinked with silica precursors to form amorphous or structured silica based organic−inorganic hybrid alternative.[22−25] Finally, sulfonic acid groups have also been introduced in the organic counterpart of metal organic frameworks (MOFs).[26,27] In the case of inorganic solid acids, a large number of very successful acid materials have been developed on the bases of amorphous and crystalline aluminosilicates. In these materials, the presence in the structure of tetrahedrally coordinated aluminum generates a negative charge on the surface that can be compensated by the positive charge associated to protons:



The success of these materials rely on the fact that it is possible to change the number of acid sites per unit weight of catalyst and the acid strength of those sites by changing the composition, that is, the Si/Al ratio. Futhermore, in the case of crystalline materials (clays and especially zeolites) and short-range amorphous materials that show long-range order, it is possible to modify the pore dimensions and pore topologies to achieve shape selectivity effects by selecting reactants and reaction transition states. It is out of the scope of this paper to review this type of material in reference to their acidic properties, but the reader is referred to classical references on the subject.[18,28−30]

Finally, solid Bronsted catalysts based on heteropolyacids have also been prepared with surface areas close to 200 m^2 g^{-1}, and they have also been successfully used in acid catalysis.[18]

We will present below that researchers have attempted to substitute the liquid acids working in homogeneous conditions by some of the solid catalysts briefly described above while working with heterogeneous catalytic systems. When the solid catalysts have large surface areas and optimum adsorption characteristics, they can be very useful for catalyzing multistep reactions in which the intermediate products have to be adsorbed.

In the case of solid Lewis acids, one can envisage metals or salts supported on high surface carriers, or well-defined single Lewis acid sites as they exist in zeolites, aluminophosphates and mesoporous structured materials that contain metals within the framework structure or even in extraframework positions. We will also show that with these metal zeolites or like materials, it is possible to control the Lewis acidity and adsorption properties resulting in excellent catalysts for one-pot multistep processes.

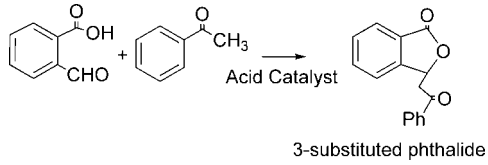
2.1.1.1. Aldol Condensation Followed by Cyclization: One-Pot Synthesis of Substituted Phthalides (Isobenzofuran-1(3H)-ones). Substituted phthalides are an important class of natural compounds with a variety of important biological properties, whose heterocyclic motif appears in many bioactive compounds.[31,32] They possess a variety of pharmacological activities such as anticonvulsivant, antibacterial, anti-HIV, anesthesia prolongation, or antitumor activities. Particularly, 3-alkylidene phthalides derivatives possess antispasmodic, herbicidal, and insecticidal properties.[33−35] Numerous methods have been developed for their synthesis which include cyclization of carboxylic acid derivatives catalyzed by strong acids (trifluoroacetic acid)[34] or strong bases.[36−38]

Recently, Landge et al.[39] proposed the microwave-assisted synthesis of 3-substituted phthalides in one pot, by reacting phthalaldehydic acid with substituted ketones using Montmorillonite K10 as a heterogeneous acid catalyst (Scheme 1).

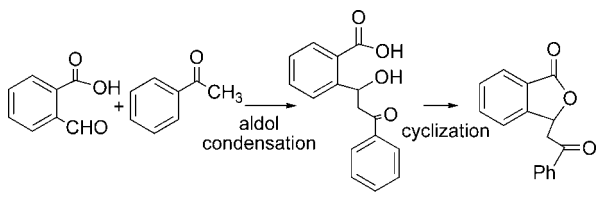
The synthesis is based in two consecutive steps which involves first the condensation of the phthalaldehydic acid with the ketone following the regular mechanism of an acid-catalyzed aldol condensation, giving an aldol intermediate which subsequently lactonize to the target compound (Scheme 2). The authors suggest that although Montmorillonite possesses both Lewis and Bronsted acid sites on its surface, in this case the reaction is driven by the Bronsted acid sites.

Reactions with different ketones, performed in the absence of solvent under optimized reaction conditions, that is, phthalaldehydic acid (0.8 mmol), ketone (1 mmol), K10 (500 mg), at 170 °C, MW power = 250 W, gave excellent yields

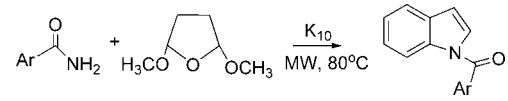
Scheme 1. Synthesis of Substituted Phthalides



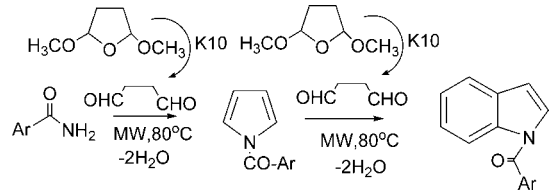
Scheme 2. Consecutive Steps Involved in the Formation of Substituted Phthalides



Scheme 3. One-Pot Synthesis of *N*-Acylindoles



Scheme 4. Suggested Mechanism for the Formation of N-Acylindoles



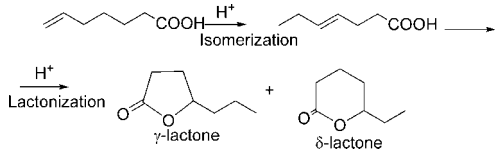
(90−98%) of the target compounds in only 20−30 min of reaction. This reaction time was the optimum since shorter times gave low yields, whereas longer times cause decomposition of the product and secondary reactions resulting in a decrease of the yield. Interestingly, when the reaction was performed by heating in an oil bath at 170 °C during 20 min, multiple products were detected, being the phthalide yield only 45%, indicating the benefit of microwave heating versus the traditional setup.

2.1.1.2. Cycloalkylation Followed by Annelation: One-Pot Synthesis of *N*-Acylindoles. The indole structure is present in many pharmacologically and biologically active compounds.[40−42] Most routes for the preparation of *N*-acylindoles involve two or more steps resulting in some cases in low yield. They are usually synthesized from indoles in the presence of a strong base and subsequent acyl chloride adition[43] or by 1,3-dicyclohexylcarbodiimide-induced coupling of indoles with carboxylic acids.[44] Recently, Abid et al.[45] have reported a novel one-pot synthesis of these compounds via tandem cycloalkylation−annelation process catalyzed by K10 Montmorillonite under microwave irradiation. The process involves the reaction between an aromatic amide and 2,5-dimethoxytetrahydrofuran as alkylating agent under solvent-free conditions (Scheme 3).

Optimization of the reaction conditions showed that the amount of alkylating agent had an important influence on the chemoselectivity of the reaction, being the maximum yield of indole achieved when 2 mol equiv of 2,5-dimethoxytetrahydrofuran were used. The authors showed the scope of this methodology by reacting a wide variety of commercially available aromatics amides giving 60−85% yields of the corresponding indoles in very short reaction times (5−30 min).

The authors suggest a mechanism (Scheme 4) in which the 2,5-dimethoxytetrahydrofuran underwent rearrangement on the catalyst surface, which results in the formation of 1,4-butanedial. The dialdehyde formed in the first step reacts very fast with the amide and cyclizes into pyrrole following the Paal−Knorr cyclization mechanism. Owing to the high reactivity of the pyrrol toward electrophilic substitution, it reacts with the excess of 1,4-butanedial undergoing an annelation and forming the corresponding indole (see Scheme 4). The authors propose that the annelation process occurs in a stepwise manner; that is, one of the formyl groups react with the pyrrol ring in the 2-position, after activation on the acid sites of the catalyst, giving a hydroxyalkylated compound that dehydrates very fast releasing a water molecule. Subsequently, the ring closure takes place via the same hydroxyalkylation−dehydration sequence in the 3-position.

Scheme 5. One-Pot Synthesis of Lactones from Unsaturated Carboxylic Acids

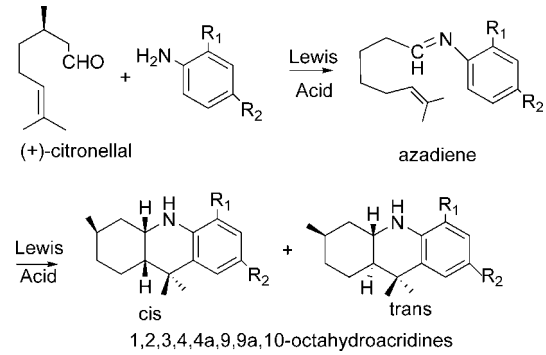


2.1.1.3. C−C Double Bond Isomerization Followed by Lactonization: One-Pot Synthesis of γ-Lactones. Lactones have a wide variety of applications such as solvents, extraction agents, and, as important intermediates for pharmaceutical, and agricultural bioactive compounds. They are also an important flavor constituent in a wide variety of foods, and they are often used as flavors and food additives.[46,47] Lactones can be synthesized through the cyclization of unsaturated carboxylic acids promoted by electrophilic reagents such as phenylselenium chloride, mercuric and palladium salts,[48−52] and protic acids such as sulfuric,[53] *p*-toluenesulfonic acid, or phosphoric acid with a catalytic amount of perchloric acid.[47] In the case of alk-3 and 4-enoic acids, cyclization to the corresponding γ- and δ-lactones can occur with no C═C bond migration. However, when the C═C bond is in another position within the molcule, isomerization of the double bond is a necessary first step in order to be able to perform the lactonization (Scheme 5). It has been reported that by working in refluxing sulfuric and trifluoroacetic acids, γ-lactones were obtained in high yields starting from alkenoics acids with the C═C bond in the 2-, 3-, 4-, 5-, or 6-positions.[54] This approach has been used to synthesize γ-lactones starting from long chain unsaturated acids, such as oleic acid, achieving in this case γ-stearolactone in 91% yield, though a high concentration of a strong acid (70% perchloric acid) is required.[55]

Recently, Zhou et al.[56] have reported the tandem isomerization−lactonization of several olefinic acids for the synthesis of γ-lactones using acid resins as solid catalysts, instead of strong Bronsted conventional acids. Among different acid resins tested, Amberlyst-15 and Nafion SAC-13 result in the most active catalysts. The authors performed the reactions at reflux of chlorobenzene and found that for 3- and 4-alkanoic acids, in which double bond isomerization is not required for γ-lactone formation, yields were between 95−100%. For 5-, 6-, 9-, 10-enoic acids the lactone yield decreases as the distance between the C−C double bond and carboxylic groups increases, achieving moderate yields (64−25%). In addition, the authors found that in the tandem reaction of long chain unsaturated acids the six-membered ring δ-lactones are also formed at the beginning of the reaction as a primary product, but they are converted with time into the corresponding γ-lactone.

2.1.1.4. Imine Formation Followed by Intramolecular Hetero-Diels−Alder Cyclization: One-Pot Synthesis of Octahydroacridines. Hetero-Diels−Alder reaction of 2-azadienes is a powerful synthetic tool for the synthesis of nitrogen containing six-membered heterocycles[57] as it is the case for the synthesis of octahydroacridine (OHA) derivatives.[58−60] Particularly, 1,2,3,4,4a,9,9a,10-octahydroacridines (Scheme 6) are compounds of pharmacological interest due to their activity as gastric acid secretion inhibitors.[61,62] Among the different methodologies described for the synthesis of the OHA skeleton, the most atom-economic process, is the two-step Lewis acid catalyzed reaction involving the reaction between an unsaturated aldehyde and an aniline derivative forming the corresponding imine (an azadiene) followed by

Scheme 6. One-Pot Synthesis of Octahydroacridines



hetero-Diels−Alder cyclization (Scheme 6)[58−60] giving the corresponding OHA in high yields, and in some cases 100% stereoselectivity. However, the main drawbacks of this approach are the long time required, low temperatures, expensive Lewis acid, and the use of hazardous organic solvents. In order to overcome these problems, Jacob et al.[63] performed the synthesis several of 1,2,3,4,4a,9,9a,10-octahydroacridines derivatives by a one-pot process starting from (+) citronellal and *N*-arylamines (Scheme 6) in the presence of a solid Lewis acid catalyst, $ZnCl_2$ supported on SiO_2, under microwave irradiation and in the absence of any solvent.

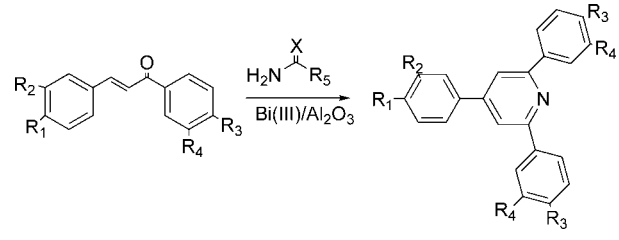
Optimization of the reaction conditions lead to the corresponding OHA in good yields (75−92%) in only a 3 min reaction time. For all the studied anilines, a *cis* and *trans* mixture of OHAs was formed in variable ratios. The comparative study performed by heating reactants in an oil-bath instead of by MW showed that the target compound was obtained in poor yield.

2.1.1.5. Dimerization of Chalcones Followed by Heteroannulation: One-Pot Synthesis of 2,4,6-Triarylpyridines. Polyarylpyridines are important intermediates in preparative organic synthesis[64,65] as substrates for the preparation of supramolecules[66,67] and have application as therapeutic agents. Particularly, those possessing the 2,4,6-triarylpyridine structure are of special interest as potential therapeutic agents for photodynamic cell-specific cancer treatment due to their close structural resemblance with triaryl-thiopyrylium, -selenopyrylium, and -telluropyrylium photosensitizers which have been recommended for this type of therapy.[68]

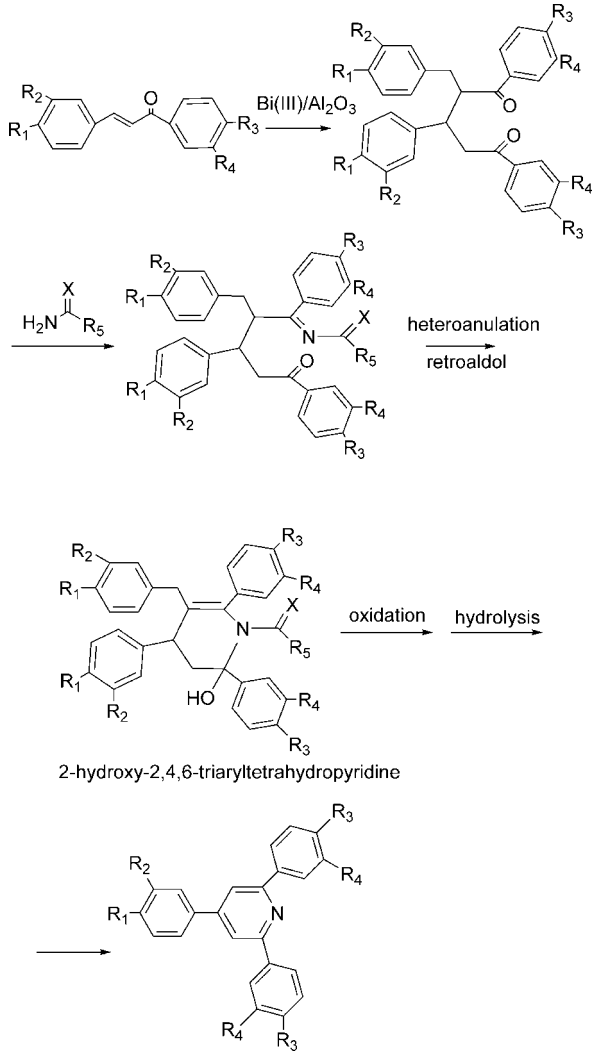
The synthesis of 2,4,6-triarylpyridines involves in most cases laborious multistep processes, under harsh or environmentally hazardous reaction conditions.[69,70] Some synthesis have been performed employing complex heterocyclic compounds[71] or using triarylpyridinum substrates.[71,72] Recently, Kumar et al.[73] reported the use of Bi(III) nitrate immobilized on neutral alumina as a heterogeneous Lewis acid catalyst for the one-pot synthesis of 2,4,6-triarylpyridine derivatives using chalcones and urea derivatives as reactants (Scheme 7).

For this process, the authors suggest a mechanism which involves as the first step the dimerization of the chalcone

Scheme 7. One-Pot Synthesis of 2,4,6-Triarylpyridines



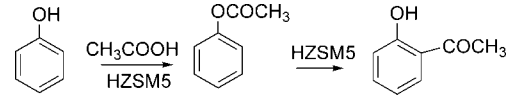
Scheme 8. Suggested Mechanism for the Formation of 2,4,6-Triarylpyridines



through a Michael addition to a second α,β-unsaturated ketone to form a 1,5-diketone enolate adduct. Subsequently, the diketone adduct can undergo the heteroannulation with urea or its derivatives via condensation and retroaldol disproportionation leading to a 2-hydroxy-2,4,6-triaryltetrahydropyridine derivative which on dehydration, oxidation, and finally hydrolysis yields the 2,4,6-triarylpyridine (Scheme 8). Reactions performed at 130 °C gave the target compounds in 65−85% yield. 2,4,6-Triaryl-3-methylarylpyridines were obtained using the same methodology using Bi(III) nitrate immobilized on neutral alumina and $ZnCl_2$ as cocatalysts.[74] In the type of reactions catalyzed by salts impregnated on a solid carrier, it is mandatory to check if there is any leaching occurring and if the leached species can act as catalysts.

2.1.1.6. Esterification Followed by Fries Rearrangement: One-Pot Synthesis of Hydroxyacetophenones. *Ortho* and *para* hydrodroxyacetophenones are valuable intermediates in the pharmaceutical industry. The *ortho* isomer can be used for the synthesis of salicylic acid, while the *para* isomer is a key intermediate in the Hoechst Celanese process for the manufacture of paracetamol.[75] They are conventionally obtained by two methods: the Friedel−Crafts acylation of phenol with acetic acid or its derivatives, and by the Fries rearrangement of phenyl acetate derivatives in the presence of a Lewis acid ($AlCl_3$, BF_3).[76]

Scheme 9. One-Pot Synthesis of Hydroxyacetophenones



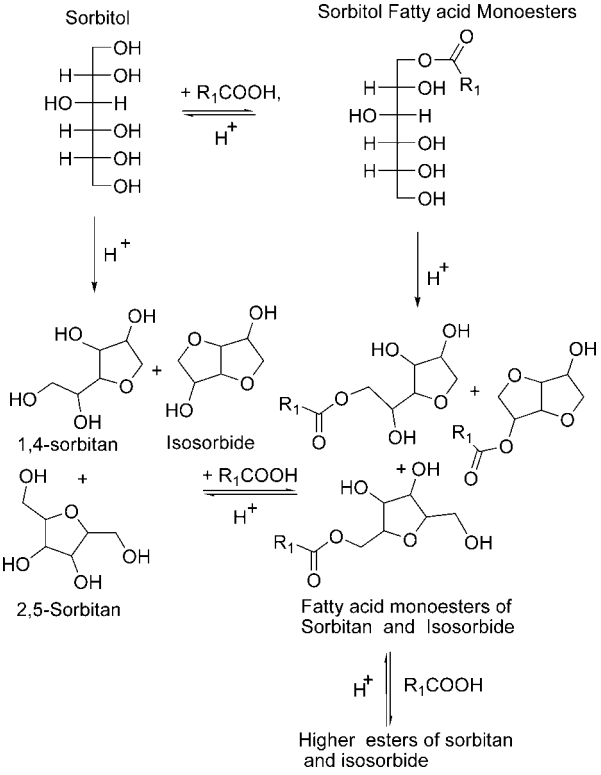
Kuriakose et al.[77] have reported the synthesis of *o*- and *p*-hydroxyacetophenones catalyzed by acid zeolites (Y, Beta, and ZSM5) through a one-pot two-step process involving the esterification of phenol with acetic acid yielding phenylacetate which subsequently undergo the Fries rearrangement to give the *o*- and *p*-hydroxyacetophenones (Scheme 9). Reactions were performed using phenol and acetic acid or acetic anhydride as reagents in liquid and in gas phase. The authors found that in the liquid phase (under refluxing conditions) the reaction yielded exclusively phenylacetate (26−80%). However, in the gas phase when acetic acid is used as a acylating agent, zeolite catalysts formed phenylacetate followed by the Fries rearrangement to yield selectiviely *o*-hydroxyacetophenone (40%), the *o*-hydroxyacetophone/phenylacetate molar ratio being very high with ZSM5 catalyst, which was attributed to shape selectivity due to the pore dimensions and pore topology of ZSM5 zeolite.

2.1.1.7. Acetal Hydrolysis Followed by Esterification: One-Pot Synthesis of Sorbitol Fatty Acid Esters. Fatty acid esters of sorbitol are nonionic surfactants widely used in the food and cosmetic industries as emulsifiers and stabiliziers.[78] Esterification of fatty acids with sorbitol is usually carried out at elevated temeperatures in the presence of homogeneous acids,[79,80] base catalysts,[81,82] or mixtures of an acid and a base.[83] During the esterification, anhydrization of sorbitol (giving sorbitan and isosorbide) and sorbitol esters occurs, and depending on the method of synthesis and reaction conditions, the final mixtures contain different proportions of sorbitol anhydride esters with different degrees of hydroxyl substitution (Scheme 10). One way to measure the degree of esterification and etherification of sorbitol and hence the quality of the final product is by means of the hydroxy value, in such a way that if only monoesters of sorbitan are obtained the hydroxy value would be 394, while isosorbide monoester will give a value of 137. Commercial samples, marked as sorbitan monoesters and which are mixtures of mono-, di-, and triesters of sorbitan where the monoesters are present in high proportion, have hydroxy values on the order of 160.

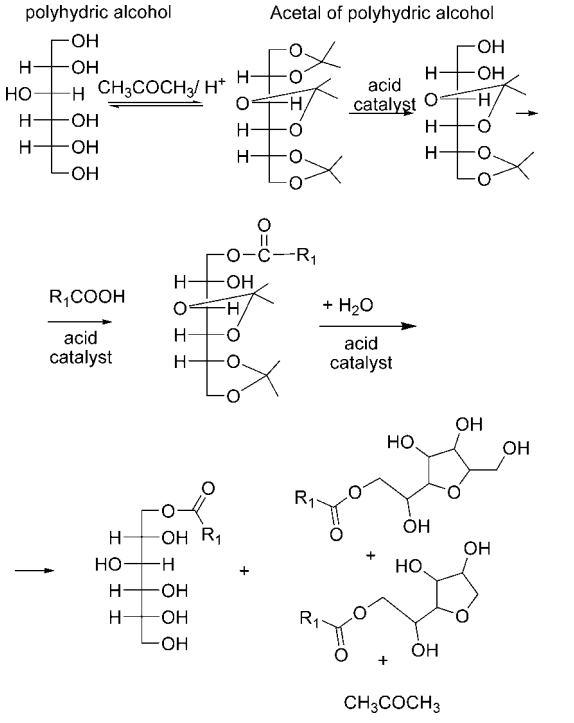
Recently, we have performed the synthesis of sorbitol fatty acid esters by reacting protected sorbitol (sorbitol ketalized with acetone) with oleic acid in the presence of zeolites as acid catalysts.[84] This synthesis of sorbitol esters involves one acid catalyst that in a cascade-type reaction is able to hydrolyze in a controlled way some of the ketal functions, thus deprotecting OH groups which can then react with the fatty acid (Scheme 11). The objective of this process was to control the number of free hydroxyl groups during the reaction to decrease the rate of formation of higher esters (di-, tri-, tetraesters) as well as to avoid the anhydrization of the sorbitol with formation of dianhydride ethers.

Reactions were performed using zeolites (Beta, Mordenite, ITQ-2) and a Cs exchanged heteropolyacid as solid acid catalysts (Table 1). When the process was carried out with a tridirectional zeolite (Beta) and, especially, with a monodirectional zeolite (Mordenite), positive shape selectivity was observed such that the ratio of mono- to diesters, as well as the hydroxy value of the final mixture, were higher than when the process was carried out under homogeneous catalysis. The benefit of this cascade process for the

Scheme 10. Reactions Taking Place in the Esterification of Sorbitol



Scheme 11. One-Pot Synthesis of Sorbitol Fatty Acid Esters



production of sorbitol esters with a high enough quality to be directly used commercially, was evidenced when these results were compared with those obtained using the same catalysts for the direct reaction between sorbitol and oleic acid. In this case, the formation of anhydrized sorbitol esters, with a low hydroxyl number (≈100) was mainly produced.

2.1.1.8. Acetal Formation Followed by Acetal Hydrolysis and Subsequent Aldol Condensation: Synthesis of Jasminaldehyde. Jasminaldehyde (α-*n*-amylcinnamaldehyde) is a compound with a violet scent traditionally used in perfumery. Its conventional synthesis involves the aldol condensation between benzaldehyde and heptanal under homogeneous base catalysis (sodium or potassium hydroxides).[85] In this synthesis, the most important undesired byproduct comes from the self-condensation of heptanal to form 2-*n*-pentyl-2-*n*-nonenal (Scheme 12).

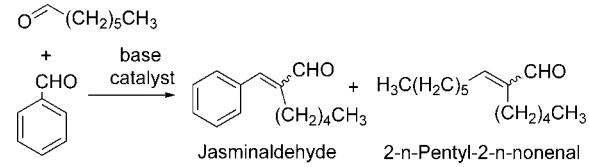
Table 1. Esterification of Sorbitol Ketal with Oleic Acid (OA) in the Presence of Different Solid Acid Catalysts[a]

catalyst (Si/Al)	hydroxy value	*t* (h)	conv (%) (OA)	yield (%) (esters) mono-	di-	tri-	select. (%) monoester
none		48	44	38	6	0	86
Mor (10)		24	45	30	15	0	66
	222	48	83	54	22	7	65
Beta (13)		24	47	46	1	0	97
	205	48	85	54	25	7	63
ITQ-2(15)		24	48	44	4	0	92
	185	48	77	35	29	13	46
$H_{0.5}Cs_{2.5}PW_{12}O_{40}$		24	86	58	23	5	68
	190	48	88	51	31	6	58

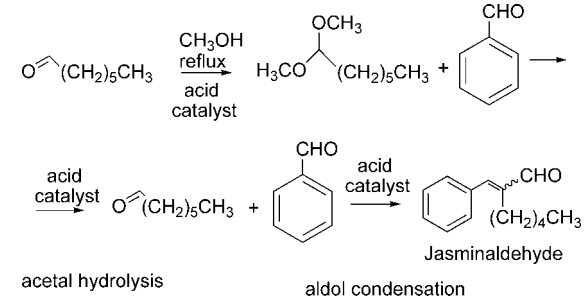
[a] Reaction conditions: oleic acid/ketalized sorbitol molar ratio of 1, 34 wt % of catalyst with respect to the total amount of reagents at 135 °C in the absence of solvent.

The heptanal self-condensation can be avoided, to some extent, by maintaining a very low concentration of heptanal with respect to benzaldehyde in the reaction mixture. That involves the use of high molar ratios of benzaldehyde/heptanal or a slow addition of heptanal to the reaction mixture. In the latter case, long addition times are required when working in a batch reaction system, and the methodology can hardly be used for working with plug-flow continuous reactors. In order to overcome these drawbacks, Climent et al.[86] have reported a new heterogeneous acid catalyzed cascade process for the synthesis of jasminaldehyde with high selectivity using low ratios of benzaldehyde/heptanal. The one-pot process uses solid acid catalysts and involves three consecutive steps in the same pot (Scheme 13). In the first one, heptanal dimethyl acetal is formed by refluxing heptanal with an excess of methanol in the presence of the solid catalyst. In the second step and when the dimethyl acetal yield is around 80%, the methanol is removed by distillation, and then benzaldehyde is added. Under these reaction conditions, heptanal dimethyl acetal undergoes deacetaliza-

Scheme 12. Conventional Synthesis of Jasminaldehyde



Scheme 13. Synthesis of Jasminaldehyde through the Sequential Acetalization−Acetal Hydrolysis−Aldol Condensation Process



tion at a controlled rate giving heptanal which condenses with benzaldehyde under acid catalysis.

To depress the self-condensation of heptanal, the control of the concentration of this aldehyde on the catalyst surface is of paramount importance, and this can be achieved by adjusting the rates of the deacetalization and aldol condensation. In order to do this, optimization of the acidity and structure of the catalyst, as well as reaction conditions, was carried out. Thus, the optimum catalyst in terms of activity and selectivity to jasminaldehyde was the mesoporous aluminosilicate MCM-41 with a Si/Al ratio of 14. Thus, reactions performed using a benzaldehyde/heptanal molar ratio of 1.5, 5 wt % of MCM-41 catalysts at 100 °C, yielded jasminaldehyde with a selectivity higher than 90% for conversions larger than 80%. It is interesting to notice that when the synthesis of jasminaldehyde is performed through a direct aldol condensation between benzaldehyde and heptanal in a molar ratio 5:1 using MCM-41 catalyst[87] or using two typically strong solid bases such as MgO and a Al/Mg mixed oxide[88] as catalysts selectivities for jasminaldehyde were sensibly lower (56−43%) for similar conversion levels, showing the advantage of the cascade process for the synthesis of this fragrance molecule.

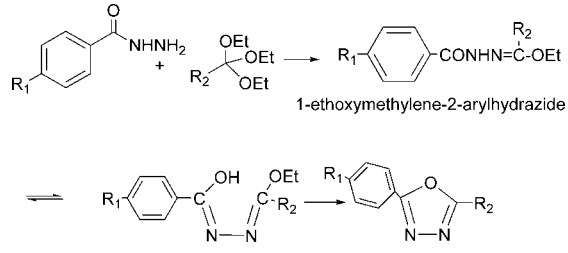
2.1.1.9. Condensation Followed by Cyclization: One-Pot Synthesis of 1,3,4-Oxadiazoles and 1,3,4-Thiadiazoles. 1,3,-Oxadiazoles and 1,3,4-thiadiazoles derivatives are an important class of bioactive heterocycles with a wide range of pharmaceutical and biological activities.[89−91] Particularly, tiodazosin[92] and nesapidil,[93] which are commercial antihypertensive agents, and antibiotics such as furamizol[94] contain the oxadiazol nucleus.

Most of the synthetic methods reported in the literature are multistep processes which generally involve the cyclization of acid hydrazides with different reagents such as thionyl chloride, phosphorus oxychoride, or sulphuric acid, usually under harsh reaction conditions.[95−98] Ainsworth[99] reported for the first time a one-pot synthesis of 1,3,-oxadiazoles derivatives by reacting acid hydrazides with orthoformates, but a high excess of orthoformate and long reaction times are required in this synthesis procedure in order to achieve good yields. According to Ainsworth,[99] the process involves the condensation of the acid hydrazide with the orthoester giving a 1-alkoxymethylene-2-arylhydrazide derivative which cyclizes through its enol form to the corresponding oxadiazole ring (Scheme 14).

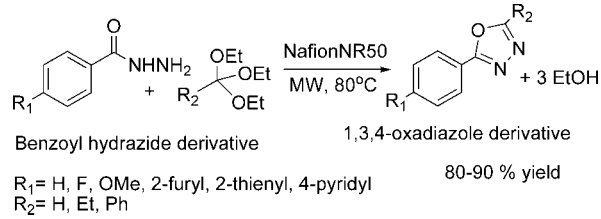
Recently, Polshettiwar et al.[100] have reported the one-pot synthesis of a variety of 1,3-oxadiazoles derivatives by means of the Ainsworth protocol under microwave irradiation using Nafion NR50 as a solid Bronsted acid catalyst and in the absence of any solvent (Scheme 15).

Reactions of different substituted benzoic hydrazides with orthoesters performed at 80 °C under MW irradiation gave excellent yields (80−90%) of oxadiazole in only a

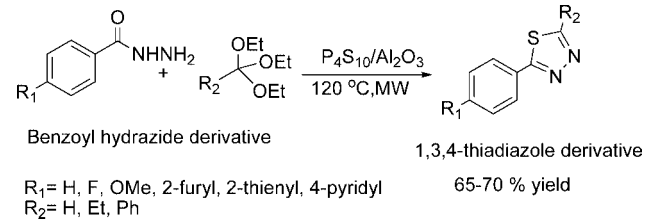
Scheme 14. One-Pot Synthesis of 1,3,4-Oxadiazoles from Acid Hydrazides



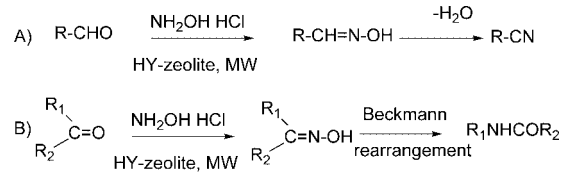
Scheme 15. One-Pot Synthesis of 1,3,4-Oxadiazoles Using Nafion NR50 as Acid Catalyst



Scheme 16. One-Pot Synthesis of 1,3,4-Thiadiazoles



Scheme 17. One-Pot Synthesis of Nitriles (A) and Amides (B) using HY Zeolite As Acid Catalyst



10 min reaction time. Different heterocyclic substituted oxadiazoles were also synthesized using the same approach with good yields. This protocol was extended for the one-pot synthesis of 1,2,3-thiadiazoles from acid hydrazides using phosphorus pentasulfide on alumina (P_4S_{10}/Al_2O_3) as a source of sulphur. The reaction proceeds efficiently with moderate to good yields in a 10 min reaction time (Scheme 16).

2.1.1.10. Oxime Formation Followed by Dehydration or Rearrangement: One-Pot Synthesis of Nitriles and Amides. Nitriles are important intermediary compounds since they can be converted to amines, amides, amides, carboxylic acids, ketones, and esters. They can be prepared from aldehydes by dehydration of the corresponding aldoximes.[101] Srinivas et al.[102] reported the one-pot conversion of aldehydes into nitriles using HY zeolite, under microwave irradiation. The reaction involves the formation of the corresponding aldoxime by treating the aldehyde with hydroxylamine hydrochloride followed by dehydration (Scheme 17A).

Reactions were performed under microwave irradiation and by conventional heating. Excellent yields of nitriles (84−96%) were achieved in short reaction times (1−2 min) under microwave irradiation, while the conventional heating afforded the corresponding nitriles in moderate yields (68−79%) after long reaction times (7−8 h). Using a similar approach, the authors performed the one-pot preparation of amides from ketones. Thus, ketones are converted in ketoximes by reaction with hydroxylamine hydrochloride, which subsequently undergoes the Beckmann rearrangement to the corresponding amide (Scheme 17B). In this case, under microwave irradiation, amides were obtained in higher yields (see Table 2) in short reaction times than under conventional heating. In addition, the catalyst recovered after reaction can be recovered and reused in a second run giving a similar yield of the product.

Table 2. Conversion of Ketones (R_1COR_2) into Amides R_1NHCOR_2

		time		isolated yield of amides	
R_1	R_2	MW (min)	conventional (h)	MW	conventional
C_6H_5	CH_3	2	9	94	62
C_6H_5	C_6H_5	2.5	10	95	65
4-(OH) C_6H_4	CH_3	3	11	82	56
4-(MeO)C_6H_4	CH_3	2	9	95	67
4-(Cl)C_6H_4	CH_3	2.5	10	92	61
4-(Br)C_6H_4	CH_3	2.5	11	86	58
4-(Me)C_6H_4	CH_3	2	9	94	60
-$(CH_2)_5$-		2	9	95	64

In this process, the first step does not require catalyst and the role of the acid zeolite is to catalyze the dehydration and the Beckmann rearrangement. Indeed, acid zeolites such as HY, Beta, and ZSM5 have been shown to catalyze the Beckmann rearrangement,[103−105] while aluminum free zeolites can catalyze the reaction at high temperature (370 °C). The cascade process to produce the amides in Scheme 17B is performed at a much lower temperature (110 °C) and therefore aluminosilicate HY with strong acid sites is then required.[103]

2.1.1.11. Acylation of Toluene with Phthalic Acid Followed by Intramolecular Acylation: One-Pot Synthesis of 2-Methylanthraquinone. 2-Methylanthraquinone is an important building block for the synthesis of a variety of compounds such as pharmaceuticals,[106] agrochemicals,[107] dyes and pigments.[108] The traditional synthetic route is a two-step process which involves the acylation of benzene and its derivatives with phthalic acid using $AlCl_3$ as a catalyst to afford 2-(4′-alkylbenzoyl) benzoic acid and its derivatives, followed by intramolecular acylation with concentrated sulfuric acid giving the anthraquinone nucleus (Scheme 18).[109,110] Recently, Hou et al.[111] have performed the one-pot synthesis of 2-methylanthraquinone by reacting toluene and phthalic acid or phthalic anhydride through a cascade acylation/acylation in liquid phase over different acid zeolites. Among the different zeolites tested (HBeta, HY, HMor, and HZSM-5), HBeta (Si/Al ratio = 11) was the most active and selective catalyst (Table 3).

Under optimized reaction conditions and using phthalic acid as an acylating agent, a maximum yield of 82.2% of 2-methylanthraquinone was obtained in a 5 h reaction time (Scheme 18). In addition, the catalyst could be reused four times with only a slight decrease in activity.

2.1.1.12. Cellulose Hydrolysis to Monosaccharides Followed by Fischer Glycosidation with Alcohols: Synthesis of Alkyl Glycosides. Long-chain alkyl glycosides are nonionic

Scheme 18. One-Pot Synthesis of 2-Methylanthraquinone

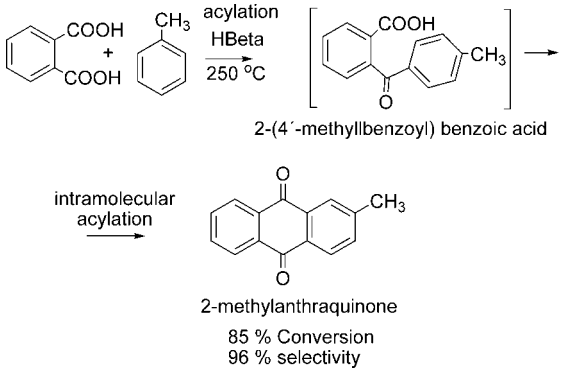
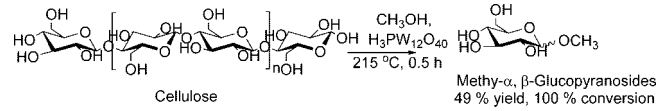


Table 3. Effects of Zeolite Structure on the Catalytic Performance[a]

catalyst (SiO_2/Al_2O_3)	pore size (nm)	conv (%)	selectivity (%)	yield (%)[b]
HBeta (22)	0.75 × 0.67	52.6	86.2	45.3
HY (5.5)	0.74 × 0.74	44.3	25.8	11.5
HMOR(10)	0.65 × 0.70	41.1	29.5	12.1
HZSM-5 (76)	0.56 × 0.53	15.4	3.6	0.6

[a] Reaction conditions: phthalic anhydride (PHA) (0.05 mol); toluene/PHA molar ratio = 3; catalysts (0.27 wt % with respect to the weight of PHA; 5 h at 250 °C. [b] HPLC yield.

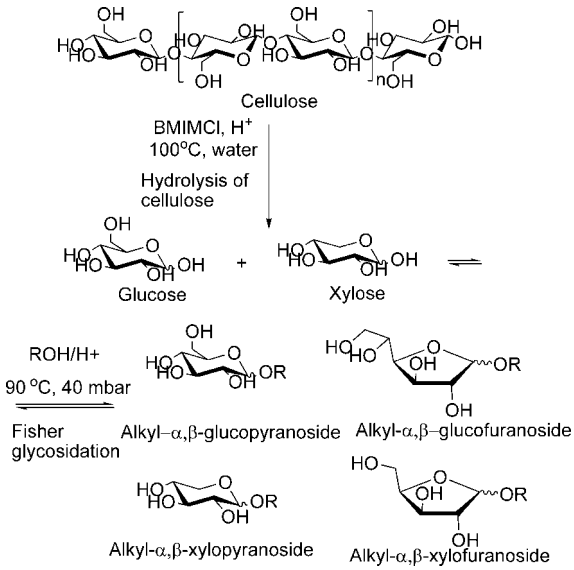
Scheme 19. Conversion of Cellulose into Methyl-α,β-glucosides



surfactants with low toxicity and good biodegradability[112] that are widely used in cosmetic, detergents, food, and pharmaceutical formulations.[113] The general procedure for the preparation of alkyl glycoside surfactants is the Fischer glycosidation which involves the acid catalyzed acetalization of a carbohydrate, usually glucose, with a fatty alcohol. One important source of glucose is the acid hydrolysis of cellulose which is a polymer of D-glucopyranoside units linked by β-1,4 glycosidic bonds. However, the robust crystalline structure of cellulose makes the hydrolysis process difficult, and concentrated H_2SO_4 (30−70%) is required in order to achieve a high yield of glucose. The hydrolysis of cellulose with dilute acids (<1%), which is more convenient for a commercial production, affords lower glucose yields.[114] Recently, heterogeneous catalytic processes using carbon materials bearing SO_3H groups or layered metal oxides such as $HNbMoO_6$ have been reported;[115−117] however they afford low glucose yields. Improved yields (40−60%) of glucose can be achieved if cellulose is previously pretreated with trifluoroacetic acid or ball milling to decrease its crystallinity.[117] Thus, the transformation of cellulose under mild conditions into glucose still remains a significant challenge. Recently, Deng et al.[118] have reported the acid-catalyzed direct transformation of cellulose into methyl glucosides in the presence of several acid catalysts using methanol as a solvent (Scheme 19). Results showed that dilute sulfuric acid, solid acids bearing SO_3H groups and heteropolyacids (i.e., $H_3PW_{12}O_{40}$ and $H_4SiW_{12}O_{40}$), were able to catalyze this transformation with good yields (>40%). Particularly, $H_3PW_{12}O_{40}$ gave the highest TON for the formation of methyl glucosides, and more than 80% of $H_3PW_{12}O_{40}$ could be recovered after reaction and reused without significant changes in catalytic activity. In addition, it was shown that the conversion of cellulose in methanol is more facile than that in water, and methyl glucosides formed in methanol are more stable against further degradation than glucose in water. However, when reacting longer chain alcohols than methanol lower yields of alkyl glucosides were obtained.

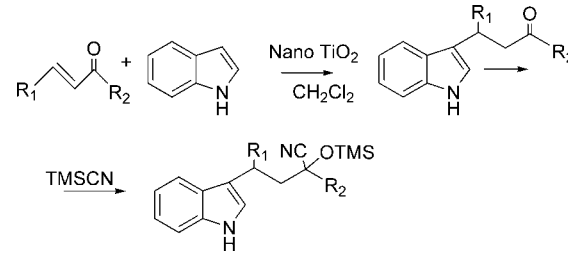
Very recently, we have shown that it is possible to obtain alkyl α,β-glycoside surfactans in process under very mild conditions starting from cellulose, by coupling hydrolysis of cellulose with the Fischer glycosidation with C_4 to C_8 alcohols (Scheme 20).[119] Among the different catalysts tested for the hydrolysis step in the presence of an ionic liquid (butyl methyl imidazolium chloride, BMIMCl), the sulfonic resin Amberlyst 15Dry (A15) and $H_3PW_{12}O_{40}$ gave the best performances.

Scheme 20. Conversion of Cellulose into Alkyl-α,β-glycoside Surfactants



Thus, the process, that is, cellulose hydrolysis followed by Fischer glycosidation, was studied using A15 catalyst. It was found that the amount of water in the reaction media is an important variable to control the rate and extension of both cellulose hydrolysis and glycosidation reaction, while long reaction times during the hydrolysis step favors glucose degradation. Thus, in order to depress glucose degradation, the alcohol was added after a shorter time of hydrolysis. The results presented in Table 4 (entries 5−9) show an optimum at 1.5 h with 98% total conversion and 82 wt % yield of octyl α,β-glycosides (entry 8), while 5-hydroxymethyl furfural (HMF) generated by degradation of glucose was only 6%. $H_3PW_{12}O_{40}$ also gave good results under optimized conditions (entry 13). By using a fixed bed column with silica gel with a mixture of methanol and ethyl acetate, the ionic liquid and alkyl glucosides could be separated and the ionic recycled. Finally, the A15 catalyst could be reused after regeneration of the acidic sites with a H_2SO_4 solution allowing the production of octyl-α,β-glycosides with a mass yield of 77.8%.

Scheme 21. One-Pot Synthesis of α-Silyloxy-γ-indolyl Nitriles



2.1.2. Solid Lewis Acid Sites

2.1.2.1. Michael 1,4-Addition Followed by 1,2-Nucleophilic Addition: One-Pot Synthesis of α-Silyloxy-γ-indolyl nitriles. Silylated cyanohydrins are highly versatile intermediates for the synthesis of a wide variety of important compounds such as α-hydroxyacids, α-aminoacids, and β-aminoalcohols.[120,121] Particularly, the synthesis of α-silyloxy-γ-indolyl nitriles can be performed by Michael 1,4-addition of indoles to α,β-unsaturated ketones and subsequent 1,2-addition of trimethylsilyl cyanide (TMSCN) in the presence of catalytic amounts of $InBr_3$.[122] Recently, Kantam et al.[123] have used the same approximation for the synthesis of α-silyloxy-γ-indolyl nitriles using nanocrystalline TiO_2 (10−20 nm) as the heterogeneous acid catalyst (Scheme 21).

The process is performed in two steps at room temperature; first, the Michael 1,4-addition of indole derivative to an α,β-unsaturated ketone occurs giving a β-indolyl ketone, and after complete conversion of the α,β-unsaturated ketone in about 10 h, TMSCN is added resulting in the formation of the corresponding silylated cyanohydrine in yields between 54−73%.

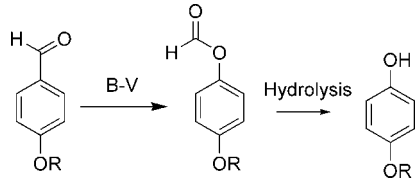
2.1.2.2. Baeyer−Villiger Oxidation of Alkoxybenzaldehydes Followed by Ester Hydrolysis: One-Pot Synthesis of Alkoxyphenols. 4-Alkoxyphenols are important intermediates for manufacturing drugs, agrochemicals, and dyes.[124] Moreover, they have antioxidant properties for food and cosmetics[125] and are also used as polymerization inhibitors and stabilizers for polyesters.[124] The conventional route for preparation of 4-alkoxyphenol involves the monoalkylation of hydroquinone.[126,127] However, this route gives poor

Table 4. Transformation of Cellulose into Alkyl Glycoside Surfactants[a]

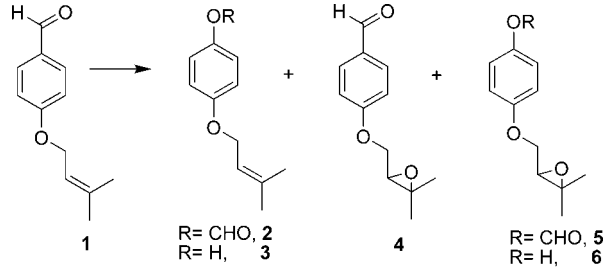
			yield (mol %)[c]						
entry	alcohol	conv (%)[b]	cellobiose	glucose	xylose	HMF	alkyl-α,β-glucoside (yield wt%)	alkyl-α,β-xyloside (yield wt%)	total yield of surfactant (wt%)
1	butanol[d]	96	5.8	16.4	6.9	3.8	5.0 (7.2)	traces	7.2
2	hexanol[d]	96	7.1	18.7	6.9	5.3	5.8 (9.4)	1.2 (1.7)	11.1
3	hexanol[e]	95	4.8	9.7	2.7	5.2	17.1 (27.8)	4.8 (6.9)	34.7
4	octanol[e]	95	4.4	8.1	2.7	3.8	17.3 (31.3)	5.4 (8.7)	40.0
5	octanol[f]	98	traces	3.4	3.2	15.1	24.3 (43.8)	2.8 (4.5)	48.3
6	octanol[g]	96	0.7	3.4	3.2	8.0	31.7 (57.1)	4.1 (6.7)	63.8
7	octanol[h]	94	0.6	3.1	2.3	7.4	33.9 (61.2)	5.4 (8.8)	70.0
8	octanol[i]	98	0.5	3.0	2.1	6.1	38.8 (70.0)	7.3 (11.7)	81.7
9	octanol[j]	96	1.5	4.4	2.8	4.8	27.7 (50.0)	6.6 (10.7)	60.7
10	octanol[k]	98	1.0	17.4	4.3	10.1	25.1 (45.2)	4.7 (7.6)	52.8
11	hexanol[i]	95	0.8	3.2	2.8	5.8	36.9 (60.1)	8.5 (12.3)	72.4
12	octanol[l]	99	0.2	1.8	0	1.6	39.7 (71.5)	0	71.5
13	octanol[m]	95	0.8	1.1	1.1	4.1	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 the hydrolysis, the alcohol (43 mmol) was added in the solution and the temperature was decreased at 100 °C. The reaction was carried out at 40 mbar for 24 h. [b] Calculated by the weight difference of cellulose before and after the reaction. [c] Determined by HPLC. [d] A15 (80 mg, 0.37 mmol H^+), hydrolysis time: 5 h and Fisher glycosidation carried out at atmospheric pressure. [e] A15 (80 mg, 0.37 mmol H^+). [f] Hydrolysis time: 5 h. [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 H^+), hydrolysis time: 1 h.

Scheme 22. One-Pot Synthesis of Alkoxyphenols



Scheme 23. One-Pot Synthesis of Alkoxyphenols from Aldehydes Bearing C−C Double Bond



selectivity because dialkylation products are also formed. An alternative route for the preparation of 4-alkoxyphenols is the Baeyer−Villiger oxidation of alkoxybenzaldehydes. The process involves two consecutive steps, that is, the Baeyer−Villiger oxidation of the benzaldehyde derivative giving the corresponding formate ester, followed by hydrolysis of the formate to the corresponding phenol (Scheme 22).

This route has been performed using conventional oxidants in the homogeneous phase, such as percarboxylic acids (metachloroperbenzoic,[128] and monopersuccinic acids[129]), H_2O_2/seleninic acid,[130] or H_2O_2/methanol/sulfuric acid,[131] achieving excellent yields to the corresponding alkoxyphenols. However, the use of these homogeneous systems has important drawbacks as they involve poisonous or corrosive reagents. When using percarboxylic acids, special care should be taken to minimize explosion risks. Furthermore, the oxidation process is concomitant with the formation of at least one molecule of the acid that has to be separated and reoxidized to produce the peracid.

Corma et al.[132−135] have shown that Sn-Beta zeolite and Sn-MCM-41 are active and selective Lewis catalysts for the Baeyer−Villiger oxidation of several carbonyl compounds using H_2O_2 as oxidant. This process avoids the use of peracids, while H_2O is the only byproduct formed. Thus, the system H_2O_2/Sn-Beta was used for the production of 4-substituted alkoxyphenols starting from different benzaldehyde derivatives giving, under optimized reaction conditions, the 4-alkoxyphenol derivatives with good selectivities.[136] As an example, during the synthesis of 4-methoxyphenol starting from 4-methoxy benzaldehyde, when ethanol or aqueous acetonitrile were used as solvents, the 4-alkoxyphenol was obtained with 99 and 96% selectivity at 59 and 57% conversion respectively after a 7 h reaction time. In addition, the catalyst could be regenerated by calcination and the initial activity and selectivity was restored. The authors found that Al-Beta zeolite samples bearing Bronsted acid sites is an efficient catalyst for performing Baeyer−Villiger oxidation and ester hydrolysis (95% selectivity at 87% conversion) provided that the molecule does not contain olefinic groups. However, when the aldehyde derivative possesses an olefinic substituent (Scheme 23), the Al-Beta gives no reactivity, and a solid Lewis acid catalyst such as Sn-Beta can promote the formation of the corresponding unsaturated phenols with high chemoselectivity as is shown in Table 5. In addition, other conventional oxidation systems such as methyltrioxorhenium and *m*-chloroperbenzoic acid exhibit low selectivity to the target compounds.

Table 5. Chemoselectivities for Different Oxidation Methods in the Baeyer−Villiger Oxidation of *p*-(3-Methylbut-2-enoxy)-benzaldehyde (1)[a]

		product distribution (%)			
oxidation system	conversion (%)	**2 + 3**	**4**	**5 + 6**	other[c]
Al-Beta/H_2O_2	0	0	0	0	0
Sn-Beta/H_2O_2	61	85[b]	0	0	15
MTO[d]	15	0	62	6	32
mCPBA[e]	20	28	12	29	31

[a] Reaction conditions: 1 (1.4 mmol), H_2O_2 (2.3 mmol, 50% aqueous solution of H_2O_2), 1.5 g of acetonitrile, 25 mg of catalyst at 80 °C. [b] 1:4 ratio of ester 2 to phenol 3. [c] Unidentified higher oxidation products excluding epoxide. [d] Methyltrioxorhenium. [e] *m*-Chloroperbenzoic acid (0.3 equiv). Al-Beta (Si/Al = 30); Sn-Beta (2 wt % SnO_2).

Scheme 24. Cascade Process for the Synthesis of 4-Methoxybenzyl 1-Methylpropyl Ether

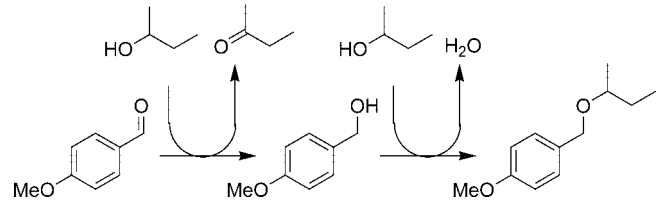


Table 6. Results for the Synthesis of 4-Methoxybenzyl 1-Methylpropyl Ether by a Tandem Hydrogenation/ Etherification Sequence Using Solid Lewis Acid Catalysts[a]

catalyst (mg)	*t* (h)	total conversion (%)	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.

2.1.2.3. Meerwein−Ponndorf−Verley Reaction Followed by Etherification: One-Pot Synthesis of 4-Methoxybenzyl 1-Methylpropyl Ether. The 4-methoxybenzyl 1-methylpropyl ether (Scheme 24) is a fragrance with a fruity pear odor. Commercial preparation involves two steps in which the first step consists of the reduction of 4-methoxybenzaldehyde to the corresponding alcohol that is separated and purified before going into a second process (etherification).[46] Corma et al.[137] have integrated the reduction (hydrogenation)−etherification steps in a one cascade process using Sn- and Zr-Beta zeolites as acid Lewis catalysts. This alternative preparation procedure involves the reduction of the 4-methoxybenzaldehyde to the corresponding alcohol through a Meerwein−Ponndorf−Verley reaction with 2-butanol, followed by etherification of the benzyl alcohol intermediate with 2-butanol which is in excess (Scheme 24).

Results of Table 6 show that both catalysts are active giving the desired fragrance in high yield, Zr-Beta being more active for the global process. It is interesting to notice that although this process can be carried out using a conventional Lewis acid such as aluminum isopropoxide the fact that water is formed during the etherification limits the use of the conventional aluminum isopropoxide. When using less polar Sn- or Zr-Beta zeolites, it is not necessary to continuously remove the water formed during the etherification step. With these catalysts, the surface hydrophobicity makes the water concentration near to the Lewis acid sites low improving the catalyst efficiency.

Recently, Corma et al.[138] reported the synthesis of Nb and Ta-Beta zeolites. These catalysts were also tested in the one-pot process described above for the synthesis of 4-methoxybenzyl 1-methylpropyl ether. Ta-Beta exhibited similar activity and selectivity as Sn-Beta, while Nb-Beta resulted in a considerably lower selective to the target molecule.

2.2. Multistep Sequential Processes on Single-Site Basic Catalysts

Perhaps the most common basic catalysts used in organic synthesis and also for production of chemicals and fine chemicals are alkaline hydroxides, carbonates, and alkyl ammonium hydroxides. Trying to substitute those by solid catalysts is a difficult task, especially for industrial processes. The reason for this is the relatively low cost of alkaline hydroxides and the fact that the companies are used to deal with such types of compounds and the wastes that they generate. Nevertheless, researchers have made important efforts to prepare high surface area solid base catalysts. In this way, high surface magnesium oxides,[139] layered magnesium aluminates,[140,141] and nitrurated aluminum phosphates (ALPONS) have been prepared and are able to catalyze a large variety of reactions, though at higher temperatures than alkaline hydroxides.[139,142−147] Stronger basicities have been achieved with supported alkaline oxides and even metals on alumina and zeolites[148−154] or supporting potassium fluoride on alumina.[155,156] Of course, when using the very basic solid catalysts, attention has to be paid to avoid catalyst poisoning by CO_2 or H_2O. Extensively reviews on solid base catalysts and their use can be found in literature.[157−161]

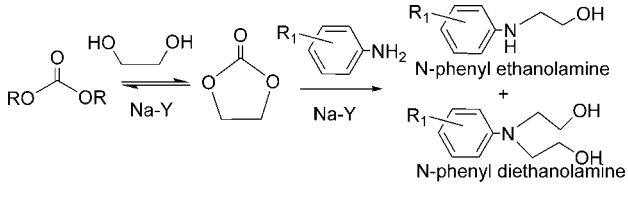
In this section, we will show how those solid base catalysts have been used successfully to catalyze multistep reactions.

2.2.1. Transesterification of Alkylcarbonates Followed by N-Alkylation: One-Pot Synthesis of β-Amino Alcohols

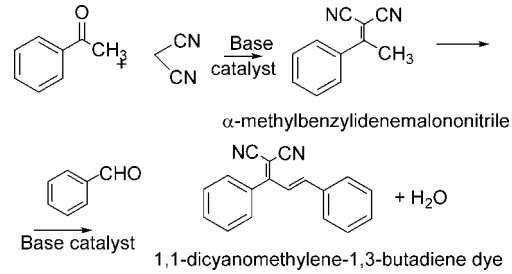
β-Amino alcohols are versatile compounds extensively used in the preparation of biologically active products, artificial aminoacids, and quiral auxiliaries for asymmetric synthesis.[162] They are also useful intermediates for the synthesis of perfumes,[163] dyes,[164] and photo developers.[165] β-Amino alcohols are usually synthesized by reacting alkylene oxides and amines.[164] However, another route to synthesize β-amino alcohols which avoids the use of hazardous alkylene oxides is the reaction between alkylene carbonates and amines.[166−169] Shivarkar et al.[170] have reported the selective one-pot synthesis of β-amino alcohols from aniline, dialkyl carbonate, and ethylene glycol catalyzed by a basic Na exchanged Y zeolite. In this synthesis, ethylene carbonate was generated in situ by transesterification reaction between a dialkyl carbonate and ethylene glycol which subsequently undergoes N-alkylation of aniline to give β-amino alcohol (Scheme 25).

For instance, when the reactions were performed by mixing dimethyl carbonate, ethylenglycol, and aniline along with the catalyst in a parr autoclave pressurized with N_2 at 34 bar and 170 °C, it was observed that the selectivity to N-phenyl ethanolamine was very poor (55%) owing to the formation of the *N*-methyl aminoalcohol. However, the selectivity to mono β-amino alcohol could be improved (>91%) when the reaction was performed under one-pot conditions using diethyl carbonate while removing the ethanol formed and the excess of diethyl carbonate by reactive distillation. Reaction of various aromatic anilines (with electron donating substituents) and organic carbonates were tested under these conditions achieving good to moderate yields (73−91%) to the corresponding mono β-amino alcohols. It was found that diethyl carbonate was the most suitable organic carbonate for the tandem reaction, due to its lower activity as the N-alkylating agent and giving higher selectivity to β-amino alcohols. The main advantage of this cascade process where ethylene carbonate is formed in situ is to avoid the isolation and purification steps required for production of alkylene carbonates.

Scheme 25. One-Pot Synthesis of β-Amino Alcohols



Scheme 26. One-Pot Synthesis of 1,1,-Dicyanomethylenebutadiene Derivatives

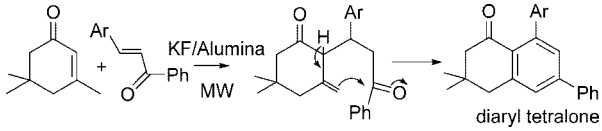


2.2.2. Knoevenagel Condensation Followed by Aldol-Type Condensation: One-Pot Synthesis of 1,1-Dicyano-2,4-diphenyl-1,3-butadiene

Dicyanomethylene derivative dyes have a variety of applications such as textile dyes,[171] in sensitizing photopolymerization in imaging systems,[172] dye lasers,[173] and optical recording.[174] Particularly, 1,1-dicyanomethylenebutadiene derivatives are used as disperse dyes[175] with interesting nonlinear optical properties.[176,177] The conventional synthesis of 1,1-dicyanomethylenebutadiene derivatives involves two reaction steps. The first one is the Knoevenagel condensation between acetophenone derivatives and malononitrile in refluxing benzene and using a mixture of ammonium acetate and glacial acetic acid as a catalyst giving the corresponding α-methylbenzylidenemalonolnitrile which after subsequent separation and purification is reacted with benzaldehyde derivatives to give the corresponding 1,1-dicyanomethylenebutadiene derivative.[176,178] Climent el al.[179] reported the two-step synthesis of this type of compound using heterogeneous base catalysts in the absence of solvent and at moderate temperature (Scheme 26).

In order to find the most appropriate catalyst able to perform the one-pot process successfully, different heterogeneous base catalysts were tested for each individual step. Results showed that the optimum catalyst in terms of activity and selectivity for both steps was an aluminophosphate oxinitride[180] (ALPON) with a nitrogen content of 13.7%. Thus, the reaction was performed using this catalyst, by reacting acetophenone with malononitrile at 100 °C until the yield of α-methylbenzylidenemalonolnitrile was 90% (100% selectivity). At this point, the required amount of benzaldehyde was added and the temperature increased at 150 °C. After a 6 h reaction time, 100% conversion with a 92% yield

Scheme 27. One-Pot Synthesis of Diaryl Tetralone



of the 1,1-dicyanomethylenebutadiene derivative was obtained. These results are far better than what can be achieved by using ammonium acetate and glacial acetic acid as catalyst, and with a much easier workup.

2.2.3. Michael Addition and Subsequent Robinson Annulation: One-Pot Synthesis of Diarylmethyl-α-tetralones

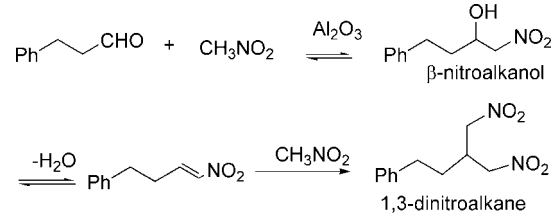
α-Tetralones derivatives are important compounds due to their wide variety of pharmacological activities, such as hypotensive, bronchodilator,[181] and antibacterial[182] activities. In addition, the hydronaphthalene ring is found in a number of natural products and is particularly important in the fragrance and cosmetic industries.[183] The most important approaches to the synthesis of the α-tetralone ring are the Diels−Alder reactions between cyclohexenones as dienophiles and different dienes and the tandem Michael addition-Robinson annulation.[184,185] Rissafi et al.[186] reported the preparation of diaryl tetralones in a one-pot reaction which involves in a first step the Michael addition of isophorone with different chalcones under basic catalysis followed by cyclization (Robinson annulation) (Scheme 27). The reactions were performed in solvent-free conditions under microwave irradiation using KF/alumina as basic catalysts and mineral support. The reaction times ranged from 5 to 8 min at 108−115 °C, achieving yields of the α-diaryltetralone derivatives between 80−92%. However, only moderate yields (50−60%) were obtained when reactions were carried out under solvent-free classical heating. Using NaOEt as the base under phase-transfer catalysis conditions and microwave irradiation, the yields of α-diaryltetralone derivatives were similar to those obtained with the heterogeneous base catalyst.

2.2.4. Nitroaldol Reaction Followed by Michael Addition: Synthesis of 1,3-Dinitroalkanes

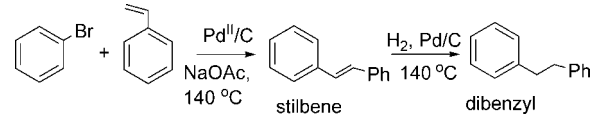
1,3-Dinitro compounds are important intermediates for the synthesis of a variety of 1,3-difunctionalized molecules, carbohydrate derivatives,[187] and heterocycles.[188] The conventional synthesis of 1,3-dinitroalkanes is performed through the Michael addition of nitroalkanes to nitroolefins[187−189] under basic catalysis. On the other hand, the synthesis of nitroalkenes involves the base catalyzed nitroaldol reaction between aldehydes and aliphatic nitrocompounds followed by dehydration of the corresponding β-nitroalkanol intermediate to the nitroolefin.[190] However, the synthesis of nitroalkenes often proceeds in poor yields due to their dimerization and polymerization.

Ballini et al.[191] have reported the one-pot preparation of 1,3-nitroalkanes by reacting aldehydes with an excess of nitromethane in the presence of basic alumina as solid catalyst. The reaction is a cascade process which starts with the nitroaldol condensation between an aldehyde with nitromethane (which acts both as nucleophile and as solvent) giving the corresponding nitroalkanol intermediate which dehydrates to the conjugated nitroalkene. Further Michael nucleophilic addition of a second molecule of nitromethane

Scheme 28. One-Pot Synthesis of 1,3-Dinitroalkanes



Scheme 29. One-Pot Synthesis of Dibenzyls



gives the target compound (Scheme 28). The advantage of this cascade process is that the in situ trapping of the nitroalkene derivative with nitromethane avoids any possible polymerization of the nitroolefin leading to high yields of 1,3-dinitroalkanes. The reactions were performed at a reflux temperature of nitromethane with aliphatic, aromatic, and heteroaromatic aldehydes giving good yields of the dinitroalkane derivative (60−78%) within a 3−5 h reaction time.

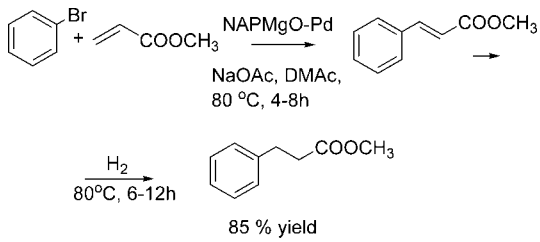
2.3. Multistep Sequential Processes on Single-Site Metal Catalysts

2.3.1. Palladium and Other Metals

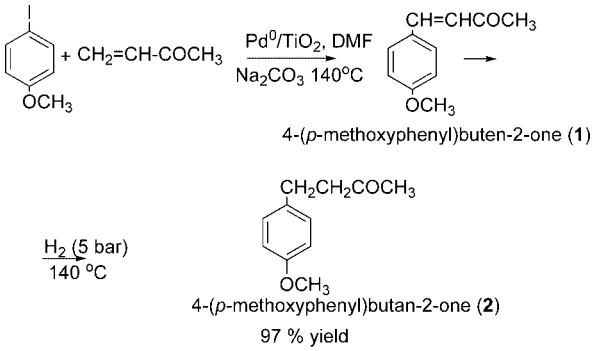
2.3.1.1. Heck Coupling Reaction Followed by Hydrogenation. *2.3.1.1.1. Synthesis of Dibenzyl.* Dibenzyl is a structure which is found in a variety of compounds of interests in the agrochemical and pharmaceutical industry.[192−194] Gruber et al.[195] reported the preparation of dibenzyl through a one-pot Heck-hydrogenation sequence which involves the Heck coupling of bromobenzene with styrene followed by hydrogenation in the presence of Pd^{II}/C (0.1 mol %) as a catalyst (Scheme 29). Heck coupling was performed at 140 °C using an excess of styrene, and quantitative conversion of bromobenzene with 92% yield of E-stilbene intermediate was achieved after 4 h. Then, hydrogenation of the C═C double bond was performed at 140 °C during 8 h giving dibenzyl in 93% total yield. Reuse of the catalyst showed a strong deactivation after the first run, giving only 12% of conversion for the Heck coupling after the second run. Cusati et al.[196] have also performed the same process using commercial available Pd(0)/C, achieving yields of dibenzyls between 27−100%; however, the reaction was limited to activated aryl bromides.

Dibenzyls and alkyl phenyl esters have also been obtained in one pot using nanocrystalline magnesium oxide stabilized Pd(0) catalyst (NAPMgO-Pd).[197] Among different Pd based catalysts such as Pd/SiO_2, Pd/C, Pd/LDH, Pd/TiO_2, or Pd/Al_2O_3, NAPMgO-Pd was the most active and selective catalyst for performing both steps, that is, Heck cross-coupling followed by reduction. Using NAPMgO-Pd (1.43 mol %), the Heck coupling was performed at 80−100 °C in dimethylacetamide solvent, and hydrogenation was carried out at room temperature under H_2 atmosphere. In this way, a variety of dibenzyls as well as alkyl phenylpropionates (Scheme 30) were synthesized in high yields (75−98%). Leaching of Pd was not observed and the catalyst was stable and maintained the catalytic activity after six consecutive runs.

Scheme 30. One-Pot Synthesis of Alkyl Phenyl Esters



Scheme 31. One-Pot Synthesis of (4-(*p*-Methoxyphenyl)butan-2-one)



2.3.1.1.2. Synthesis of Raspberry Scent Fragrance (4-(p-Methoxyphenyl)Butan-2-one). The synthesis of the fragrance 4-(*p*-methoxyphenyl)butan-2-one with raspberry scent has been prepared through one-pot Heck-hydrogenation sequence with excellent yield and selectivity.[198] Commercially, this compound is prepared by the Friedel−Crafts alkylation of anisole with 4-hydroxybutan-2-one or methyl vinyl ketone using Lewis or Bronsted homogeneous acid catalysts.[199] However Friedel−Crafts alkylation leads to many side reactions such as isomerization, transalkylation, polyalkylation, and polymerization, giving low yields and selectivities to the target compound, while producing large amounts of byproduct. An alternative catalytic process for the synthesis of 4-(*p*-methoxyphenyl)butan-2-one involves the Heck coupling of iodoanisole with methyl vinyl ketone in the presence of a heterogeneous palladium catalyst, to yield the intermediate 4-(*p*-methoxyphenyl)buten-2-one which is subsequently hydrogenated to the desired compound (Scheme 31).[198] To prevent the hydrogenation of methyl vinyl ketone and the dehalogenation of iodoanisole, the Heck reaction is performed in the absence of hydrogen and when completed hydrogen is introduced yielding the final hydrogenated product. Among several palladium supported catalysts tested for the overall process, it was found that 1 wt % Pd^0/TiO_2 was an excellent catalyst to perform both reactions in a system (Table 7). Thus, using this catalyst and working at 140 °C, the coupling step was completed in 2 h, and the consecutive hydrogenation gave 97% yield of the 4-(*p*-methoxyphenyl)butan-2-one. The catalyst was regenerated and used in a second cycle displaying the same catalytic activity. When a homogeneous palladium complex[200] was used for the same reaction sequence, a high yield for the Heck reaction but very poor activity for the consecutive hydrogenation step was obtained, yielding only 18% of the target compound.

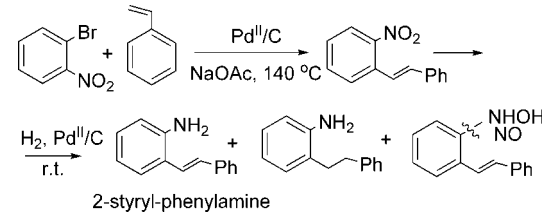
2.3.1.1.3. Synthesis of 2-Styryl-phenylamine. The chemoselective tandem synthesis of 2-styryl-phenylamine, an intermediate for indoline synthesis,[201] has been performed by coupling the Heck reaction with hydrogenation using 0.1 mol % Pd^{II}/C as catalyst.[195] The overall process involves a consecutive Heck C−C coupling between 2-bromo-nitrobenzene with styrene giving the 2-styryl-nitrobenzene. After the completion of the C−C coupling, reduction of NO_2 group is performed with hydrogen (Scheme 32). Under optimized reaction conditions, that is, working at 140 °C, and using as a solvent a mixture of DFM/H_2O/MeOH = 3:2:1, the Heck reaction proceeds with a quantitative yield after 6 h. At completion, the hydrogenation of the nitro group was performed with 5 bar hydrogen at room temperature, without affecting practically the double bond. The target molecule was obtained in 35% yield and 90% selectivity after a 12 h reaction time. By-products as presented in Scheme 32 were obtained in lower amounts (5%).

Table 7. Results of the Heck Reaction and Hydrogenation Steps Obtained Using TiO_2 with Different Amounts of Palladium Loading and in the Presence of an Homogeneous Catalyst (Pd-AO)[a]

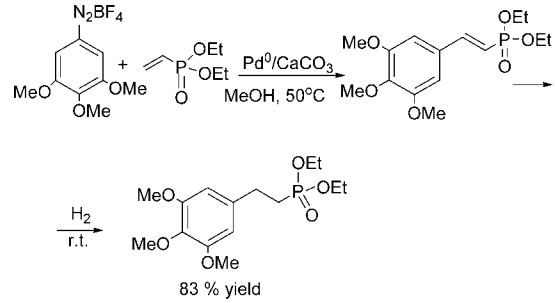
	Heck reaction		hydrogenation[f]
x-catalysts[g]	conversion of iodoanisole (%)	yield 1 (%)	yield 2 (%)
0.2-Pd-TiO_2	99	99	30[d]
1-Pd-TiO_2	100	100	97[d]
2-Pd-TiO_2	100[b]	100	97[e] (99)
Pd-AO	98[c]	98	18[d]

[a] Reaction conditions: 4.4 mmol of iodoanisole, 8.8 mmol of MVK, 5.4 mmol of sodium carbonate, 4.5 mL of DMF, 2 h, 300 mg of catalyst, at 140 °C. [b] 1 h. [c] 7 h. [d] 15 h. [e] 10 h. In brackets results at 24 h. [f] Hydrogen (5 bar) at 140 °C. [g] Metal loading (wt %).

Scheme 32. One-Pot Synthesis of 2-Styryl-phenylamine



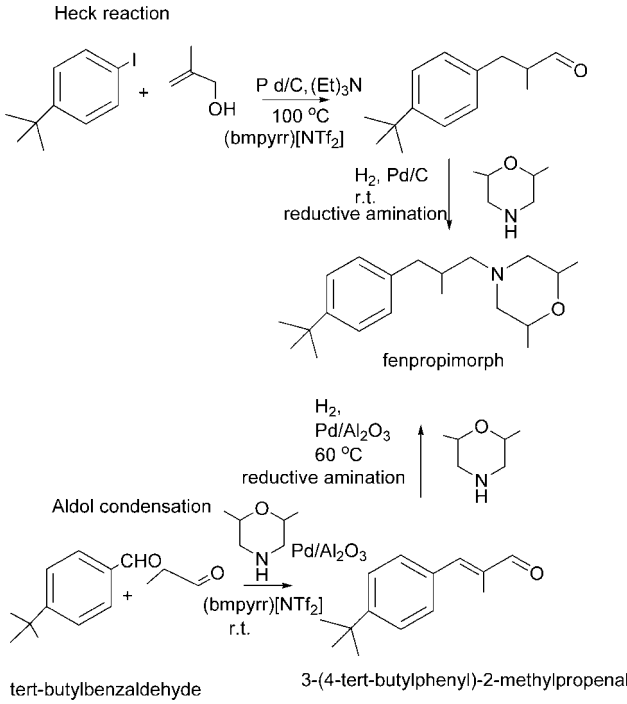
Scheme 33. One-Pot Synthesis of Wadsworth−Emmons Reagents



2.3.1.1.4. Preparation of Wadsworth−emmons Reagents. Brunner et al.[202] have reported a one-pot process for the preparation of useful Wadsworth-Emmons reagents which involves the Heck cross-coupling of aryldiazonium salts with vinylphosphonates followed by a hydrogenation step catalyzed by $Pd^0/CaCO_3$ (2 mol % Pd) (Scheme 33). The higher reactivity of aryldiazonium salts with respect to conventional arylhalides allowed the use of mild reaction conditions (50 °C), without addition of any ligand and base, affording excellent yields of the corresponding phosphonates (83−99%).

2.3.1.2. Heck or Aldol Condensation Followed by Reductive Amination: One-Pot Synthesis of the Fungicide Fenpropimorph. Fenpropimorph is a fungicide widely used in agricultural formulations for the control of disease in cereal

Scheme 34. One-Pot Synthesis of the Pesticide Fenpropimorph

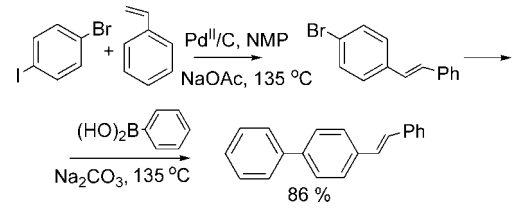


crops. The current industrial process consists of two steps which involve the condensation of 3-(4-*tert*-butylphenyl)-2-methylpropenal with 1-(2-hydroxypropylamino)-propan-2-ol using a solid catalyst Dowex 50 resin. The resulting intermediate oxazolidine is isolated by distillation and hydrogenated at 240 °C and 15−25 atm H_2 using Pd/C catalyst, the overall yield of Fenpropiomorph being 52%.[203] If the yield of the aldol condensation to form the starting 3-(4-*tert*-butylphenyl)-2-methylpropenal (50%) is taken into account, the overall yield starting from *tert*-butylbenzaldehyde is lower than 30%. Recently, Forsyth et al.[204] reported two one-pot routes for the preparation of fenpropimorph via a Heck coupling or aldol condensation followed by a reductive amination reaction using homogeneous and heterogeneous catalysts (Scheme 34).

The Heck coupling between 4-*tert*-butyliodobenzene and 2-methyl-2-propen-1-ol was performed at 100 °C using as catalysts Pd/C (5 wt % Pd) or $PdCl_2$. After completion, the reductive amination was accomplished by adding the 2,6-dimethylmorpholine under 10 atm of hydrogen at room temperature. Using as a solvent an ionic liquid (1-butyl-1-methylpirrolidinium bis((trifluoromethyl)sulfonyl)amide (bmpyrr)[NTf_2], both Pd/C and $PdCl_2$ give very good conversions for the Heck coupling (99%) while in the reductive amination, the homogeneous catalyst gives higher yield (81%) of fenpropimorph than the heterogeneous Pd/C (65%). In addition, the Pd/C catalyst could not be recycled due to leaching of Pd into the reaction mixture during the reductive amination.

If one follows the second route in Scheme 34, the first step is the aldol condensation between *tert*-butylbenzaldehyde and propanal. This was performed in (bmpyrr)[NTf_2] as a solvent and 5 wt % Pd/Al_2O_3, by adding slowly the propanal to the *tert*-butylbenzaldehyde, in order to avoid the self-condensation of propanal, and using 60 mol % of 2,6-dimethylmorpholine which is acting as reagent for the second step and as basic catalyst. After complete conversion, the reductive amination was performed by further adding 2,6-dimethylmorpholine and hydrogen. After 20 h fenpropimorph was obtained in 75% overall yield. The product could be recovered by decantation and the ionic-liquid-catalyst system could be recycled; however, lower conversion and selectivities were obtained when reused in a second run.

Scheme 35. One-Pot Synthesis of 4-Styryl-biphenyl

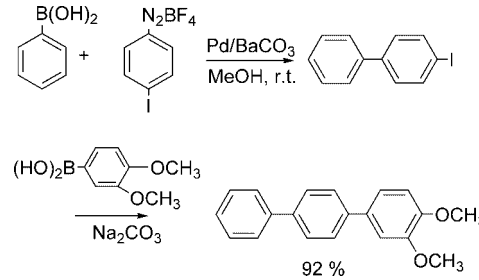


The authors showed that both strategies are viable for the synthesis of fenpropiomorph; however, the aldol condensation process is environmentally more friendly since its atom economy is 67%, while the Heck process has an atom economy of 46%. Moreover, the E factor in the aldol condensation is sensibly lower (0.37) than for the Heck process (1.26).

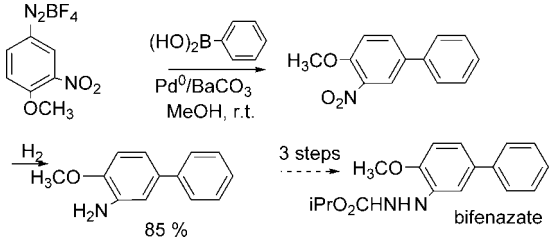
2.3.1.3. Heck Coupling Followed by Suzuki Reaction: One-Pot Synthesis of 4-Styryl-biphenyl. Several 4-styryl-biphenyl derivatives have important pharmacological activities such as antiinflamatory[205] and antitumor activity.[206] Gruber et al.[195] reported the synthesis of 4-styryl-biphenyl in a one-pot process which involves the Heck and Suzuki coupling (Scheme 35). The first step, the Heck reaction between *p*-bromo-iodobenzene with styrene, was performed in the presence of Pd^{II}/C (0.1 mol %) at 135 °C. The reaction was selective and quantitative after 40 h. Then, phenyl boronic acid was added giving the target compound in 86% yield. The authors stated that if the Suzuki coupling was performed first, the reaction was not selective enough as phenylboronic acid reacted with both iodo- and bromoarenes. Reuse of the catalyst indicated that the activity of Pd^{II}/C decreased slowly but selectivity remained high (≥93%) after five runs.

2.3.1.4. Double Suzuki Cross-Coupling Reactions: One-Pot Synthesis of Terphenyls. Terphenyls are polyphenyl systems with a wide range of biological activities such as potent immunosuppressant, neuroprotective, antithrombic, anticoagulant, and cytotoxic activities.[207] Moreover, they are also important as structural elements in liquid crystals[208] and fluorescent compounds.[209] Felpin et al.[210,211] reported the one-pot synthesis of unsymmetrical terphenyls (Scheme 36) using bromo- and iodo-substituted aryl diazonium salts through a double Suzuki cross-coupling reactions using Pd^0/C (5 mol % Pd) and $Pd^0/BaCO_3$ (2 mol % Pd) respectively as catalyst. Because of the greater reactivity of the diazonium function with respect to bromide and even iodide the consecutive Suzuki reactions take place chemoselectively under mild reaction conditions, giving yields of terphenyls between

Scheme 36. One-Pot Synthesis of Terphenyls



Scheme 37. One-Pot Synthesis of the Acaricide Bifenazate



65−92%. In addition, when Pd^0/C was used as a catalyst, leaching of the metal was not observed and the catalyst could be recovered by simple filtration. In contrast, $Pd^0/BaCO_3$ could not be recovered due to the partial decomposition of the support during the reaction.

The authors applied this approach to the synthesis of the acaricide bifenazate (Scheme 37). In this process, the dual reactivity of $Pd^0/BaCO_3$ for C−C coupling and hydrogenation was used to shorten the overall process. The last three steps were performed according to reported literature and were not fully optimized. The total process afforded bifenazate with 18% yield.

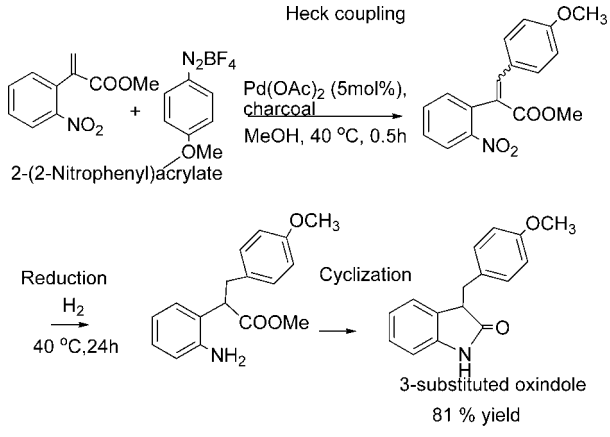
2.3.1.5. Heck Coupling Followed by Reduction and Cyclization: One-Pot Synthesis of Oxindoles. Oxindole-containing heterocycles substituted at the C3 position are very common structures in natural products[212] and pharmaceutical compounds[213] displaying a wide range of biological activities such as antiarthritis,[214] antitumoral,[215] and antiviral properties.[216] However, selective monofunctionalization at C3 by alkyl, alkenyl, or benzyl groups of N-unsubstituted oxindoles is difficult because N-alkylated products are also produced. Therefore, a preferred method for preparing 3-substituted oxindoles involves the reduction of 3-alkylidene or 3-arylideneoxindoles prepared by condensation of unsubstituted oxindoles with aldehydes and ketones.[217,218] An interesting work reported recently by Felpin et al.[219,220] showed a novel strategy where C3 benzylated oxindoles are produced through a cascade process. This approach starts with the Pd-catalyzed Heck cross-coupling of an aryl diazonium tetrafluoroborate salt with a 2-(2-nitrophenyl)acrylate. After the cross-coupling is completely accomplished, this is followed by Pd-mediated reductions of the double bond and the nitro group with H_2 giving the corresponding aniline, which spontaneously cyclizes to give the 3-substituted oxindole (Scheme 38).

Different Pd-based catalysts which include commercial Pd(II)/C, and $Pd^0/BaCO_3$, Pd/MgO, Pd/CeO_2, Pd/zeolite, Pd/graphite, and Pd/multiwall carbon naotubes where tested for this process, being Pd(II)/C generated in situ by mixing $Pd(OAc)_2$ and charcoal the most active catalyst. The authors found that while the Heck coupling proceeds very well either with or without addition of charcoal, in the absence of a support the subsequent reduction−cyclization steps proceeds only partially giving oxindole in moderate yield. The scope of the process was demonstrated by reacting a variety of diazonium salts with different substituted 2-(2-nitrophenyl)-acrylates, achieving the corresponding oxindoles in 70−80% yield. The recycling tests showed that a strong deactivation of the catalyst after the first run occurs, leading to lower yields of oxindole. The reused catalyst was less active for the Heck coupling but still maintained activity for the reduction−cyclization steps. It was suggested that the reduced form Pd(0)/C of the reused catalyst is detrimental for the success of the Heck cross-coupling, for which a Pd(II) precatalyst is preferred. On the other hand, the reduction−cyclization step requires a Pd with a low degree of oxidation.

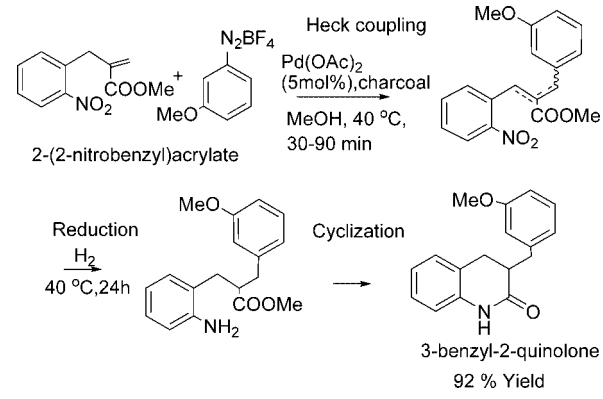
2.3.1.6. Heck Coupling Followed by Reduction and Cyclization: One-Pot Synthesis of 2-Quinolones. Following the approach described in Scheme 38, Felpin et al.[221] reported the synthesis of 2-quinolones by sequential Heck reduction−cyclization using a heterogeneous (in situ generated Pd/C) or mixed homogeneous/heterogeneous multitask palladium catalysts with charcoal as a support. The process consists of the Heck cross-coupling of 2-(2-nitrobezyl)acrylate with a aryl diazonium salt, followed by a palladium-catalyzed reduction of the C=C double bond and the nitro group under H_2 atmosphere. The product formed, that is, the corresponding aniline, cyclizes in situ to the 3-benzyl-2-quinolone derivatives (Scheme 39). With this protocol, a variety of C3-benzylated 2-quinolones were prepared with good yields using "in situ" generated Pd/C in methanol as a solvent.

In order to enlarge the scope to the preparation of C3-unsustituted, alkylated, and arylated 2-quinolones, the authors devised a complementary approach which involves the Heck cross-coupling of a diazonium salts with a nitro group at the *ortho* position, with variously substituted acrylates followed by reduction and cyclization steps (Scheme 40). Unfortunately, it was found that 2-nitrobenzene tetrafluoroborate was highly prone to dediazonization in MeOH, and an aprotic solvent such as dioxane had to be used. Using dioxane, excellent yields for the Heck cross-coupling reaction were achieved, although a homogeneous catalyst was required. Thus, an optimized protocol for preparing 2-quinolones was developed, where the first Heck coupling step was done using a homogeneous Pd catalyst ($Pd(OAc)_2$) in dioxane, followed by the reduction−cyclization sequence in the presence of charcoal under H_2 atmosphere. A variety of

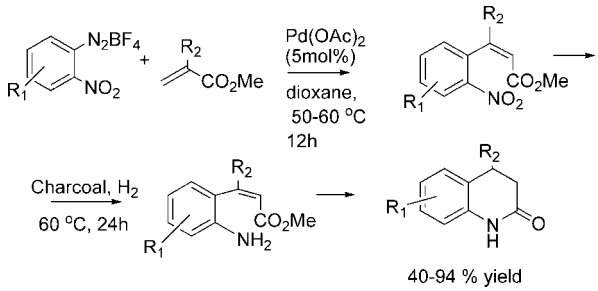
Scheme 38. One-Pot Synthesis of Oxindoles



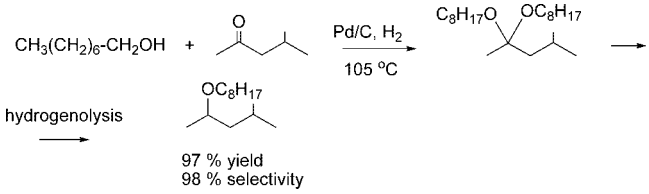
Scheme 39. One-Pot Synthesis of 2-Quinolones



Scheme 40. One-Pot Synthesis of 2-Quinolones



Scheme 41. One-Pot Synthesis of Unsymmetrical Ethers

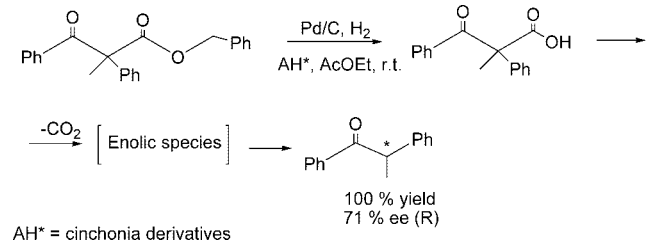


electron-rich and -deficient diazonium salts could be coupled with a variety of acrylate-type olefins giving the corresponding 2-quinolones in modest to good yields. In addition, the authors found that the HBF_4 generated during the cross-coupling can act as a cocatalyst promoting the reduction and the cyclization steps.

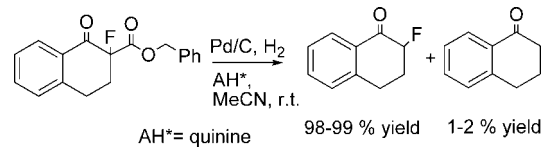
The catalyst could be easily separated from the reaction mixture by simple filtration. However, as occurs in the case of the synthesis of oxindoles,[219] the reused Pd/C showed a strong deactivation leading to low yields of 2-quinolone.

2.3.1.7. Acetalization Followed of Hydrogenolysis: One-Pot Synthesis of Unsymmetrical Ethers. An alternative to the Williamson synthesis of asymmetrical ethers is the hydrogenolysis of acetals (or ketals) formed from primary or secondary alcohols with carbonyl compounds.[222] Because of the capability of Pd to catalyze acetalization under hydrogen atmosphere,[223,224] unsymmetrical ethers have been obtained in a one-pot process from alcohols and carbonyl compounds in the presence of hetereogeneous Pd^0 catalysts and hydrogen.[225−229] According to Lemaire et al.,[226,227] the hemiacetal initially formed would produce the ether by either hydrogenolysis or dehydration affording the corresponding enol ether whose double bond is subsequently hydrogenated. Bethmont et al.[226,230] and Fujii et al.[228] reported that ethers could be obtained from alcohols and carbonyl compounds in good yields (>80%) using Pd/C as a catalyst under hydrogen atmosphere. However, the proposed methods have some limitations for being used in laboratories and in industries, since high hydrogen pressure (>40 atm) and low concentration of reagents are required. More recently, Fujii et al.[231] reported an improved one-pot method for the synthesis of ethers from alcohols and carbonyl compounds in the presence of a Pd/C catalyst at one bar of hydrogen, when the water produced in the reaction was continuously removed by bubbling hydrogen in the reaction mixture (Scheme 41). The authors found that the removal of water during the reaction was required to the synthesis of ethers. Thus, reactions between different alcohols and carbonyl compounds performed in the absence of solvent and in the presence of neutral Pd/C (5 wt % Pd), under a stream of hydrogen at temperatures of 105 or 160 °C while removing water with Dean−Stark system afforded the corresponding ethers (dialkyl and alkyl fluoroalkyl ethers) in very good yields and selectivities. The authors propose a mechanism where both acetal and hemiacetal can act as intermediates.

Scheme 42. One-Pot Synthesis of Asymmetric Linear Ketones



Scheme 43. One-Pot Synthesis of Optically Active α-Fluoro Ketones



Primary and secondary alcohols have also been etherified with ketones with good yield at atmospheric hydrogen pressure using a heterogeneous Pt catalyst.[232] In this case, the water is removed with molecular sieves. More recently, Zaccheria et al.[233] have reported the direct etherification of aromatic ketones and aliphatic alcohols by the use of Cu^0 catalyst supported on silica−alumina. The bifunctional character of the catalyst (acid-metal) allows obtaining the corresponding ethers in high yields (80−99%) and selectivities (97−99%) by reacting the ketone and alcohol at moderated temperature (60−80 °C), and at atmospheric pressure, without removal of the water formed.

2.3.1.8. Deprotection, Decarboxylation, and Asymmetric Tautomerization of *β*-Ketoesters: One-Pot Synthesis of Asymmetric Linear Ketones. The synthesis of linear ketones bearing an α-stereogenic center is an important topic in pharmaceutical and agricultural chemistry. One efficient methodology involves the asymmetric protonation of metal enolates generated by ketones[234] or ketenes[235] by stoichiometric quantities of a chiral protic source. An alternative palladium/chiral base-catalyzed cascade process for the synthesis of linear α-asymmetric ketones starting from racemic benzyl *β*-ketoesters has been reported by Roy et al.[236] The process involves as a first step an heterogeneous Pd/C catalyzed hydrogenolysis of the benzylic ester group leading to the reactive *β*-ketoacid. In the presence of the chiral base, the *β*-ketoacid decarboxylates leading to a prochiral enolic species which is protonated by the chiral base inducing the stereoselectivity to the tautomer carbonyl compound (Scheme 42).

The chiral bases used in catalytic amounts were cinchona derivatives, cinchonidine and cinchonine being the best chiral inductors. Particularly with cinchonidine, yields to ketones were high but with moderated *ee* (49−71%) and influenced by the nature of the solvent used.

The authors exploited this approach for the one-pot synthesis of optically active *a*-fluoro ketones.[237] Thus, 2-fluoro-1-tetralone could be obtained from the corresponding fluorinated *β*-ketoester in good yields and moderated enantioselectivity (65%) using Pd/C and commercial quinine or quinidine (Scheme 43). However, the authors found that the reaction is sensitive to the nature of Pd catalyst and reproducibility problems were observed.

2.3.1.9. Oxidation of Benzyl Alcohols Followed by Condensation with Amines: One-Pot Synthesis of Imines and Secondary Amines. Imines are valuable intermediates in the synthesis

Scheme 44. One-Pot Synthesis of Imines and Secondary Amines

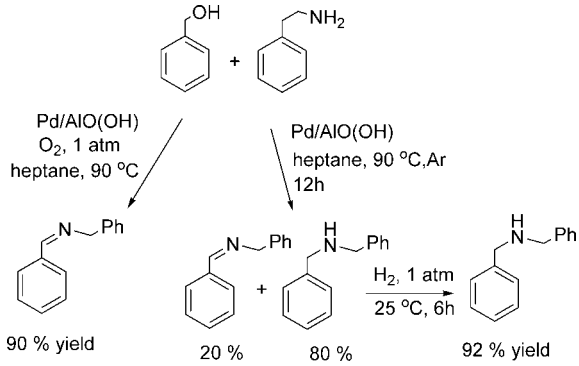


Table 8. One-Pot Coupling of Benzyl Alcohol and 2-Phenylethylamine with Different Palladium Supported Catalyst[a]

catalyst	yield (%)[b]
Pd/AlO(OH)	90 (57)[c]
5% Pd/C	19
5% Pd/Al_2O_3	42
5% $Pd/CaCO_3$	3
5% $Pd/BaCO_3$	13
5% Ru/Al_2O_3	8
5% Rh/Al_2O_3	0

[a] Reaction conditions: benzyl alcohol (1.0 mmol); 2-phenylethylamine (1.2 mmol); catalyst (2.0% mol of metal) in heptane (5.0 mL) at 90 °C under 1 bar of O_2 for 20 h. [b] Determined by ^1H NMR with an internal standard. [c] After 10 h.

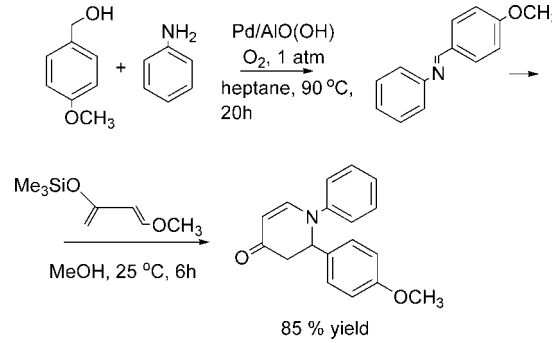
of propargylamines[238,239] and secondary amines[240,241] with applications for fine chemicals, and agrochemicals[242−244] and pharmaceuticals such as β-lactams;[245] moreover, they have potential for therapeutic applications such as anti-inflammatory and anticancer agents.[246] The most used methodologies to obtain imines include the condensation of amines with carbonyl compounds[247] or the direct oxidation of secondary amines.[248−250] Kwon et al.[251] have developed a heterogeneous palladium catalyst (Pd/AlO(OH)) that is composed by palladium nanoparticles entrapped in boehmite nanofibers able to perform the C−N coupling reaction of various benzyl alcohols with amines giving imines or secondary amines by controlling the reaction conditions. The one-pot process for the production of imines involves the oxidation of the alcohol into the carbonyl compound on the metal sites followed by its condensation with the amine. Thus, by reacting benzyl alcohol with 2-phenylethylamine in the presence of Pd/AlO(OH) (2% mol Pd) for 20 h at 90 °C under oxygen atmosphere, the corresponding imine (Scheme 44) was obtained in 90% yield, while other commercial palladium catalysts such as Pd/C, Pd/Al_2O_3, $Pd/CaCO_3$, $Pd/BaCO_3$ gave very poor yields (Table 8).

The scope of this approach was investigated by reacting different substituted benzyl alcohols with amines, achieving exellent yields to the corresponding imines (90−98%), the electronic effect of substituents groups on the aromatic ring being insignificant.

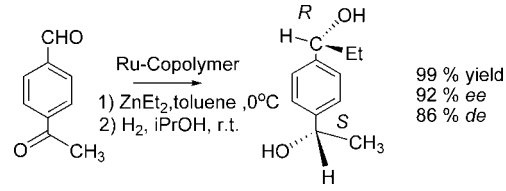
Taking advantage of the direct formation of imines, the authors also performed the one-pot aza Diels−Alder reaction of imines (starting from benzyl alcohols and aniline) with Danishefsky's dienes (Scheme 45).

On the other hand, under anaerobic conditions, secondary amines were produced through the sequence involving alcohol oxidation-imine formation and imine hydrogenation.

Scheme 45. One-Pot aza Diels-Alder Reaction of Imines with Danishefsky's Dienes



Scheme 46. One-Pot Process of Chiral Diols

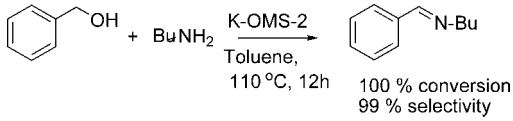


Thus, when the coupling reaction between benzyl alcohol and 2-phenylethylamine was performed under argon atmosphere, a mixture of amine/imine (80:20) was obtained which was subsequently hydrogenated to pure amine (92% yield) (see Scheme 44).

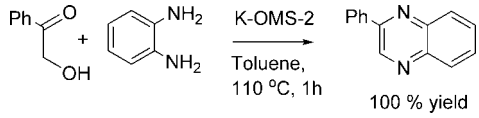
2.3.1.10. Asymetric Diethylzinc Addition Followed by Hydrogenation: Synthesis of Chiral Diols. Yu et al.[252] reported the synthesis of a Poly(BINOL-BINAP) ruthenium complex which was used as a catalyst in a tandem catalytic asymmetric process to generate chiral diols. The tandem process involves the diethylzinc addition to *p*-acetybenzaldehyde followed by an asymmetric hydrogenation of the ketone function (Scheme 46). The combination of the optically active 1,1-bi-2-naphtol (BINOL) and 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) ligands, which are able to coordinate with Ru in a copolymer structure, leads to a chiral catalyst able to perform the tandem process, with excellent conversion and stereoselectivities, similar to those found with the corresponding monomer catalysts when used independently. In addition, the copolymer could be recovered and reused in a second run, showing only a small decrease in diastereoselectivity for the hydrogenation step.

2.3.1.11. Oxidation of Alcohols to Aldehydes Followed by Condensation with Amines: One-Pot Synthesis of Imines. As was said before, the most general method to obtain imines is by condensation of aldehydes or ketones with amines.[101] Following this methodology, imines have been synthesized directly from alcohols through a tandem oxidation-imine formation with active manganese oxide.[253] However, the method requires an excess of the active manganese oxide as the stoichiometric oxidant and 4 Å molecular sieves as the dehydrating agent. Recently, Sithambaram et al.[254] have reported the catalytic application of manganese oxide octahedral molecular sieves (K-OMS-2) for the synthesis of imines directly from alcohols. K-OMS-2 is a cryptomelane-type manganese oxide with the composition $KMn_8O_{16}\cdot nH_2O$, that consists of MnO_6 octahedral units, which are edge and corner shared to form a 2 × 2 tunnel structure.[255] It contains Mn^{4+}, Mn^{3+}, and Mn^{2+} ions in the framework and the average oxidation state of Mn is ≈3.8. The imine formation proceeds via two mechanistically distinct reaction process promoted by K-OMS-2 which acts

Scheme 47. One-Pot Synthesis of Imines from Alcohol and Amine



Scheme 48. One-Pot Synthesis of Quinoxaline from Hydroxyl Ketone and *o*-Phenyldiamine

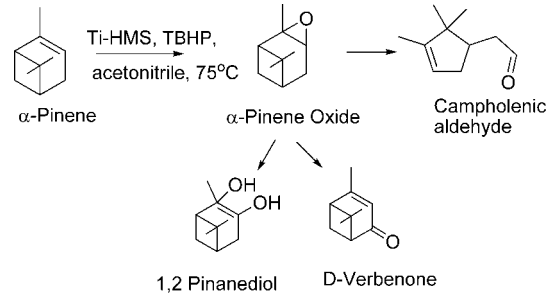


as a bifunctional catalyst. The first step involves the aerobic oxidation of the alcohol to its corresponding carbonyl compound. In the second step, the nucleophilic attack of the amine on the in situ generated carbonyl takes place and it is catalyzed by Lewis acid sites of K-OMS-2[256] (Scheme 47). A variety of aromatic and aliphatic amines were reacted with different alcohols achieving in general high conversions and selectivities to the corresponding imine under mild reaction conditions. The catalyst was reusable up to four cycles without any appreciable loss of activity. In spite of the good performances of the K-OMS-2 catalyst, it is interesting to point out that Au supported on hydroxyapatite (Au/HAP) showed higher catalytic activity to perform this transformation (see Table 14).[257]

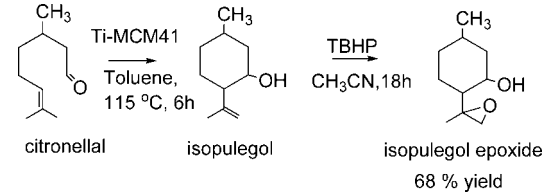
2.3.1.12. Oxidation of Hydroxyl Ketones Followed by Condensation with Ortho-Diamines: One-Pot Synthesis of Quinoxalines. Quinoxalines are interesting organic compounds with a variety of applications such as biocides,[258] pharmaceuticals,[259] and organic semiconductors.[260] In addition, they constitute useful intermediates in organic synthesis.[261] Conventionally, quinoxalines are synthesized by a double condensation reaction involving a dicarbonyl compound and *ortho*-phenylenediamine.[261,262] Because of the high reactivity of dicarbonyl compounds, other alternative routes have been proposed, which involve the use of epoxides[263] or hydroxy ketones[264] using a stoichiometric amount of manganese oxides as oxidants and nonrecoverable homogeneous catalysts, respectively. Sithambaram et al.[265] have reported a one-pot synthesis of quinoxalines starting from hydroxy ketones and diamines using K-OMS-2 as a heterogeneous catalyst (Scheme 48). The reaction proceeds via two steps, that is, the oxidation of the hydroxy ketones to their corresponding diketones and then the condensation of diketones with a diamine to form the quinoxaline derivative. Using this protocol, a range of hydroxyl ketones was reacted with a variety of *ortho*-phenylenediamines achieving the corresponding quinoxalines in good yields. The catalyst could be recovered and reused without loss of activity.

2.3.1.13. Epoxidation Followed by Rearrangement: One-Pot Synthesis of Campholenic Aldehyde from α-Pinene. Campholenic aldehyde is a compound widely used in the fragrance industry which is obtained by isomerization of α-pinene epoxide. The use of mild Lewis acids favors the production of campholenic aldehyde, while Bronsted acid sites bring about the formation of other isomers such as *trans*-carveol, *trans*-sobrerol, and *p*-cymene.[266] A variety of heterogeneous catalysts have been applied for the catalytic epoxidation of α-pinene[267−269] as well as for the catalytic isomerization of the α-pinene epoxide into campholenic aldehyde.[270−272] Shu et al.[273,274] attempted the one-pot synthesis of campholenic aldehyde from α-pinene over Ti-

Scheme 49. One-Pot Synthesis of Campholenic Aldehyde from α-pinene



Scheme 50. One-Pot Synthesis of Isopulegol Epoxide from Citronellal

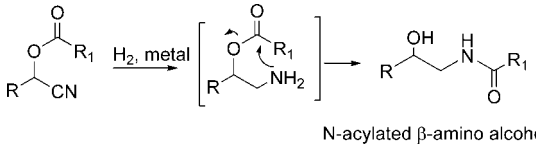


substituted mesoporous molecular sieves (Ti-HMS) using *tert*-butyl hydroperoxide (TBHP) as an oxidant at 75 °C (Scheme 49). 35% conversion of α-pinene with very low selectivity to campholenic aldehyde and pinene oxide was obtained after 24 h, while the maximum selectivity was toward verbenone (50%). Selectivity to campholenic aldehyde could be increased to 55% at 35% of conversion of α-pinene when the water contained in the oxidant (TBHP) and the molecular oxygen in the reaction system were previously removed. In this process, titanium sites are acting both as epoxidating sites during the first step and as Lewis acidic sites in the isomerization step to campholenic aldehyde.

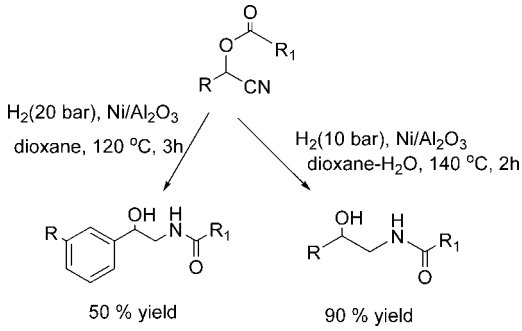
2.3.1.14. Cyclization Followed by Epoxidation: One-Pot Synthesis of Isopulegol Epoxide. Guidotti et al.[275] have also taken advantage of the dual activity of titanium as acidic and epoxidating site in Ti-containing MCM-41 materials for the one-pot two-step conversion of citronellal to isopulegol epoxide, a compound with fungicidal and insect-repellent activity. Ti-MCM-41 obtained by grafting an organotitanium precursor onto the MCM-41 surface showed better catalytic activity than when Ti was incorporated into the framework. Since cyclization is favored by apolar solvents while epoxidation is carried out in aprotic polar solvents, the choice of the solvent was essential to achieve good results. Thus, the cyclization step was performed using toluene as a solvent until citronellal was completely converted into isopulegol; then, a polar solvent such as acetonitrile and the oxidant TBHP was added to achieve the isopulegol epoxide in a global yield of 68% (Scheme 50).

2.3.1.15. Hydrogenation of Cyanohydrins Esters Followed by Intramolecular Migration of the Acyl Group: Synthesis of N-Acylated β-Amino Alcohols. N-Acylated β-amino alcohols are precursors of β-sec-amino alcohols (such as etilerine, denopamine, and bamethane) which are an important class of compounds in the pharmaceutical and agrochemical industries. The conventional route to N-acylated β-amino alcohols involves the reduction of the nitrile to amino followed by acylation of the amino group.[276,277] These reactions are usually performed using stoichiometric amounts of hydride salts as reductant agents ($LiAlH_4$ or BH_3) or by catalytic hydrogenation under strongly acidic conditions.[278−280] However, there is an alternative approach to the

Scheme 51. One-Pot Synthesis of N-Acylated β-Amino Alcohols from Cyanohydrin Esters



Scheme 52. One-Pot Synthesis of N-Acylated β-Amino Alcohols from Cyanohydrin Esters Using Ni/Al_2O_3 Catalyst



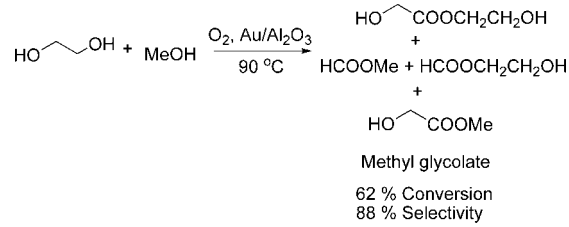
synthesis of N-acylated β-amino alcohols which integrates the reduction and acylation steps in a one-pot procedure.[281] This process starts from cyanohydrin esters which are stable against racemization and in addition can act as a potential intramolecular acyl donor. Thus, after the reduction of the nitrile group, the amino group formed acts as a strong nucleophile which reacts with the neighboring acyl group via a five-membered transition state to yield the N-acylated β-amino alcohol (Scheme 51). However, during the catalytic hydrogenation of cyanohydrin esters the competitive reductive cleavage of the C−O bond occurs easily, particularly in the case of benzylic cyanohydrins esters, leading to β-phenyl alkyl amines in large amounts.[282]

In order to optimize the catalyst and reaction conditions for the one-pot approach, Veum et al.[283] performed a study combining a multistep design of experiments (DoE) and high-throughput experimentation. It was found that Ni/Al_2O_3 in dioxane gave a better performance than other conventional hydrogenation catalysts such as Pd/C and PtO_2 used in acidic conditions (Scheme 52). For aliphatic substrates yields up to 90% of the corresponding N-acyl β-amino alcohols were obtained, and it was found that in the case of an enantiopure aliphatic cyanohydrin acetate, the chiral center remained unchanged during the process. However, for the more sensitive benzylic substrates, only up to 50% yield was achieved, while a small amount of razemization was observed for an enantiopure benzylic substrate.

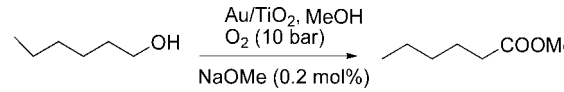
2.3.2. Gold Catalyzed Reactions

2.3.2.1. Direct Esterification of Primary Alcohols to Methyl Esters. Esterification is an important reaction in organic synthesis that can be performed using a variety of methodologies[284] including new environmentally friendly procedures which have attracted considerable interest in the past few years.[134,285] A number of methyl esters are important chemicals as a solvents, extractants, diluents, and as intermediates. The direct formation of methyl esters by oxidation of primary alcohols in methanol is well documented;[286−289] however, all methods employ stoichiometric amounts of oxidants and long reaction times. An attractive alternative for the synthesis of methyl esters is the heterogeneously catalyzed direct oxidative esterification of primary alcohols

Scheme 53. Direct Esterification of Primary Alcohols to Methyl Esters



Scheme 54. Direct Esterification of Primary Alcohols to Methyl Esters Using Au/TiO_2 as Catalysts



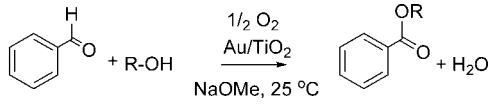
or aldehydes in the presence of methanol using molecular oxygen as an oxidant. Several examples using supported gold catalysts have recently been reported in the literature.[290−294] It has been proposed that the oxidation of primary alcohols to its corresponding methyl esters occurs through the formation of an aldehyde as intermediate, this being the rate determining step. The second step, the oxidation to form the methyl ester, proceeds relatively fast, the hemiacetal being identified as the key intermediate for the ester formation.

Using nanogold particles supported on metal oxides as catalysts, Hayashi et al.[295−297] developed a new liquid-phase aerobic oxidation process for the one-step direct production of methyl glycolate (which is useful as a chemical intermediate and monomer for various materials) from ethylene glycol and methanol. In this reaction, four types of esters can be produced (two glycolates and two formiates) (Scheme 53). The selectivity toward the methyl glycolate could be increased by increasing the MeOH/ethylene glycol molar ratio, nanogold (gold particles size of 1−5 nm) being much more selective than Pd and Ru based catalysts. The authors suggest that this enhanced selectivity is due to the specific adsorption properties of substrates on the supported nanogold catalyst. Nippon Shokubai Co. Ltd. has developed a new continuous production process of methyl glycolate consisting of an aerobic oxidation process using gold-based catalysts followed by the separation and purification step,[295,296] obtaining methyl glycolate with high purity (98%).[295,296]

More recently, Christensen et al.[298] performed the aerobic oxidation of primary alcohols to methyl esters catalyzed by Au/TiO_2 (Scheme 54). Using the oxidation of 1-hexanol to form methyl hexanoate as reaction model, they found that the presence of a base ($NaOCH_3$) is not essential for achieving complete conversion (90% selectivity to the ester), but it does have an important influence on the reaction rate, shortening considerably the time of reaction from 24 h to 1 h. On the other hand, the selectivity toward the methyl ester increases when increasing the excess of methanol, which can be caused by the more favored formation of the methyl hemiacetal with respect to the hexyl hemiacetal. It was also found that the primary alcohols are oxidized much more readily than methanol, and the procedure was extended to other substrates than 1-hexanol, achieving excellent yields of the corresponding methyl esters, showing the versatility of this methodology.

The oxidative esterification of aldehydes is also a synthetically useful one-pot transformation which in general proceeds toward esters much more efficiently than the corresponding alcohols. Christensen et al.[299] have reported the oxidative

Scheme 55. One-Pot Oxidative Esterification of Aldehydes



R=- CH_3, $-CH_2CH_3$, $-(CH_2)_2CH_3$, $-(CH_2)_3CH_3$, $-CH_2(C_6H_5)$

Table 9. Oxidative Esterification of Benzyl Alcohol in the Presence of Methanol over Various Gold Catalysts[a]

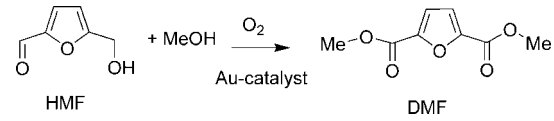
		selectivity (%)		
catalysts	conv (%)	ester	aldehyde	acetal
Au/β-Ga_2O_3	90	93.3	4.1	1.2
Au/β-Ga_2O_3-c[b]	71	22.6	32.1	43.4
Au/γ-Ga_2O_3[b]	77.4	81.6	14.9	2.5
Au/$Ga_3Al_3O_9$	97	85	9.2	4.4
Au/TiO_2[b]	70	64.5	20.7	13.1
Au/Fe_2O_3[b]	36.8	45	27.1	26.3
Au/C[b]	5.5	12	31.2	54.2
Au/β-Ga_2O_3[c]	88	93.9	3.7	2.1

[a] Reaction conditions: Benzyl alcohol (3.5 mmol) and Au catalysts (0.29 mol %) in methanol (10 mL) at 90 °C, 5 atm O_2, 2 h. [b] Commercial samples. [c] Results from the fift run.

esterification of benzaldehyde with different alcohols using Au/TiO_2 (1 wt % Au) and air as a source of oxygen (Scheme 55). Reactions were carried out in an open glass flask, using a molar ratio of benzaldehyde/alcohol 1:30 and 0.2% mol of Au. Focusing on the reaction of benzaldehyde with MeOH, the authors found that the reaction temperature is the rate determining factor below 25 °C, while increasing the reaction temperature above 25 °C there is no difference in the rates of reaction. This fact was attributed to the amount of the dissolved oxygen in the solution (which is expected was approximately the same at 25 °C as at 40 °C) that in this case should be the rate determining factor. When the reaction was performed in the absence of base, the reaction rate was very slow and more than 30 h were required for complete conversion. However, in the presence of NaOMe (10 mol %) the reaction took place in approximately 30 min. The esterification with longer chain alcohols produces the corresponding alkyl benzoates in high yields. However, a decrease of the reaction rate when increasing the alcohol chain length was observed. Additionally, methyl acrylate was synthesized from acrolein using the same protocol with 87% selectivity at 97% conversion.

Recently Su et al.[294] showed the excellent activity of gold supported on nanocrystalline β-Ga_2O_3 as a catalyst for the oxidative esterification of a variety of aromatic and aliphatic primary alcohols with methanol, ethanol, and propanol. Using molecular oxygen as oxidant and working at 90 °C with 0.29 mol % Au in the absence of any base, the corresponding esters were achieved in high yields and selectivity in short times for aromatic alcohols, although longer reaction times were required for aliphatic alcohols. The nanocrystalline Au/β-Ga_2O_3 catalyst was more active than Au supported on conventional β-Ga_2O_3 and other commercial gold catalysts such as Au/TiO_2, Au/Fe_2O_3, and Au/C (see Table 9). Oxidative esterification of different aldehydes and dimethyl acetals was also performed with excellent success on nanocrystalline Au/ β-Ga_2O_3. The high performance of the catalyst was attributed to their bifunctional character. The surface Lewis acidity of β-Ga_2O_3, which is enhanced on nanocrystalline samples, promotes the hemiacetal formation, which subsequently undergoes the gold-catalyzed oxidation to the corresponding ester.

Scheme 56. One-Pot Synthesis of 2,5-Dimethylfuroate from HMF



Gold nanocluster catalysts immobilized on polystyrene-based polymers with cross-liking moieties (PI) have also been effective catalysts for aerobic oxidations of alcohols and aldehydes to the corresponding methyl esters under mild reaction conditions.[300] Thus, oxidative esterification of *p*-methylbenzyl alcohol is performed under O_2 (1 atm) at room temperature with Au/PI, 1 mol %, giving the corresponding methyl ester in >99% yield. However, the presence of base (K_2CO_3 (0.5 equiv)) and a long reaction time (24 h) are required. The gold catalyst is stable against leaching and could be reused several times without significant loss of activity.

2,5-Furandicarboxylic acid (FDA) and the dimethyl ester, 2,5-dimethylfuroate (DMF), can be obtained from the oxidation of 5-hydroxymethyl-2-furfural (HMF). They are regarded as valuable biomass derivatives that can replace the oil-dependent therephthalic acid monomer in the production of polyethylene therephthalate plastic.[301] It has been reported that FDA and DMF can be obtained with excellent yields from HMF oxidation using Au/TiO_2,[302,303] and Au supported on nanoparticulated ceria (Au/CeO_2)[304,305] catalysts. When HMF oxidation is performed in water in the presence of stoichiometric amounts of aqueous base, FDA is obtained in very good yields.[302,305] However, when the reaction is performed in methanol, DMF is obtained through the one-pot oxidative esterification of the 5-hydroxymethyl-2-furfural (HMF)[303,304] (Scheme 56).

The reactions have been performed in methanol, over Au/TiO_2[303] and Au supported on nanoparticulated ceria (Au/CeO_2)[304] as catalysts, using a molar ratio HMF/Au of 300 and at 130 °C with oxygen as oxidant. In the case of Au/TiO_2, the addition of 8% of NaOMe to the reaction mixture was necessary in order to shorten the reaction time, achieving 98% yield of DMF after 3 h reaction time. However, the use of Au/CeO_2 catalyst has the advantage that the reaction can take place in the absence of any base achieving the same yield in a similar reaction time, while Au/TiO_2 requires 24 h to achieve similar results working under the same reaction conditions in the absence of base (see Table 10). Other gold-based catalysts such as Au/C and Au/Fe_2O_3 gave poor yield to DMF, while Au supported onto no nanoparticulated CeO_2 required longer reaction times in order to achieve 85% yield of DMF (Table 10).

A full reaction scheme has been established[304] (Scheme 57), and it was found that the rate-limiting step of the reaction is the alcohol oxidation into aldehyde. After this, the reaction proceeds via aldehyde conversion into hemiacetal and further oxidation into the corresponding ester. Particularly, Au/CeO_2 result as a stable catalysts and gold leaching was not observed, their reuse being possible during five consecutive runs with a small loss of activity, but maintaining high selectivity toward DMF.

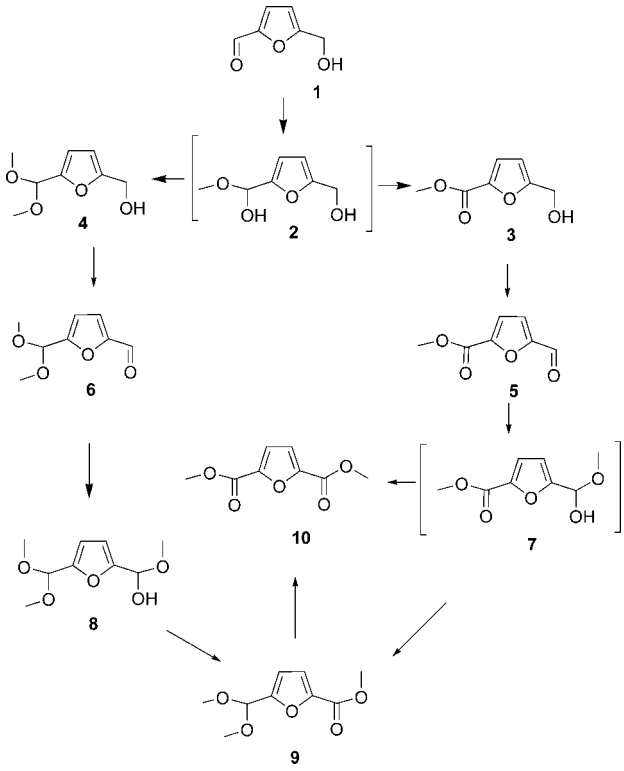
2.3.2.2. Direct Synthesis of Lactones from Diols. Lactones can be synthesized by dehydrogenation or oxidation of the corresponding α,ω-diols and cyclic ketones (Scheme 58). Current methods for the synthesis of lactones involve the use of strong reaction conditions and oxidants[306,307] or

Table 10. Oxidation−Esterification of HMF using Au Nanoparticles onto Different Supports[a]

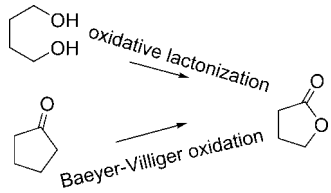
						yield (mol %)[b]		
entry	catalyst	TOF_1[e] (h^{-1})	TOF_2[e] (h^{-1})	t (h)	conv (mol %) HMF	**3**	10 DMF	**4**
1	Au−Fe_2O_3	120	4	24	94	34.7	6.2	17.5
2	Au-TiO_2	305	57	3	97	49	30	2
				24	>99	3.7	96.3	0
3	Au−C	480	0.5	24	96	20.2	7.6	17.4
4	Au-CeO_2	320	137	2	98	37	54	1
				5	>99	0	>99	0
5	Au-CeO_2[c]			24	58	3.8	0	51.8
6	CeO_2			24	61	0	0	53.1
7	Au-CeO_2[d]	155	10	72	>99	0	85	15

[a] Reaction conditions: molar ratio HMF/Au of 300 at 130 °C and 10 bar oxygen in methanol. [b] Other byproduct which complete molar balance are the following: 5-methoxymethyl-2,2-dimethoxylfurane, 5-methoxymethyl-2-methylfuroate and 6. [c] As in (a) but oxygen was replaced by nitrogen. [d] No-nanometric CeO_2 was used as support. [e] Calculated from the conversion of HMF (1) and yield to DMF (10), respectively, after 15 min divided by mols of Au.

Scheme 57. Reaction Scheme for the Oxidative Esterification of HMF to DMF



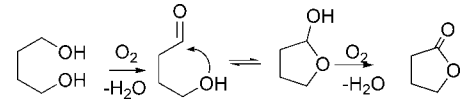
Scheme 58. Common Routes for the Synthesis of Lactones



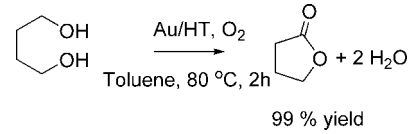
the sacrifice of a series of cooxidants such as aldehydes[308] and N-oxides.

A green and sustainable alternative is the catalytic oxidative lactonization of diols. Heterogeneous Cu based catalysts have been used for the dehydrogenation of 1,4-butanediol to γ-butyrolactone; however, high reaction temperature was required and conversions were low.[309] Improved results have been achieved using gold based catalysts. Huang et al. have reported the oxidative lactonization of diols over Au/TiO_2[310] and Au/FeOx.[311] The oxidation of 1,4-butanediol to γ-butyrolactone were performed at 140 °C, using tributyl phosphate as a solvent under 1.25 MPa of air. In the case of Au/TiO_2 catalyst, it was found that both calcination temperature of the catalyst and gold content play a significant role in the catalytic activity. The best results were obtained on the catalyst with 3 wt % gold loading and calcined between 300−400 °C. Taking into account that the metallic gold was the active site, this result was attributed to the small gold particle (4−5 nm) and the total degree of reduction of gold achieved under these conditions. Using 0.5 mol % Au, both conversion and selectivity to γ-butyrolactone were >99% after 8 h reaction time and the TOF was 64 h^{-1}. Improved TOF values (624 h^{-1}) for the oxidative lactonization of 1,4-butanediol to γ-butyrolactone were found using gold supported on nanosized FeOx prepared by a hydrothermal method, and changing the nature and morphology of the oxide by calcinations at different temperatures. The best catalytic materials were Au/FeOx samples calcined at 300 and 400 °C, which exhibited a much higher activity than gold supported on commercial γ-Fe_2O_3. Using 0.36 mol % of Au, high conversion (95−93%) and selectivity (99%) to γ-butyrolactone were achieved in the oxidative lactonization of 1,4-butanodiol with these samples; however, the oxidation of 1,5-pentanediol afforded the corresponding six ring δ-lactone with very poor selectivity.

Scheme 59. One-Pot Synthesis of Lactones from Diols



Scheme 60. One-Pot Synthesis of Lactones from Diols Using Au/HT as Catalyst



It is suggested that the mechanism of the oxidative lactonization involves as a first step the oxidation of 1,4-butanediol to 4-hydroxybutanal, which is in equilibrium with the hemiacetal, tetrahydrofuran-2-ol, that subsequently is dehydrogenated to the target product γ-butyrolactone (Scheme 59).

An interesting work for one-pot selective synthesis of lactones from diols was reported by Kaneda et al.[312] using Au supported on Al/Mg layered double hydroxide (hydrotalcite) (Au/HT) (Scheme 60). Thus, with 0.45 mol % of Au on HT, a variety of five and six ring lactones were

Table 11. Oxidation of 1,4-Butanediol Using Supported Gold Catalysts[a]

catalysts	conversion (%)	yield	particle size (nm)
Au/HT	99	99	2.7
Au/HT[b]	99	99	
Au/HT[c]	96	96	
Au/MgO	72	70	3.1
Au/Al_2O_3	51	51	3.6
Au/TiO_2	18	16	3.7
Au/TiO_2[d]	64	64	3.7
Au/SiO_2	1<	1<	14
Pd/HT	42	19	
Ru/HT	1	1<	
Ag/HT	1<	1<	

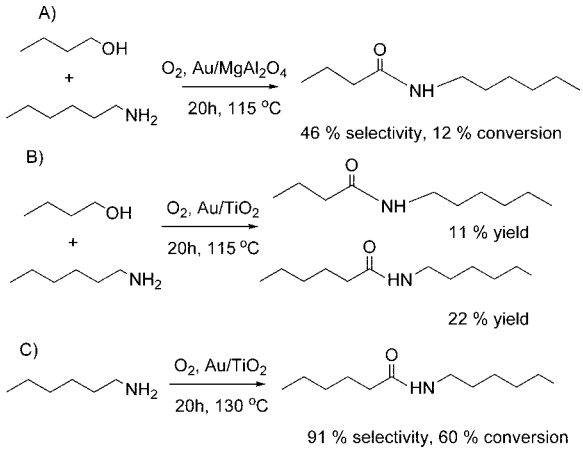
[a] Reaction conditions: 1,4-butanediol (1 mmol), supported Au catalysts (Au 0.45% mol), toluene 5 mL, at 80 °C, 2 h under O_2 balloon. [b] Reuse 1. [c] Reuse 2. [d] Na_2CO_3 (3 mmol) was added.

obtained with excellent yields (88−99%) under atmospheric pressure of oxygen and toluene as a solvent. Comparatively, Au/HT gave higher yields than Au/MgO and Au/Al_2O_3, while Au/TiO_2 and Au/SiO_2 were much less active catalysts achieving low yields (18 and <1%, respectively) (Table 11). Other metal particles such as Pd, Ru, and Ag supported on HT were much less active catalysts than Au in promoting the oxidative lactonization. The high catalytic activity of Au/HT was attributed to the basicity of the support and the small size (2.7 nm) of the Au particles. In addition, the catalyst is very stable and can be reused in two consecutive cycles without loss of activity and selectivity.

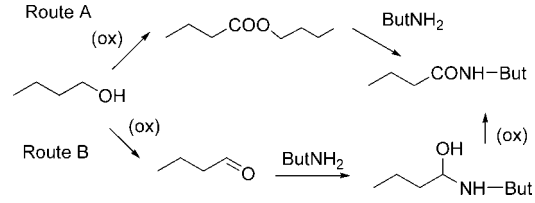
A possible reaction mechanism is proposed based on a cooperative action of Au and HT support. Thus, the basic sites of the HT could promote the formation of an Au-alcoholate species, allowing the oxidation of one of the hydroxyl groups of the diol to hydroxyaldehyde which is in equilibrium with the hemiacetal (Scheme 59). Subsequent oxidation of the hydroxyl group of the hemiacetal intermediate assisted by the basic sites of the support affords the corresponding lactone.

2.3.2.3. Oxidative Condensation of Amines with Butanol and Methanol: One-Pot Synthesis of Amides. The oxidative condensation of amines with alcohols to obtain amides has been recently reported using molecular oxygen and gold nanoparticles on different supports as catalysts.[313,314] Thus, Christensen et al. performed the oxidation of mixtures of *n*-hexylamine and 1-butanol with 1 wt % $Au/MgAl_2O_4$ achieving N-hexyl butanoic amide in low yield (12% conversion, 46% selectivity) (Scheme 61A). However, when

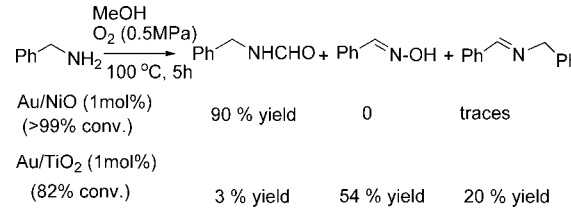
Scheme 61. One-Pot Synthesis of Amides from Amines and Primary Alcohols



Scheme 62. Possible Reaction Pathways in the Formation of N-Hexyl Butanoic Amide



Scheme 63. One-Pot Synthesis of Formamides

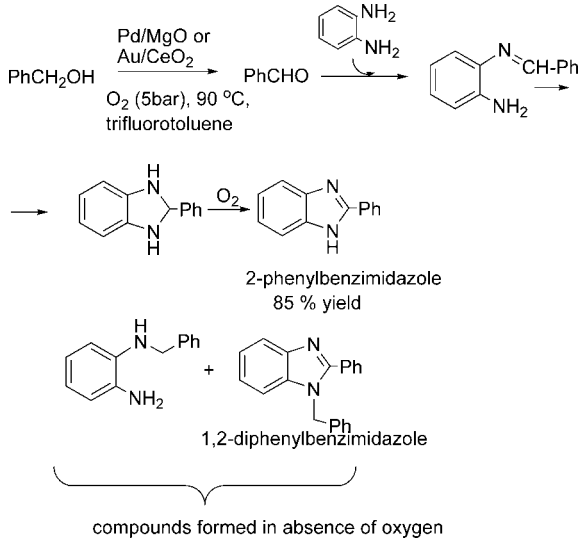


1 wt % Au/TiO_2 was used as a catalyst, both N-hexyl butanoic amide and N-hexyl hexanoic amide were obtained (Scheme 61B). The formation of N-hexyl butanoic amide can be explained via two different reaction pathways which involve either the oxidation of butanol to butyl butanoate followed by aminolysis to afford the amide (Scheme 62A), or oxidation of the hemiaminal of butanal and *n*-hexylamine directly to the amide (Scheme 62B). However, the formation N-hexyl hexanoic amide can be only explained by the amine being initially oxidized in the presence of Au/TiO_2. In fact, when the reaction was performed in the absence of butanol, N-hexyl hexanoic amide was obtained with excellent selectivity, 91% (60% conversion) (Scheme 61C). The authors also showed that oxidation 1,6-hexane diamine using Au/TiO_2 afforded the corresponding amide, caprolactam, although yields were very low. In spite of the moderate to low yields obtained in these cases, this is the first example in which a heterogeneous gold catalyst can be used to oxidize amines directly to amides with molecular oxygen.

More recently, Ishida and Haruta[313] reported that formamides can be directly synthesized from amines with MeOH and O_2 over gold supported nanoparticles. Benzylamine, aniline, morpholine, and cyclohexylamine were converted in the corresponding formamides in moderate to good yields. The authors found that among the different gold catalysts tested, Au/NiO and Au/Al_2O_3 give the best performances, the former being the most active and selective catalyst to the corresponding formamide, while Au/TiO_2 exhibited oxime selectivity (Scheme 63). It was observed that the main product obtained was remarkably influenced by the nature of the metal oxide support. Thus, while Au/NiO and Au/Al_2O_3 showed alcohol affinity, Au/TiO_2 prefers amines to alcohols as reactants.

2.3.2.4. Oxidation of Alcohol to Aldehyde Followed by Cyclocondensation with Diamines: Synthesis of Benzimidazoles. The nucleus of the benzimidazole molecule is found in a wide variety of compounds with pharmaceutical activity such as antiulcers, antihypertensive antivirals, antifungals, and anticancer, among others.[315−317] Two main routes for the synthesis of benzimidazoles have been developed; one of them involves the coupling of phenylenediamines with carboxylic acids or their derivatives. This method requires the use of strong acidic conditions and sometimes very high temperatures or the use of microwaves.[318,319] The second method involves a two-step procedure that includes the cyclodehydrogenation of aniline Schiff's bases, which are

Scheme 64. One-Pot Synthesis of 2-Phenylbenzimidazoles



usually generated in situ from the condensation of phenylenediamines and aldehydes, followed by oxidation using a stoichiometric amount of oxidants.[320,321] Recently, Ruiz et al.[322] have reported a new environmentally friendly catalytic procedure for the synthesis of benzimidazoles through a one-pot multistep process using gold and palladium-based catalysts. The global process involves as a first step the metal catalyzed aerobic oxidation of benzyl alcohol to benzaldehyde, followed by cyclocondensation of benzaldehyde with *o*-phenylenediamine and finally the catalytic aerobic oxidation of the C−N bond to give the 2-phenylbenzimidazole (Scheme 64).

The oxidation of benzyl alcohol did not occur in the presence of the diamine, probably due to a strong competitive adsorption of this reactant on the metal, and consequently the diamine was incorporated to the reaction system when almost all the benzyl alcohol was oxidized. The reaction was performed using different Pd and gold supported catalysts (Pd/MgO, Pd/C, Au/CeO_2, Au/TiO_2, Au/Fe_2O_3). Particularly, gold catalysts showed significant differences in activity and selectivity to benzimidazole depending on the support. Among the different catalysts tested, Pd/MgO and Au on nanoparticulated CeO_2 were the most active and selective catalysts achieving in both cases 85% isolated yield of benzimidazole. It is important to notice that both reaction steps (oxidation and cyclization) have to be carried out under oxygen atmosphere, since in the absence of oxygen (or even under air) the yield of the benzimidazole decreases, while the secondary amine from the reduction of the imine intermediate, and 1,2-diphenylbenzimidazole are also formed in considerable extension (see Scheme 64).

The scope of the reaction was demonstrated by synthesizing a variety of benzimidazoles from different aromatic and aliphatic alcohols and substituted *o*-phenylene diamines in the presence of Au/CeO_2 with excellent yields and selectivities. Interestingly, this protocol was applied to the synthesis of 1-(2,6-difluorobenzyl)-2-phenylbenzimidazole molecule with inhibitory activity against human immunodeficiency virus type-1 (HIV-1), and that is synthesized with moderate yield (40%) through a multistep process.[323]

In a first aproximation, the synthesis can be performed by coupling the one-pot three-step process described above, with the N-alkylation of the corresponding 2-phenylbenzimidazole. Pd/MgO was selected as a catalyst since palladium deposited on a strong basic support could catalyze the N-alkylation reaction (Scheme 65, route 1). Thus, the reaction was performed in such way that once the formation of 2-phenylbenzimidazole was completed, the N-alkylation reaction with 2,6-difluorobenzylbromide afforded the target compound with moderate yield (entry 1, Table 12).

Scheme 65. Synthesis of 1-(2,6-Difluorobenzyl)-2-phenylbenzimidazole through Different One-Pot Synthetic Strategies

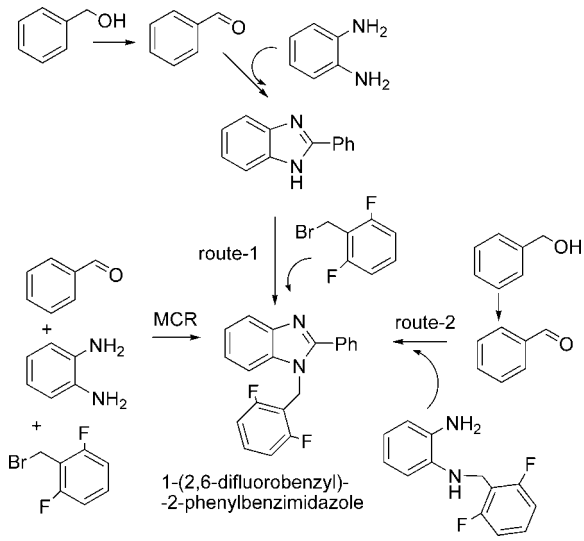


Table 12. Synthesis of 1-(2,6-Difluorobenzyl)-2-phenylbenzimidazole through Different Synthetic Strategies[a]

entry	route	catalyst	oxidation (%)[b]	cyclization (%)[c]	yield (%)[d]
1	1	Pd-MgO	95	91	40
2	2	Pd-MgO	93	95	88
3	2	Au-CeO_2	89	95	85
4	MCR	Pd-MgO			44
5	2	Pd-MgO[e]	90	90	86
6	2	Au-CeO_2[e]	88	96	82

[a] Reaction conditions: 1 mmol of alcohol, 1 mmol of diamine, 1 mmol of 2,6-difluorobenzylbromide, 0.5% mmol of metal (Au-CeO_2 or Pd-MgO), 1 mL of trifluorotoluene, oxygen (PO_2 = 5 bar), T^a = 90 °C and 0.2 mL of DMF as cosolvent to carry out the N-alkylation step. [b] Conversion calculated by GC on the bases of benzyl alcohol transformed; [c] Conversion calculated by GC on the bases of benzaldehyde transformed; [d] Isolated yield. [e] Recovered and reused catalysts.

An alternative route (route 2, Scheme 65) was developed by the same authors[322] starting from the monoalkylated diamine *N*-(2,6-difluorobenzyl)benzene-1,2-diamine. Using bifunctional Pd/MgO and Au/CeO_2 catalysts high yields of 1-(2,6-difluorobenzyl)-2-phenylbenzimidazole were obtained (see entries 2 and 3 in Table 12). Finally, in another synthetic strategy, a multicomponent reaction (MCR) was performed, where the three starting reactants, benzaldehyde, *o*-phenylenediamine and the alkyl bromide were simultaneously reacted. In this case, using Pd/MgO as a catalyst, the yield of the target compound was in the same order that those obtained with the conventional multistep procedure previously reported[323] (see entry 4, Table 12). Both Pd/MgO and Au/CeO_2 catalysts could be reused in a second cycle maintaining its initial activity (see entries 5 and 6, Table 12) while no metal leaching was observed.

2.3.2.5. Hydrogenation of Nitroaromatics to Anilines Followed by Oxidation: One-Pot Synthesis of Aromatic Azo Compounds from Nitroaromatics. Aromatic azo compounds are important chemicals widely used as dyes, pigments, food additives, and drugs.[324−326] Currently, the

Scheme 66. One-Pot Synthesis of Aromatic Azo Compounds from Nitroaromatics

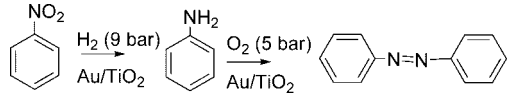


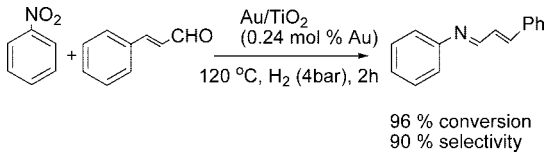
Table 13. Synthesis of Azobenzene from Nitrobenzene through a Two-Step, One-Pot Process

catalyst	*T* (°C)	*P* (bar)	time (h)	yield (%)	conversion (%)	selectivity (%)
1.5% $AuTiO_2$	120	9 (H_2)	6	94.6 aniline	98.5	96
	100	5 (O_2)	9	92 azobenzene	100	92

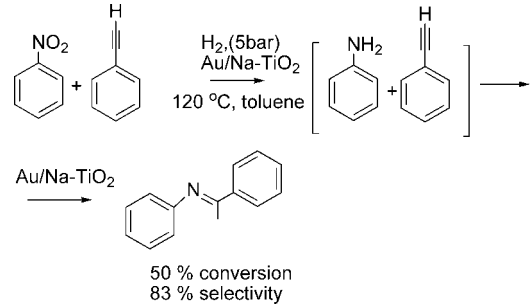
preparation of aromatic azo compounds is carried out either by reduction of nitroaromatics (for instance, with lead metal)[327,328] or by oxidation of anilines using oxidants such as lead tetraacetate.[329] These methodologies involve the use of stoichiometric reagents and frequently environmentally unfriendly transitions metals. An alternative method to synthesize asymmetrically substituted aromatic azo compounds involves the coupling of diazonium salts with electron-rich aromatic compounds.[330] This process requires stoichiometric amounts of nitrite salts and generates equivalent amounts of inorganic salt waste. Recently, Grirrane et al.[331] reported the aerobic oxidation of aromatic anilines to aromatic azo compounds over gold nanoparticles on different supports. Among the different catalysts Au supported on titanium dioxide (1.5 wt % Au) and nanoparticulated cerium dioxide (0.44 wt % Au) gave excellent results for the oxidation of aromatic anilines (symmetrically and asymmetrically substituted) with yields of the corresponding azo compound above 98%. The reaction was performed at 100 °C, using toluene as a solvent, 5 bar of oxygen, and metal/substrate mol ratio of 1%. Other gold-based catalysts such as Au/C and Au/Fe_2O_3 as well as Pd and Pt supported catalysts did not show activity. Since it was previously established that Au/TiO_2 is able to catalyze the chemoselective hydrogenation of nitroaromatics to anilines,[332] the authors designed a new one-pot two-step process to transform nitrobenzenes into aromatic azo compounds (Scheme 66) by combining the reduction of the nitroaromatic and the oxidation of the aniline form. As can be seen in Table 13, excellent conversions and selectivity to the corresponding product in each step are achieved under mild reaction conditions.

2.3.2.6. Hydrogenation of Nitroaromatics to Anilines Followed by Condensation with Carbonyl Compounds: One-Pot Synthesis of Imines. Santos et al.[333] have recently reported the chemoselective synthesis of different aryl substituted imines through a cascade reaction which involves the hydrogenation of nitroaromatics in the presence of an aldehyde using Au/TiO_2 as a catalyst (Scheme 67) followed by the amine condensation with benzaldehyde. The reactions were performed under H_2 pressure until exhaustion of the nitroaromatic compound (95−98%), and then the reactor was depressurized and left at the same temperature until completion of the cascade process. Au/TiO_2 showed high selectivity for the hydrogenation of the nitro aromatic compound to the corresponding aniline, while the carbonyl group and the C═N bond remained unaffected, leading to high yields of the corresponding imines. In addition, when other reducible groups such as double bonds or halide functional groups were present in the nitroaromatic or in the aldehyde, its reduction was not observed and imines were obtained with selectivity over 90% at conversion levels above 90%. It is interesting to notice that although a similar approach has been recently reported by coupling nitrobenzenes and aldehydes with Fe(0) powder,[334] the process requires the presence of a strong mineral acid (HCl), while the selectivity to imine is sensibly lower when olefinic groups are present.

Scheme 67. One-Pot Synthesis of Imines from Nitroaromatic and Carbonyl Compounds



Scheme 68. Synthesis of Imines by Hydrogenation of Nitroaromatics to Anilines Followed by Amine−Alkyne Coupling



2.3.2.7. Hydrogenation of Nitroaromatics to Anilines Followed by Amine−Alkyne Coupling: Synthesis of Imines. Since it has been found that gold catalyzes the coupling reaction between alkynes and amines with excellent performances.[239,335] a new alternative cascade-type process was envisaged for the synthesis of imines starting from nitroaromatics and alkynes.[333] This approach is a real challenge because the catalyst has to hydrogenate chemoselectively the nitro to amino group without hydrogenating the triple bond, while it also has to activate the alkyne function for the subsequent amine-alkyne coupling (Scheme 68). The reaction between nitrobenzene and phenylacetylene in the presence of Au/TiO_2 allowed the corresponding imine to be obtained without producing other byproducts such as styrene, ethylbenzene, or the hydrogenated imine (*N*-(1-phenylethyl)aniline). However, after 2 h of reaction a conversion of 55% with only 55% selectivity to the imine was achieved. The low selectivity to imine is due to the hydrolysis reaction that yields aniline and acetophenone. These results contrast with those obtained using anilines and benzaldehyde to form the corresponding imines, where the imine hydrolysis was not observed. Thus, it appears that in this case, the presence of the methyl group adjacent to the nitrogen atom affects the reactivity of the C═N bond favoring the attack of nucleophiles such as water. Since the water released during the process and the presence a Lewis acid are responsible for undesired hydrolysis reaction, it should be possible to reduce the rate of hydrolysis by decreasing the acidity of the Au/TiO_2 system. To do that, the surface of TiO_2 was doped with a controlled amount of sodium acetate. Then, when the reaction was performed with this modified catalyst the selectivity to imine increased up to 83%. Improved selectivities were also observed with other substituted nitrobenzenes, showing the importance of this new synthetic approach for the preparation of substituted imines and related derivatives.[333]

Scheme 69. One-Pot Synthesis of Imines by Oxidation of Alcohols to Aldehydes Followed by Condensation with Amines

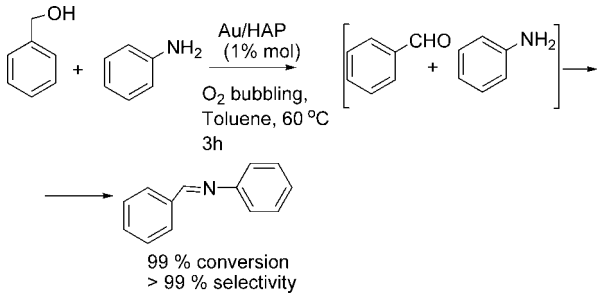


Table 14. Direct Tandem Synthesis of Benzylimine from Benzyl Alcohol and Aniline by Various Catalysts[a]

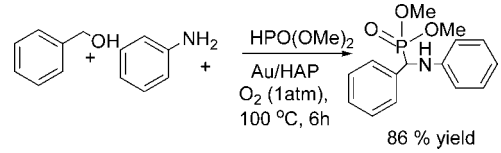
		selectivity (%)	
	conversion (%)	imine	aldehyde
Au/HAP	99	>99	<1
Ru/HAP	49	99	<1
Pd/HAP	15	90	10
Au/CeO_2	53	74	25
Au/Fe_2O_3	10	99	<1
Au/TiO_2	36	88[b]	10
Au/C	1	99	<1
Au/β-Ga_2O_3	13	97	3
K-OMS-2	8	58	42
none	n.r.		
HAP	n.r.		

[a] Reaction conditions: alcohol (1 mmol), amine (1 mmol), catalyst (metal: 1 mol %), toluene (10 mL), 60 °C, O_2 bubbling (20 $mLmin^{-1}$), 3 h. [b] As noted by Grirrane et al.,[331] in the case of Au/TiO_2 aniline also underwent the oxidative reaction, leading to the formation of azobenzene. In the present case, the yield of the azocompound is ca. 23% based on aniline conversion.

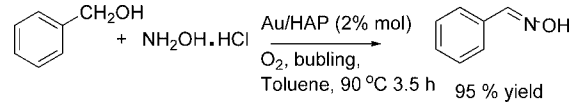
2.2.3.8. Oxidation of Alcohols to Aldehydes Followed by Condensation with Amines: One-Pot Synthesis of Imines. Sun et al.[257] have also performed selectively the one-pot synthesis of imines starting from alcohols and amines using Au supported on hydroxyapatite (Au/HAP). During the synthesis of benzylimine starting from benzyl alcohol (Scheme 69), it was found that among the various catalysts tested, Au/HAP gave higher activity (99% selectivity at 99% conversion) than palladium or ruthenium nanoparticles supported on HAP (see Table 14). In the presence of Au supported on nanosized CeO_2, conversion and selectivity was very low since benzaldehyde was obtained as main byproduct, while Au/β-Ga_2O_3, Au/TiO_2, Au/Fe_2O, and Au/C were not effective for the tandem process. In the case of Au/TiO_2, appreciable amounts of azobenzene as a consequence of the direct aerobic oxidation of aniline were observed. Au/HAP exhibited higher activity and selectivity to imines than other reported catalysts such as K-OMS-2[254] and Pd/AlO(OH).[251] The higher activity exhibited by the Au/HAP was attributed to the presence of Lewis acid sites on the HAP support which accelerates the condensation step between aniline and benzaldehyde. In fact, the condensation step was strongly inhibited when Au/HAP was impregnated with a basic oxide such as MgO.

The general applicability of the Au/HAP catalyst was demonstrated by reacting different substituted benzylic, allylic, and aliphatic alcohols with aniline, achieving excellent yields and selectivities although catalytic activity for most aliphatic alcohols was significantly lower than for benzylic and allylic alcohols. A surprising increase in the rate of formation of imine was achieved using aliphatic amines instead of aniline, suggesting that the high basicity of alkyl amines can facilitate the proton abstraction step in the oxidation of alcohols,[336] and confirming that the alcohol oxidation step is the rate-controlling step in this cascade process.

Scheme 70. One-Pot Synthesis of α-Aminophosphonates



Scheme 71. One-Pot Synthesis of Oximes from Alcohols and Hydroxylamine



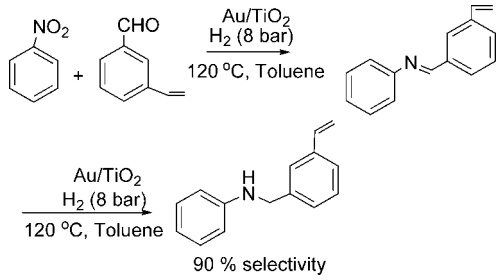
With Au/HAP as the catalyst, the authors developed a one-pot three-component approach as an alternative route for the tandem synthesis of α-aminophosphonates. These compounds, which are important core scaffolds in biologically active compounds,[337] are currently obtained by a number of multistep synthetic approaches[338,339] involving nucleophilic addition of phosphates to imines. Thus, benzyl alcohol, aniline, and dimethyl phosphate (in equimolar amounts) were reacted under O_2 at 100 °C under solvent-free conditions in the presence of Au/HAP, and after 6 h the corresponding α-aminophosphonate was isolated with 86% yield (Scheme 70).

The authors have also extended the applicability of the Au/HAP catalyst[257] to the one-pot synthesis of oximes from alcohols and hydroxylamine (Scheme 71). The one-pot synthesis of oximes from alcohols and hydroxylamine is a very useful synthetic approach; however reagents (such as Na_2SO_4 and ZnO) in higher amounts than stoichiometric are usually required, while hydroxylamine is added in excess (more than 3 equiv).[340] Kanno et al.[341] have reported an efficient one-pot synthesis of oximes from alcohols using activated manganese dioxide; however, this system only gives high yield of oximes if a dehydrating agent such as 4 Å molecular sieves is added to the reaction media.

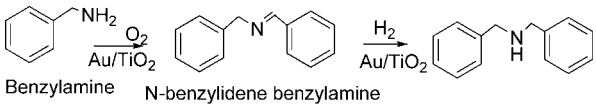
A variety of alcohols including benzylic, allylic, and heterocyclic alcohols were converted in the corresponding oximes in high yields (92−95%) in the presence of only 1 equiv of hydroxylamine using the Au/HAP catalyst. The catalyst could be reused without significant loss of activity.

2.3.2.9. Hydrogenation of Nitroaromatics followed by Condensation with Carbonyl Compounds and Subsequent Hydrogenation: One-Pot Synthesis of Substituted Secondary Amines. Taking into account that gold is able to catalyze enantioselective hydrogenation of imines,[241] the approach named above was used for the preparation of substituted secondary amines starting from nitroaromatics and aldehydes through a three-step cascade reaction.[333] Thus, nitrobenzene and 3-vinylbenzaldehyde reacts in the presence of hydrogen and Au/TiO_2 as a catalyst giving the corresponding imine which is subsequently and chemoselectively hydrogenated to the corresponding secondary amine with 90% selectivity at conversion level of 90%, while other consecutive and parallel reactions that can compete are practically avoided (Scheme 72).

Scheme 72. One-Pot Synthesis of Substituted Secondary Amines



Scheme 73. One-Pot Synthesis of Dibenzylamine



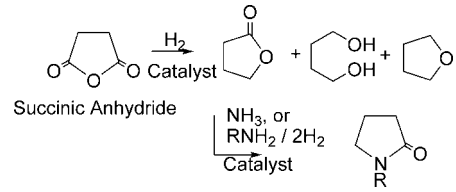
Benzylamine conversion: 100%
Dibenzylamine selectivity: 98%

2.3.2.10. Oxidative Condensation of Benzylamines to Imines Followed by Hydrogenation: One-Pot Synthesis of Secondary Benzylamines. Benzylimines are useful synthetic intermediates that can undergo a variety of transformations on the C═N double bond such as cycloadditions, nucleophilic additions, and hydrogenations. Particularly, hydrogenation of C═N double bond leads to secondary benzylamines, which are difficult to obtain in high yields by the classical SN2 mechanism of alkyl halides or aliphatic compounds bearing good leaving groups with benzylamine.[101] This is because the consecutive N-alkylation of the primary product can lead to undesired byproduct. It has recently been shown that gold nanoparticles catalyze the oxidation of benzylamines to N-benzylidene benzylamines by molecular oxygen (Scheme 73).[342] The reaction is general, and using 1 mol % Au under 5 bar O_2, at 100 °C in toluene, the oxidative condensation of *para*-substituted benzylamines, heterocyclic methanamines, as well as the cross condensation of benzylamines with aromatic or aliphatic primary amines was achieved in high yields. It was found that the oxidative condensation is a structure sensitive reaction that requires small gold particles, while the solid support of gold plays an important role in the catalytic activity, Au/C being more active catalysts that Au/TiO_2. Taking advantage of these results, the authors have devised a new route to prepare secondary benzylamines through a one-pot, two-step reaction that involves the oxidative condensation of benzylamine to N-benzylidene benzylamine followed by hydrogenation using gold catalysts (Scheme 73).

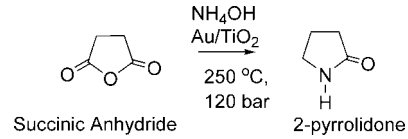
2.3.2.11. Hydrogenation of Succinic Anhydride Followed by Condensation with Ammonia and Primary Amines: Synthesis of Pyrrolidones. 2-Pyrrolidone and 2-pyrrolidone derivatives are used as industrial solvents and as building blocks for polymers and intermediates for pharmaceuticals. They are commercially produced by condensation of γ-butyrolactone with ammonia or primary amines (Scheme 4).[343−345] γ-Butyrolactone is obtained by hydrogenation of maleic or succinic anhydride, this being a complex process in which different consecutive hydrogenation steps of γ-butyrolactone can take place giving butanediol and tetrahydrofurane as byproduct (Scheme 74).

A cascade reaction involving the hydrogenation of maleic acid or succinic acid derivatives in the presence of ammonia or primary amines using heterogeneous catalysts is a more intensive and less energy consuming process to obtain

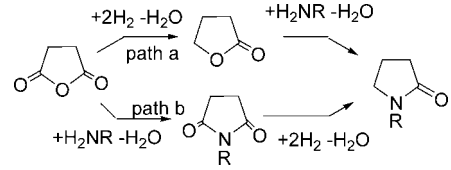
Scheme 74. Conventional Two-Step Process for the Synthesis of Pyrrolidones



Scheme 75. One-Pot Process for the Synthesis of 2-Pyrrolidones Using Gold Catalyst



Scheme 76. Possible Reaction Patways in the One-Pot Process Synthesis of Pyrrolidones

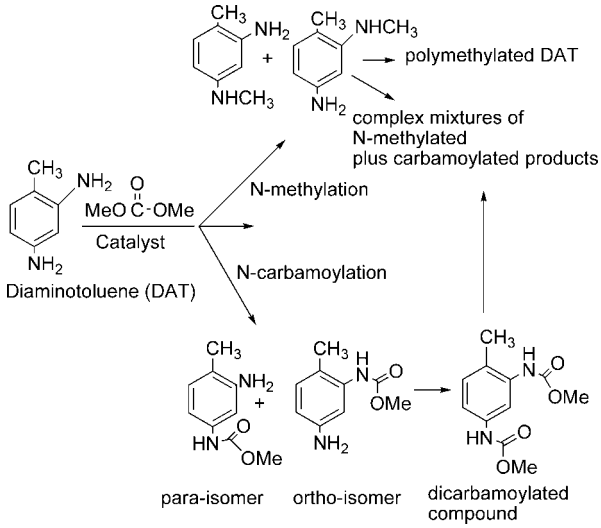


pyrrolidones that can be achieved with different supported metals as catalysts. For instance, $Pd-Al_2O_3$[346] and Rh−C[347] are able to produce pyrrolidone by reacting succinic anhydride with ammonia and hydrogen at 120 bar. Also, it has been reported that N-alkyl pyrrolidones can be produced in one-step process. Thus, N-methyl pyrrolidone can be obtained in liquid phase from maleic anhydride, methyl amine, and hydrogen using $Cu-Al_2O_3$[348] and $PdRe-Al_2O_3$[349] giving respectively 53% and 67% yield. Recently, Corma et al.[350] have reported the synthesis of pyrrolidone and pyrrolidone derivatives from succinic anhydride using Au/TiO_2 as a catalyst. Hydrogenation of succinic anhydride was performed in aqueous solution of NH_4OH (25%) at 120 bar and 250 °C in the presence of Au/TiO_2 and 80% yield of 2-pyrrolidone with 99% selectivity was obtained after 10 h reaction time (Scheme 75).

N-Phenyl pyrrolidine was also obtained by hydrogenation of succinic anhydride in the presence of phenylamine in dioxane at 110 bar at 250 °C, 52% yield of the corresponding lactame was produced after only 1 h.[350] Since gold is not a very active hydrogenation catalyst and, in many cases, hydrogen dissociation becomes the controlling step, an optimized catalyst for performing the cascade reaction was prepared, in which a small amount of Pt (100 ppm) was added to the gold catalyst to increase the rate of hydrogen dissociation. With this bimetallic catalyst, the rate of the hydrogenation step increases and higher yields in shorter times were obtained. It is suggested that the one-pot reaction could proceed through two different reaction patways: (a) the hydrogenation of the anhydride followed by the amination of γ-butyrolactone to pyrrolidone derivative and (b) amination of the anhydride to form succinimide followed by hydrogenation of the intermediate (Scheme 76).

2.3.2.12. Reduction of Nitroaromatics Followed by N-Carbamoylation: One-Pot Synthesis of Carbamates As Polyurethane Precursors. The current industrial route for manufacturing polyurethanes and polycarbonates is based on the use of phosgene.[351] However, because of the high toxicity of phosgene there is a urgent need to develop alternative

Scheme 77. Possible Products Derived from DAT As It Undergoes N-Methylation and N-Carbamoylation Reactions

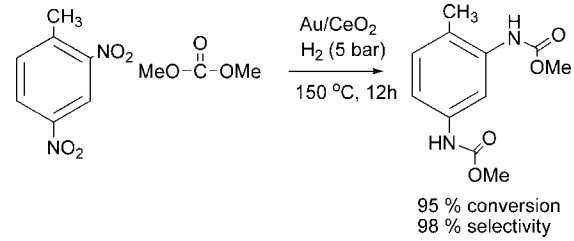


routes. Since carbamates can be easily transformed into the corresponding polyurethanes,[352] a green alternative to phosgene would be the production of carbamates by N-carbamoylation of amines with organic carbonates. While N-carbamoylation of aliphatic amines with dimethyl carbonate to form the corresponding carbamates is already well-known, aromatic diamines, which are industrially more relevant, react with dimethyl carbonate to preferentially afford the N-methylation product instead of the carbamate.

Recently, Juarez et al.[353] have reported the selective N-carbamoylation of aromatic amines, and more specifically the dicarbamoylation of 2,4-diaminotoluene (DAT) (Scheme 77), which is the most important aromatic amine for polyurethane production, with gold nanoparticles supported on nanoparticulated ceria. A variety of catalysts, including Lewis acid $Zn(OAc)_2$ as well as Au, Pd, and Pt on different supports were tested as catalysts. Reactions performed at 140 °C with an excess of dimethyl carbonate, 0.5% mol of metal with respect to DAT, indicated that the most active and selective catalyst was gold nanoparticles (2−5 nm diameter) supported on nanocrystalline CeO_2 (5 nm diameter) which affords the dicarbamoylated compound in 96% yield at 99% conversion. In addition, the catalyst can be reused at least three times without loss of activity. Interestingly, when using the commercially available CeO_2 support (40 nm particle size) the catalyst activity was much lower (65% conversion with 73% selectivity to *ortho* plus *para N*-monocarbamoylated isomers), while Au/TiO_2 and Au/Fe_2O_3 form the N-methylated products in high yields.

As the nanoparticulated Au/CeO_2 catalyst was able to activate the CO moiety promoting the transfer of a methoxycarbonyl group rather than the transfer of the methyl group giving selectively carbamates, a two-step one-pot process starting from 2,4-dinitrotoluene was developed for the production of the dicarbamoylated compound. The process involves the reduction of the nitro groups on the metal sites followed by the transfer of the methoxycarbonyl group also catalyzed by gold nanoparticles. Thus, by reacting 2,4-dinitrotoluene with dimethyl carbonate under H_2 and using Au/CeO_2 as catalyst, it was possible to achieve high conversion of 2,4-dinitrotoluene (95%) with excellent selectivity to the dicarbamate (98%) (Scheme 78).

Scheme 78. One-Pot Synthesis of Carbamates from Nitroaromatics and Dimethyl Carbonate



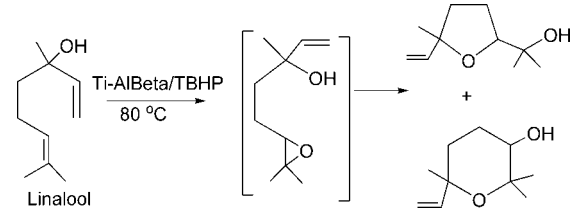
It has to be remarked that this process opens a new green route for polyurethane production that avoids the use of toxic reactants without generating any byproduct except recyclable alcohols.

2.4. Multistep Sequential Processes on Differentiated Bifunctional Acid-Metal Catalysts

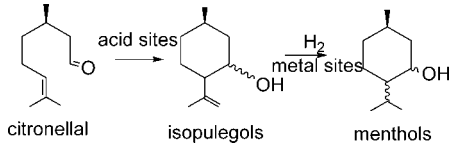
2.4.1. Epoxidation Followed by Cyclization: Synthesis of Furan and Pyran Hydroxy Ethers

Crystalline and amorphous molecular sieves allow the introduction of simultaneous Bronsted and Lewis acid sites. This can be done by performing isomorphous substitutions of silicon with trivalent elements, as for instance Al, that generate a framework negative charge that is compensated by a proton, and with other tetravalent atoms such as for instance Ti and Sn that act as Lewis acids to catalyze oxidation reactions with peroxides. Therefore, it should be possible by introducing simultaneously these different active sites to perform cascade type reactions. There are some remarkable examples taking advantage of this bifunctional system which perform in a consecutive way epoxidations plus acid catalyzed reactions of the epoxide formed that lead to commercially valuable compounds in a one-pot process. Interesting examples are the formation of substituted tetrahydrofurans and tetrahydropyrans, which are products of interest in the flavours and fragrance industry. For instance, 6,7-epoxylinalool is assumed as a natural precursor of the furan and pyran hydroxyl ethers presented in Scheme 79. They possess an intense rose odor and are selectively formed from linalool by the epoxidase enzyme. Corma et al.[354] reported that bifunctional catalysts such as Ti-AlBeta and Ti-AlMCM-41, containing framework Ti^{4+} and Al^{3+}, which has an associated H^+ as the complementary cation, are able to transform linalool to the hydroxyl ethers in reaction. Using TBHP as oxidant at 80 °C, conversions of linalool of 73 and 80% with 100% selectivity to the hydroxyl ethers were achieved with Ti-AlBeta and Ti- AlMCM-41, respectively. Interestingly, the ratio of pyrans to furans was found to be constant during the course of the reaction which was taken as a proof that the reaction first involved an epoxidation over titanium sites, followed by an in situ rearrangement over the acid protons at the aluminum sites.

Scheme 79. One-Pot Synthesis of Furan and Pyran Hydroxyl Ethers by Epoxidation of Linalool



Scheme 80. One-Pot Synthesis of Menthols from Citronellal



2.4.2. Cyclization of Citronellal Followed by Hydrogenation: One-Pot Synthesis of Menthols

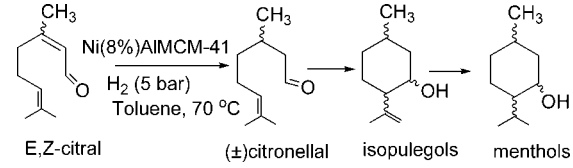
(−)-Menthol is a fine chemical compound widely used in flavouring and pharmaceutical applications. Conventional routes for the menthol production are multistep processes, such as the Haarmann and Reimer process starting from thymol[355] and the Takasago process starting from myrcene.[356] However, it has been reported that menthols can be synthesized in a one-pot process from citronellal on bifunctional catalysts, bearing acid and metal active sites. This process involves the two consecutive steps: acid-catalyzed cyclization of citronellal to isopulegol and metal-catalyzed hydrogenation of the double bond leading to menthol (Scheme 80).

Since citronellal possesses one stereogenic carbon atom along with two prochiral carbons atoms, four different isopulegol stereoisomers are produced which after hydrogenation lead to four menthol stereoisomers, of which only one of them (−)-menthol is profitable. Therefore, the one-pot process from citronellal to (−)-menthol is a very attractive option, provided that an active and selective catalyst for (−)-menthol was available. Thus, Jacobs et al.[357,358] have reported that a 3% Ir-impregnated H-BEA zeolite catalyzes the one-pot synthesis of menthol from citronellal. The first cyclization step was carried out under N_2 atmosphere during 4 h and then H_2 was added. Complete citronellal conversion was achieved after 30 h, with 95% selectivity to menthols stereoisomers, of which 75% was the desired (−)-menthol. The authors underlined that the activity for the first step (cyclization) clearly increases upon the zeolite is loaded with Ir, calcined and reduced, indicating that the Lewis acidity of nonreduced Ir might also contribute to the catalytic activity in the first step. This catalyst gives high productivity, and up to 17 g of menthol can be produced per gram of catalyst in a single run. When Ir was substituted by other metals such as Ru or Pd, selectivity to menthols decreased considerably due to the formation of undesired products.

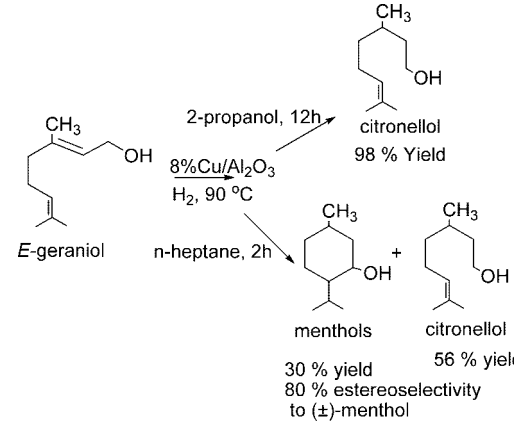
Cu based catalysts on a silica support (Cu/SiO_2)[359] as well as metallic Ru and ionic Zn immobilized together on SiO_2[360,361] also exhibit high performances to menthol. However, the productivity was low with turnover number for citronellal converted ≤1 g per gram of catalyst. More recently, Mertens et al.[362] reported that Pt loaded H-beta zeolite is highly active and selective for the production of (−)-menthol. Thus, with a 2 wt % Pt-loaded zeolite, citronellal is fully converted within 12 h, with a citronellal/Pt molar ratio of 2500. In addition, it was found that high temperature (750 °C) postsynthesis treatment of the calcined and reduced catalyst, a treatment that presumably creates extra Lewis acidity on the catalyst, improves considerably the stereoselectivity (88%) resulting in a (−)-menthol yield of 85%. Similar results were achieved by Da Silva Rocha et al.[363] using Pd-heteropoly acid/SiO_2 (Pd 5 wt %) as a catalyst.

Alternatively, menthols can also be obtained through a three-step cascade process starting from citral. This is an attractive route since citral is a renewable raw material that is obtained mainly by distillation of essential oils such as lemongrass oil. The process involves the selective hydrogenation of citral to citronellal, followed by cyclization to isopulegol and then hydrogenation of isopulegol to menthol.[364−366] Following this approach, Trasarti et al.[364] reported for the first time the highly selective synthesis of menthols starting from citral with Ni supported on Al-MCM-41 as a bifunctional acid-metal catalyst (Scheme 81). Thus, Ni was selective for the hydrogenation of the α,β C═C double bond, while the weak acid sites (Lewis and Bronsted) of Al-MCM-41 showed good activity for performing the citronellal cyclization. 94% yield of menthols with a selectivity to the racemic (±)-menthol of 70−75% was achieved using 8 wt % Ni/AlMCM-41 at 70 °C and 5 bar.[365] Others metals such as Co, Ir, or Pt were less selective toward the hydrogenation of the double bond, giving mixtures of geraniol/nerol isomers, while Pd hydrogenates at a high reaction rate the nonconjugated C═C bond of citronellal intermediate. Strong acids supports such as HBEA or SiO_2/Al_2O_3 were less selective to (±)-menthol since the strong acid sites promote the formation of unwanted compounds. Similar conclusions were previously reported by Maki-Arvela et al.[366]

Scheme 81. One-Pot Synthesis of Menthols from Citral



Scheme 82. One-Pot Synthesis of Menthols from Geraniol

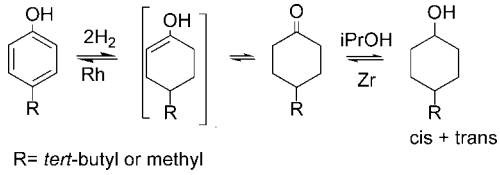


An alternative pathway to obtain menthol is the one-pot conversion of geraniol into menthol reported by Zaccheria et al.[367] The authors presented that with Cu/Al_2O_3, the hydrogenation of geraniol can be tuned by switching the solvent. Thus, geraniol can be converted in a one-pot one-step process into a mixture of citronellol and menthol in hydrocarbon solvents, or it can be reduced selectively to citronellol using 2-propanol as a solvent (Scheme 82).

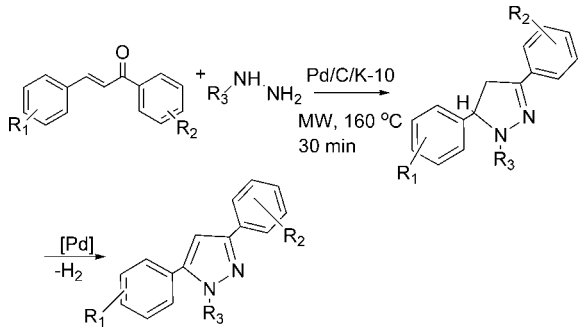
2.4.3. Hydrogenation followed by Merveein−Pondorf−Verley Reduction: Synthesis of Cyclohexanol Derivatives

A stereoselective cascade hydrogenation of 4-*tert*-butylphenol and *p*-cresol over rhodium supported on Zr- beta zeolite has been reported by van Bekkum et al.[368] Thus, over 0.5% Rh/Zr-Beta, 4-*tert*-butylphenol and *p*-cresol were transformed into the corresponding intermediate 4-alkylketones by metal-catalyzed hydrogenation, which are subsequently stereoselectively reduced with isopropanol via MPV reduction over Zr Lewis acid sites to the *cis*-alcohols. Thus,

Scheme 83. Cascade Reaction for the Conversion of 4-Alkylphenols to 4-Alkylcyclohexanols



Scheme 84. One-Pot Synthesis of Substituted Pyrazoles



cis-4-*tert*-butylcyclohexanol, which is a fragrance chemical intermediate, was obtained with 95% selectivity at 100% conversion of 4-*tert*-butylphenol, under optimized reaction conditions within 4 h reaction time (Scheme 83).

2.4.4. Cyclization of Chalcones with Phenylhydrazine Followed by Dehydrogenation: One-Pot Synthesis of Substituted Pyrazoles

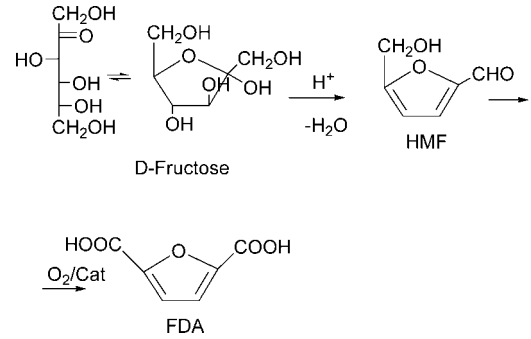
Pyrazoles are important heteroaromatic compounds due to their wide range of biological activities such as anticancer,[369,370] anti-inflammatory, or active cyclooxygenase-2-inhibitors.[371] Among the different methods available for the synthesis of pyrazoles,[372] the most interesting are regioselective cyclizations, which in most cases involve a cyclization followed by an oxidation step[372−374] using stoichiometric oxidants.

Lange et al.[375] have combined the cyclization and oxidation reactions into a two-step one-pot reaction using a bifunctional noble metal/solid acid catalyst. They performed the cyclization of chalcone with phenylhydrazine using Pd or Pt supported on the acidic K-10 montmorillonite under microwave irradiation and solvent-free conditions (Scheme 84). Thus, the acidic support promotes the condensation and cyclization of the chalcone with phenylhydrazine, while the metal dehydrogenates the intermediate to the final aromatic compound. Supported Pd catalysts were more selective than Pt toward pyrazoles, but the most active and selective catalyst was a mechanical mixture of 5% Pd/C and K-10 montmorillonite giving the corresponding pyrazole with 92 yield and 92% selectivity. The scope of the process was shown by reacting different substituted chalcones and hydrazines. Yields between 86−96% of the corresponding pyrazoles were achieved in 30 min reaction time.

2.4.5. Dehydration of Fructose to HMF Followed by Oxidation: Synthesis of 2,5-Furandicarboxylic Acid (FDA)

A promising route for the preparation of 2,5-furandicarboxylic acid (FDA), which is a potential substitute of therephthalic acid in polymeric materials, is a one-pot process starting from fructose and involving fructose dehydration to HMF as a first step followed by oxidation of HMF to FDA (Scheme 85). This approach has been intended by Kroger et al.[376] using both a membrane reactor, or encapsulation of a PtBi/C oxidation catalyst into a polymeric silicone matrix using air as oxidant. However, whatever the method considered, the yield in FDCA never exceeds 25%. Better results were reported by Ribeiro et al.[377] in the preparation of 2,5-furandicarboxylic acid directly from fructose in one pot over a bifunctional acidic and redox catalyst consisting of cobalt acetylacetonate encapsulated in sol−gel silica. Using air as an oxidant (2 MPa) at 165 °C fructose is selectively converted into FDA in a yield close to 70%.

Scheme 85. One-Pot Synthesis of FDA from D-Fructose



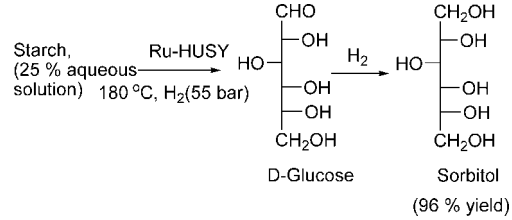
2.4.6. Hydrolysis of Polysaccharides Followed by Reduction: Synthesis of Sugar-Alcohols

Hydrogenation of carbonyl groups of carbohydrates leads to the formation of sugar-alcohols. These polyol compounds such as sorbitol, xylitol, and mannitol are widely used in the food industry as low calorie sweeteners and as precursor of important compounds such as surfactants or vitamin C.

Ru supported on H-USY zeolite (3%) has been used to perform a single-step catalytic process for the conversion of glucan-type polysaccharides (especially starch) to sorbitol.[378] In this process, the hydrolysis of the polysaccharide occurs on the acidic sites of the zeolite, followed by the hydrogenation of the carbonyl group of the sugar on the metal sites. Working in a batch autoclave at 180 °C and 55 bar H_2, quantitative conversion is reached within 1 h, with sorbitol selectivity higher than 95% (Scheme 86). Taking into account the size of the reactants involved, the Bronsted acidity required for the hydrolysis of the polymer must be provided by external surface acid sites, while the hydrogenation step can take place on metallic sites within the zeolite pores and external metallic sites (at the outside of particles) which are accessible to glucose.

Inulin is an oligosaccharide consisting of glucose-(fructose)$_n$ with a high fructose-to-glucose ratio. It is available in large amounts and therefore a potentially attractive feedstock for the production of mannitol. A one-pot process for the production of mannitol where hydrolysis and hydrogenation reactions are combined has been reported using Ru on acidic carbon as heterogeneous bifunctional catalyst[379] (Scheme 87). The hydrolysis is catalyzed by the acidic carbon support,

Scheme 86. One-Pot Synthesis of Sorbitol from Starch



Scheme 87. One-Pot Synthesis of Manitol from Inulin

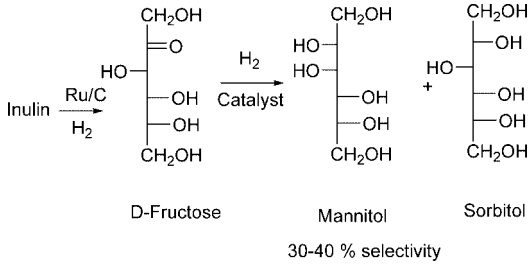
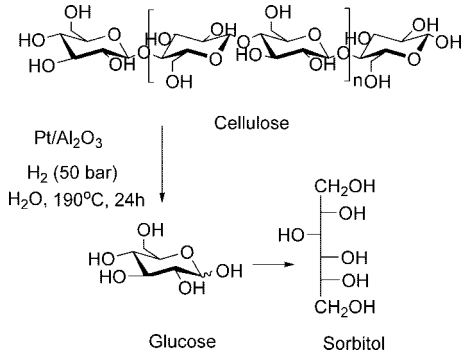


Table 15. Catalytic Hydrogenation of Cellobiose under Different Conditions[a]

			selectivity (%)			
catalyst	pH	conv (%)	sorbitol	glucose	A[c]	other polyols
Pd	2	100	0	100	0	
Rh	2	100	6.9	66.9	0	
Pt	2	100	18.5	42.6	0	
Ru	2	100	100	0	0	0
Ru	7	87.8	26.4	1.6	64.8	7.2
Ru	10	75.6	24.0	3.2	55.7	17.1
Ru/C[b]	7	100	<1	0	>99	0

[a] Reaction conditions: cellobiose (7.31 mmol); water (30 g); metal (1.67×10^{-3} mol/L); PVP: metal = 10 (mole ratio), at 120 °C, 40 bar hydrogen during 12 h. [b] Reaction conditions: the same as (a) except 0.1 g of 1% Ru/C was used as catalyst. [c] 3-β-D-Glucopyranosyl-D-glucitol.

Scheme 88. One-Pot Conversion of Cellulose to Sorbitol



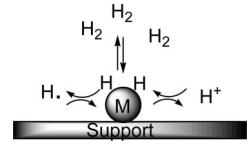
onto which acidity is introduced by preoxidation process with ammonium peroxydisulfate. Using Ru supported on this acidic carbon, selectivities to mannitol between 37−40% were achieved.

More recently, Yan et al.[380] have reported the one-step conversion of cellobiose (a glucose dimer) to sorbitol. Different metal nanoparticles (Ru, Rh, Pd, and Pt) supported on PVP (poly(*N*-vinyl-2-pyrrolidone) were tested under acidic conditions, at 120 °C and 40 bar H_2 (see Table 15). Under acidic conditions, Ru/PVP was the most active and selective catalyst, giving 100% selectivity to sorbitol. This result indicates the existence of two-step process, that is, cellulose hydrolysis to glucose followed by hydrogenation to sorbitol. However, at neutral and basic pH, 3-β-D-glucopyranosyl-D-glucitol, the corresponding sugar alcohol of cellobiose was the main product, while other C_6-alcohols (mainly dideoxyhexitol) are also observed. The results suggest that, particularly under basic conditions, the sorbitol is originated from a different reaction pathway.

Cellulose has also been converted through a one-step process into sugar alcohols. The process involves cellulose hydrolysis to glucose followed by hydrogenation to sugar alcohol (Scheme 88).

Fukuoka and Dhepe[381,382] have reported the one-pot conversion of cellulose to sugar alcohols over Pt and Ru on

Scheme 89. Proposed Mechanism for Dissociative Adsorption of Hydrogen and Spillover

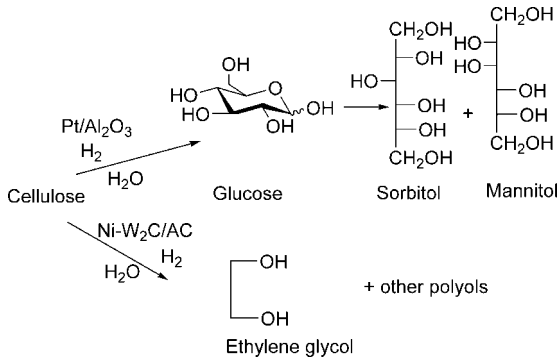


different supports such as γ-Al_2O_3, HUSY, and $SiO_2-Al_2O_3$. Reactions were performed at 190 °C in water and initial H_2 pressure at room temperature of 50 bar. The highest yield was observed over Pt/γ-Al_2O_3 achieving alcohols (sorbitol and manitol) in 31% yield (molar ratio sorbitol/mannitol 4:1). The catalyst was recycled up to three cycles giving similar yields of the sugar alcohols. Using the support materials as catalysts under the same reaction conditions, only 4% of glucose was detected, indicating that the metal promotes the hydrolysis of cellulose. It is proposed that cellulose is hydrolyzed by in situ formation of H^+ by the splitting of hydrogen on the metal surface (Scheme 89). Thus, the protons promote the hydrolysis of cellulose to glucose, which is subsequently reduced to sorbitol by the metal (Pt or Ru) with H_2.

It is known that liquid water at elevated temperatures (above 200 °C) can generate in situ H^+ ions able of performing acid-catalyzed reactions.[383,384] Thus, Luo et al.[385] have recently studied the conversion of cellulose into sugars alcohols by conducting the reaction in water at 245 °C so that water could generate H^+ ions able to catalyze the cellulose hydrolysis step. The subsequent glucose hydrogenation reaction was catalyzed by Ru/C. Thus, 38.5% conversion and 22.2% yield of hexitols (sorbitol and mannitol at a molar ratio of about 3.6:1) were obtained in 5 min at 245 °C and 60 bar. Prolonging the reaction time up to 30 min, 85.5% conversion and 39.3% yield were achieved. However, under these conditions dehydration products such as sorbitan and degradation products such as xylitol, erythritol, glycerol, propylene glycol, ethylene glycol, and methanol as well as trace amounts of CH_4 were also produced. It was demonstrated that these degradation products are originated predominantly from the hydrogenolysis of glucose, confirming that glucose is much less stable toward further reactions than the polyol. Therefore, fast hydrogenation of glucose, once it is formed from cellulose hydrolysis, is required in order to achieve high selectivity to hexitols. In the absence of Ru/C catalyst, similar cellulose conversion was achieved, but coke-like precipitates, possibly formed from further acid catalyzed condensation reactions of glucose, were observed.

Under similar reaction conditions as above, carbon supported tungsten carbide (W_2C/AC, AC = activated carbon) has been used as an effective catalyst for promoting the one-pot cellulose conversion to polyols, especially ethylene glycol (Scheme 90). Thus, with 30 wt % W_2C/AC (prepared at 800 °C) catalyst, after 30 min at 245 °C and 60 bar H_2, 98 wt % cellulose was converted, and the yield of sugar alcohols (sorbitol plus mannitol) was 2.1% while ethylene glycol (EG) was obtained as the main product in 27.4 wt % yield. Other alcohols such erythritol and 1,2-propylene glycol were also formed (6.1 wt % yield). The yield of EG was almost twice as large as that obtained over Pt/Al_2O_3. In fact, with Pt/Al_2O_3 catalyst the main product was sugar alcohols (9.5 wt % of sorbitol and 6 wt % of mannitol). When the reaction temperature was decreased at 190 °C the EG yield over Pt/Al_2O_3 was lower, while the yield of sugar alcohols increased (26.3 wt % of sorbitol and 8.9 wt % of mannitol). Such

Scheme 90. One-Pot Production of Ethylene Glycol from Cellulose



results are consistent with those reported by Fukuoka and Dhepe,[381] although they did not report any production of EG. However, with W_2C/AC under such milder conditions, EG was still produced as the main polyol. Taking into account that EG and other low molecular weight polyols originate predominantly from the hydrogenolysis of glucose, while the sugar alcohols come from glucose hydrogenation, the high selectivity to EG over W_2C/AC suggests that hydrogenolysis of glucose prevails over its hydrogenation. However, with the Pt/Al_2O_3 catalyst, where Pt can dissociate H_2 more easily than tungsten carbide, the hydrogenation of glucose to hexitols is the main process.

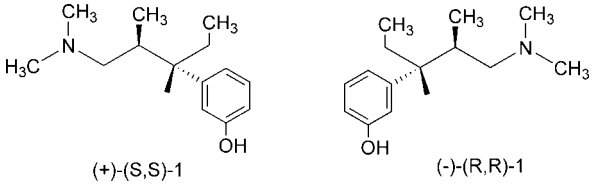
The yield of EG was increased by promoting the W_2C/AC catalyst with a small amount of nickel (Ni−W_2C/AC). Thus, with 2% Ni-30% W_2C/AC (prepared at 700 °C) catalyst, after 30 min at 245 °C and 60 bar H_2, the cellulose was completely converted into polyols, and ethylene glycol (EG) was obtained in 61 wt % yield, which is the highest yield of EG produced directly from cellulose reported to date. In addition, the catalyst was recycled up to three runs showing good reusability.

2.4.7. Dehydration of Alcohols Followed by Hydrogenation

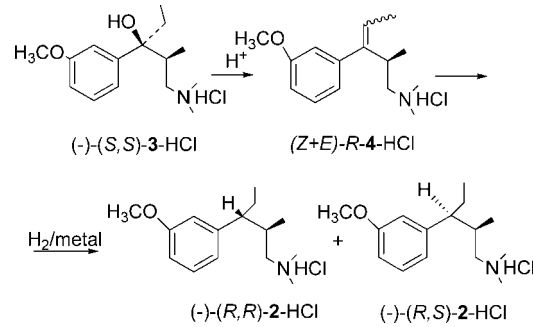
2.4.7.1. Synthesis of a New Potential Analgesic (−)-(2*R*,3*R*)-[3-(3-methoxy-phenyl)-2-methyl-pentyl]-dimethyl-amino Hydrochloride. Dimethyl-(3-aryl-butyl)-amines derivatives ((+) and (−) compound **1** in Scheme 91) exhibit a potent analgesic activity. The analgesic activity of the (+) enantiomer **1** is equivalent to morphine, while the (−) **1** has an analgesic potency between morphine and tramadol. The high analgesic activity came from removing the tertiary hydroxy group in the alcohol precursor **3** (Scheme 92).

As it is shown in Scheme 92, removal the tertiary hydroxyl group involves two consecutive steps: the acid catalyzed dehydration of the alcohol (**3**) giving the corresponding (*E*+*Z*) alkene intermediates **4**, which is subsequently hydrogenated to the corresponding dimethyl-(3-aryl-butyl)-amine derivative (**2**). Starting from (−)(2*S*,3*S*)-**3** or (−)(2*S*,3*R*)-**3** with the protected hydroxyl function in the aromatic ring and in the form of a hydrochloride salt, the

Scheme 91. Dimethyl-(3-aryl-butyl)-amines Derivatives



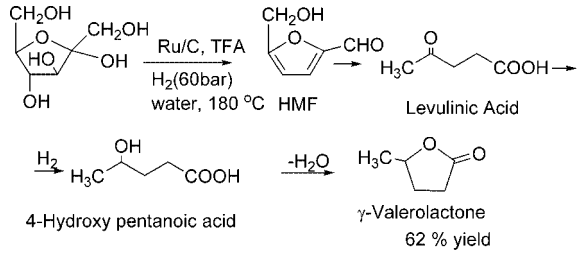
Scheme 92. One-Pot Synthesis of the Analgesic Compound (−)-(2*R*,3*R*)-[3-(3-Methoxy-phenyl)-2-methyl-pentyl]-dimethyl-amino Hydrochloride (2)



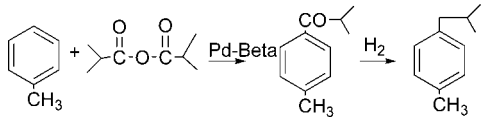
(−)-(*R*,*R*)-enantiomer **2** can be produced. Wissler et al.[386] have recently reported the synthesis of (−)-(*R*,*R*)-2-HCl combining both reaction steps in one-pot process. The (−)-2*S*,3*S*)-1-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol hydrochloride (**3**) was directly dehydroxylated in the presence of hydrogen to the analgesic (−)-(2*R*,3*R*)-[3-(3-methoxy-phenyl)-2-methyl-pentyl]-dimethyl-amino hydrochloride (**2**) using a bifunctional acid-metal catalyst, based on Pd supported on Amberlyst-15. The reaction performed under optimized conditions: 150 °C, using 1 wt % Pd, under 4 bar of hydrogen and methanol as a solvent, gave 98% conversion of **3**-HCl, 91% yield of **2**-HCl(*R*,*R*+*R*,*S*), and 64% selectivity to the desired *R*,*R* enantiomer. Although this heterogeneous system presents clear advantages over the homogeneous process using HCl catalyst, the main drawback was the deactivation of the catalyst. Although the catalyst could be reactivated to some extent by treating it with diluted HCl, the original activity was not achieved in a second cycle.

2.4.7.2. Dehydration of C6-Sugars (D-Glucose and D-Fructose) Followed by Hydrogenation: One-Pot Synthesis of γ-Valerolactone. γ-Valerolactone (GVL) is a very attractive biomass derived compound because it has a variety of applications as a solvent, or as a food additive,[387,388] and can be converted to a number of interesting derivatives with potential applications as fuel additives, acrylic and nylon monomers.[389] In addition, GVL is considered a potential biofuel and was shown to be a suitable replacement for ethanol in gasoline-ethanol blends.[388] GVL is typically obtained by catalytic hydrogenation of levulinic acid. Levulinic acid is produced by the acid catalyzed dehydration of glucose or fructose to 5-hydroxymethyl furfural which undergoes the subsequent hydrolysis to levulinic acid.[389] Taking into account this sequence of reactions, Heeres et al.[390] have reported recently a one-pot approach to produce GVL directly from C_6 sugars (D-glucose and D-fructose as well as sucrose and cellobiose) without isolation of the intermediate levulinic acid by combining a homogeneous acidic dehydration catalyst (trifluoroacetic acid) with a heterogeneous hydrogenation catalyst (Ru/C) either using molecular hydrogen or with a hydrogen donor such as formic acid. Thus, the trifluoroacetic acid (TFA) catalyzes the dehydration of the sugar to HMF which is subsequently hydrated to levulinic acid. Hydrogenation of the later compound on the Ru catalyst gives 4-hydroxypentanoic acid which easily cyclizes to GVL. Reactions were performed in water at 180 °C in the presence of hydrogen or formic acid as hydrogen source (Scheme 93). Using formic acid, the highest yield of GVL (52%) was obtained starting from D-fructose after 16 h reaction, the major byproduct being insoluble solids (humins). Also, the highest yield of GVL

Scheme 93. One-Pot Synthesis of GVL from Fructose



Scheme 94. One-Pot Synthesis of Isobutyl Toluene



(62%) was obtained with D-fructose using molecular hydrogen, while formic acid and humins were the main byproduct.

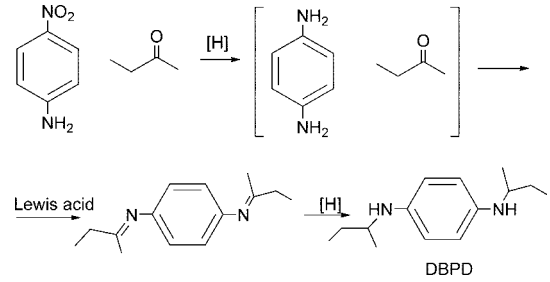
2.4.8. Acylation Followed by Hydrogenation: Synthesis of Isobutyl Toluene

Acylation of benzene with isobutyric acid derivatives followed by its hydrogenation to isobutyl benzene are the first reaction steps in the synthesis of the anti-inflammatory ibuprofen. Cejka et al.[391] found that toluene (a less toxic compound than benzene) can be easily acylated using acidic Y and Beta zeolites. Taking into account these results, the authors envisaged the one-pot synthesis of isobutyl toluene by simultaneous acylation of toluene with isobutyric anhydride and hydrogenation of the formed isopropyltolyl ketone using bifunctional Pd supported on Beta zeolites with different Si/Al ratio as catalysts[392] (Scheme 94). Acylation reactions were carried out both simultaneously or consecutively with hydrogenation in an autoclave at 130 °C, using beta zeolite loaded with 5 wt % Pd. It was found that the highest concentrations of isobutyl toluene were achieved in the consecutive mode using beta zeolites with a higher Si/Al ratio that is connected with the higher hydrophobicity of the catalyst which enables an easier desorption of polar products and faster transport of isopropyltolyl ketone to Pd-hydrogenating sites.

2.4.9. Hydrogenation of p-Nitroaniline Followed by Condensation with 2-Butenone and Subsequent Hydrogenation: One-Pot Synthesis of N,N′-Disec-butyl p-Phenylene Diamine

N,*N*′-Di-*sec*-butyl *p*-phenylene diamine (DBPD) is an antiozonant and antioxidant stabilizer widely utilized for the protection of rubber, crops, and gasoline, inhibiting in the last case the formation of gum.[393,394] The manufacture of DBPD is mainly produced via two routes: a two- step method from *p*-phenylene diamine and 2-butanone, and an one-step synthesis from reductive alkylation of *p*-nitroaniline or *p*-phenylene diamine with 2-butanone. While DBPD is expensively produced via the first route, the reductive alkylation of *p*-nitroaniline with 2-butanone provides a more environmentally friendly and economic process. Usually, the reductive alkylation is performed using transition metals,[395−397] as for instance copper and nickel, or noble metals[398,399] (e.g., platinum and palladium) based catalysts. However, the use of these catalysts presents important drawbacks. For instance, while copper-chromite is an efficient catalyst it is not environmentally friendly. Raney nickel or platinum based

Scheme 95. One-Pot Synthesis of DBPD from Nitroaniline and Ethyl Methyl Ketone



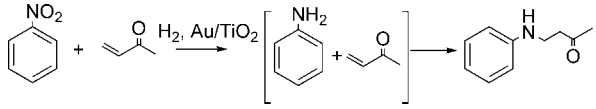
catalysts promote overreduction compounds leading to 1,4-diaminocyclohexane and C−N cleavage respectively giving undesired byproducts. More recently, Pan et al.[400] have reported the reductive alkylation of *p*-nitroaniline with 2-butanone using bifunctional (Lewis acid/metal) catalysts based on Ni−Re−K/Al_2O_3 in the presence of hydrogen. The reaction pathway of the reductive alkylation involves the hydrogenation of *p*-nitroaniline to *p*-phenylene diamine on the metallic sites followed by the nucleophilic addition of *p*-phenylene diamine with 2-butanone to form the corresponding diimine on the Lewis acid sites and finally the hydrogenation of the C═N bonds on the metallic sites yielding DBPD (Scheme 95).

Reactions were performed in a trickle-bed reactor at 110 °C using a molar ratio *p*-nitroaniline/2-butanone of 1:24 and hydrogen pressure of 5 MPa. It was found that calcination temperature of the support modifies the textural and chemical properties and has an important effect on the activity and selectivity. The study of different catalysts prepared by calcinations of the Al_2O_3 at 500, 800, 900, and 1000 °C which were impregnated with the metallic salts showed that the best selective catalyst was the Ni−Re−K/Al_2O_3 with the support calcined at 900 °C. This achieves 100% conversion with 93.7 selectivity to DBPD, while with the other samples, selectivity was lower than 65%. Characterization of the different catalyst samples showed that this optimized catalyst possessed better reducibility and the proper amount of the surface Lewis acidic sites and so it exhibited high activity and selectivity to DBPD.

2.4.10. Hydrogenation of Nitroaromatics Followed by Michael Addition to α,β-Unsaturated Ketones: One-Pot Synthesis of Substituted β-Amino Carbonyl Compounds

β-Amino carbonyl compounds are important intermediates for the synthesis of a variety of compounds with pharmaceutical applications such as amino alcohols, diamines, and β-aminoacid derivatives or β-lactams.[401−404] The general method of preparation of β-amino carbonyl compounds involves the Michael addition between amines and α,β-unsaturated ketones which is usually catalyzed by protic acids, protic bases, or Lewis acids catalyst.[404−407] However, depending on the acid or base strength and reaction conditions used, different byproducts can also be generated leading to low selectivities of the desired β-amino carbonyl compound.[408,409] Santos et al.[333] have developed a new catalytic cascade process for efficiently synthesizing β-amino carbonyl compounds starting directly from nitroaromatics and conjugated ketones using Au/TiO_2 as heterogeneous catalyst. First of all, the authors checked the catalytic activity of the mild acidic TiO_2 support for performing the Michael addition between aniline and 1-buten-3-one and they found that the reaction occurs 20 times faster than the uncatalyzed reaction.

Scheme 96. One-Pot Synthesis of β-Amino Carbonyl Compounds from Nitroaromatics



These findings open up the possibility of performing a cascade reaction by starting from nitrobenzene and 1-buten-3-one using Au/TiO_2 where the gold would act as a chemoselective catalyst able to hydrogenate the nitro in the presence of 1-buten-3-one, while the mild acidity of TiO_2 would promote the Michael addition of the amine to the α,β-conjugated double bond (Scheme 96). Indeed, working at 80 °C and under H_2 pressure the corresponding β-amino ketone is produced in excellent yield (91%) after 1 h reaction, while the reduction of the α,β-conjugated ketone is practically suppressed showing the high chemoselectivity of Au/TiO_2 for the hydrogenation of the nitro group in the presence of the α,β-conjugated carbonyl system.

At high conversion levels, the slight decrease in selectivity observed is due to the addition of a second 1-butene-3-one molecule onto the obtained ketoamine. The method was expanded to different substituted nitroaromatic compounds with sensitive functional groups such as ethyl cinnamates or nitriles achieving in all cases excellent yields (see Table 16, entries 2 and 3).

2.4.11. Hydrogenation of 1,2-Dinitro Benzene Followed by Cyclocondensation with Ketones: One-Pot Synthesis of 1,5-Benzodiazepines

Benzodiazepines and their polycyclic derivatives are important bioactive compounds which are prescribed as tranquilizers, anticonvulsant, antianxiety, analgesic, antidepressive, hypnotic, and anti-inflammatory compounds.[410,411] 1,5-Benzodiazepines are usually prepared by cyclocondensation of *o*-phenylenediamine with α,β -unsaturated carbonyl compounds,[412] β-haloketones,[413] or ketones in the presence of Lewis acids and transition metal salts as catalysts, the later being the most extended method for preparing 1,5-benzodiazepines.

Since nitroaromatics are first hydrogenated into the corresponding amines which can be condensed with ketones in a second step,[414] Climent et al.[415] have designed a bifunctional acid/metal chemoselective catalyst able to produce 1,5-benzodiazepines directly from substituted nitro aromatics and ketones through a cascade reaction. Thus, in the first step the nitro aromatics would be chemoselectively hydrogenated in the presence of the ketone on the metal sites. Then, in a consecutive step the cyclocondensation between the aromatic amine and the ketone will occur on the acid sites of the catalyst (Scheme 97). It is interesting to notice that in this process there are two critical issues: the chemoselective hydrogenation of the nitro group in the presence of the carbonyl compound, and to avoid the hydrogenation of the imine group in the 1,5-benzodiazepine product. In order to achieve high performances for the process, optimization of the two catalytic functions, that is, the acid and the hydrogenation, was performed. Thus, in the case of the acidic function, the optimized catalyst was a structured mesoporous aluminosilicate (AlMCM-41) with a Si/Al ratio of 14, which showed superior activity and selectivity than Beta and ITQ-2 zeolites for the cyclocondensation reaction between *o*-phenylenediamine and acetone to form the corresponding 1,5-benzodiazepine under mild reaction conditions. Thus, a Pt decorated TiOx, which is able to selectively reduce the nitro groups in a large variety of substituted nitroaromatics under mild reaction conditions, was selected for the hydrogenating function.[416] This catalyst was by supporting nanosized crystals of Pt on TiO_2 and decorating the exposed (111) and (110) Pt crystal faces with TiO_2 from the support by means of a simple activation at 450 °C in the presence of hydrogen. Thus, for performing the cascade process a composite catalyst was prepared by combining 0.2 wt % Pt/TiO_2 and MCM-41. As shown in Scheme 97 the reaction between 1,2-dinitrobenzene and acetone was performed under hydrogen pressure up to complete reduction of the dinitroaromatic, then the reactor was depressurized and the temperature increased at 65 °C, achieving 100% conversion with 94% selectivity to the corresponding 1,5-benzodiazepine in 2.5 h. Minor amounts of the 1,5-benzodiazepine hydrogenated at the C═N double bond was detected if hydrogen was removed when nitro groups were fully converted.

Scheme 97. One-Pot Synthesis of Benzodiazepines from Nitroaromatics

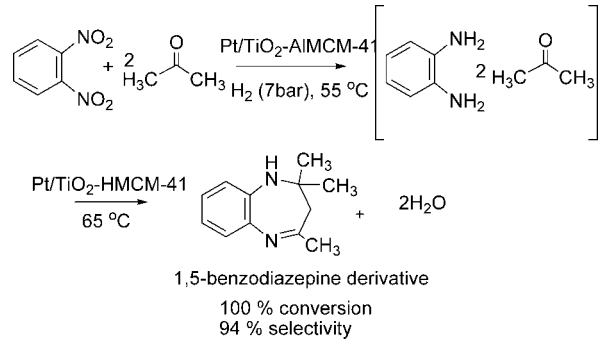
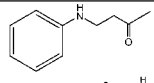
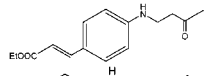
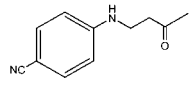
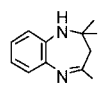
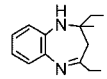
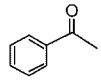
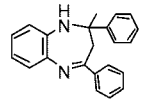
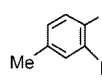
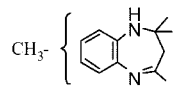
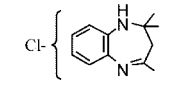
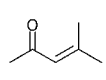
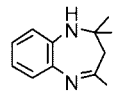


Table 16. Catalytic Results during the Synthesis of Substituted β-Amino Carbonyl Compounds from Nitroaromatics and 1-Buten-3-one by Using Au/TiO_2 Catalyst

entry	Product	T/°C	PH_2(bar)	%Au[a]	t (h)	Conversion (%)[b]	Selectivity (%)[c]
1		80	8	0.49	1	100	91
2		80	10	0.58	2	91	98
3		120	8	0.55	5	92	91

[a] Au/mol nitroaromatic × 100. [b] On the basis of aniline after complete exhaustion (>95%) of the nitroaromatic. [c] Loss of selectivity mainly due to the Michael addition of a second 1-buten-3-one molecule onto the desired β-amino carbonyl compound.

Table 17. Synthesis of Different 1,5-Benzodiazepines Using 0.2 wt % Pt/TiO_2-MCM-41(14) as Catalysts[a]

Dinitroaromatic	Ketone	Product	P (bar)[b]	$T_{hydrog.}$ (°C)	$Time_{hydrog.}$ (h)	$T_{reaction}$ (°C)	$Time_{total}$ (h)	Conversion (%)[c]	S (%)[c,d]
			7	55	1.25	65	2.5	100	94
			7	65	1	95	4	92[e]	89
			10	65	7	100	10	95[f]	84
			7	55	1.25	65	3.25	100	90
			7	55	1.75	65	3.75	100	90
			10	65	3	65	10	95[f,g]	95

[a] Reaction conditions: Dinitroaromatic (0.8 mmol), ketone (1.3 mL), 0.2 wt % Pt/TiO_2 (60 mg), MCM-41(14) (30 mg). [b] Reactions were performed under isobaric conditions. [c] Calculated by CG using *o*-xylene as internal standard. [d] Selectivity (%). [e] A 7% of 2-nitroaniline was detected. [f] Without MCM-41catalyst. [g] A 5% of 2-nitroaniline was detected.

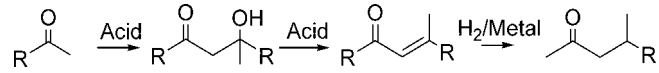
It should be remarked that if commercial 5 wt % Pt/C, Pt/Al_2O_3, Pt/C or undecorated Pt/TiO_2 are used along with AlMCM-41, complete conversions are also obtained but selectivities to the 1,5-benzodiazepines are much lower. On the other hand, as Au/TiO_2 is also a chemoselective catalyst for the hydrogenation of nitroaromatic compounds,[333,416,417] the reaction was carried out using the composite AlMCM41-Au/TiO_2. Also in this case high conversion (99%) and selectivity (93%) to 1,5-benzodiazepine were achieved after 4 h reaction but higher reaction temperature (120 °C) was required. Finally, it was found that the mild acidity of the TiO_2 support was not enough to perform efficiently the cyclocondensation step, and longer reaction times (14 h) were required for full conversion than with the composite catalyst, while the selectivity to the benzodiazepine was lower (73%).

The composite catalyst Pt/TiO_2−AlMCM-41 was active with a series of dinitroaromatics and ketones in the absence of solvent, giving a variety of 1,5-benzodiazepines with yields on the order of 90% under very mild conditions (see Table 17).

2.4.12. Aldol Condensation Followed by Dehydration and Subsequent Hydrogenation

Aldol condensation is an important C−C bond forming reaction which can be catalyzed either by acids or bases. The acid catalyzed reaction involves the nucleophilic attack of the enolic form of an aldehyde or ketone to the activated (by the acid catalyst) carbonyl group of another molecule giving an aldol intermediate which is rapidly dehydrated by the acid sites to the α,β-unsaturated carbonyl compound (Scheme 98). Then, combining acidic and hydrogenating sites it is possible to carry out one-pot transformations involving

Scheme 98. One-Pot Process Involving Aldol Condensation of Ketones Followed by Dehydration and Hydrogenation Steps



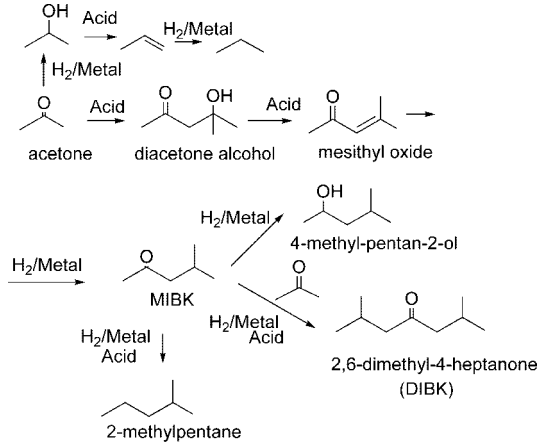
three consecutive steps, that is, aldol condensation, dehydration, and selective hydrogenation of the C=C bond (Scheme 98).

Several examples have been reported in the literature which are summarized in Table 18. One of the most studied process is the one-pot synthesis of methyl isobutyl ketone (MIBK) from acetone due to its great interest as a solvent for paints, inks, and lacquers, as well as for vinyl, epoxy, and acrylic resin production, their global demand being estimated as 300.000 t per year. The traditional process involves a catalytic three-step process where acetone is condensed in the presence of NaOH to diacetone alcohol (4-hydroxy-4-methylpentan-2-one), which is then dehydrated to mesityl oxide and the C=C bond is subsequently selectively hydrogenated on a Pd catalyst to MIBK. Because this process generates large amounts of wastes, there is a great interests to develop more ecofriendly processes based on heterogeneous catalysts, and the use of multifunctional catalysts for the one-step synthesis of MIBK is gaining importance. Several industrial processes,[418−420] as well as numerous academic studies dealing with multifunctional solid catalysts in the one-pot synthesis of MIBK, have been reported. A summary of conversions and selectivities obtained with the most promising multifunctional catalysts has been presented by Talwalkar and Mahajani.[421] A variety of bifunctional acid/metal solid catalysts have been reported in the one-pot synthesis of MIBK where most of the studies

Table 18. Examples of Reactions Involving Aldol Condensation Followed by Dehydration and Subsequent Hydrogenation

catalysts	reactant	product	conversion (%)	selectivity (%)	conditions	ref
0.5%Pd/H-ZSM5	acetone	MIBK	28	98	180 °C, 41 bar, H_2/acetone = 0.6, WHSV = 3.8 h^{-1}	418
0.03% Pt/H-ZSM5	acetone	MIBK	10	80	160 °C, 1 bar, H_2/acetone = 0.33	424
0.5%Pt/A-lZSM5	acetone	MIBK	10	75	160 °C, 1 bar, H_2/acetone = 0.33	556
1%Pd/CsH-ZSM5	acetone	MIBK	42	82	250 °C, 1 bar, H_2/acetone = 1, WHSV = 2 h^{-1}	557
0.9%Pd/SAPO11	acetone	MIBK	11	72	200 °C, 1 bar, H_2/acetone = 1, WHSV = 0.7 h^{-1}	519
0.7%Pd/SAPO11	acetone	MIBK	31	84	200 °C, 37 bar, autoclave	519
0.7%AmberlystCH28	acetone	MIBK	45	95	120 °C, 30 bar, autoclave	421
0.3Zn/Cr mixed Oxide	acetone	MIBK	40	78	180 °C, 7.5 bar, autoclave	427
0.1%Pd/CsPW	acetone	MIBK	42	90	180 °C, 7.5 bar, autoclave	558
0.2%Pd/H-FAU	cyclohexanone	Cyclohexyl cyclohexanone	30	75	200 °C,, 1 bar, H_2/cetone = 0.33	429
0.5%Pd/H-FAU	acetophenone	1,3-diphenylbutan-1-one	10	27	250 °C, 1 bar, H_2/cetone = 0.25	430
0.5%Pd/MnAPSO-31	butyraldehyde + acetone	heptan-2-one	70	70	150 °C, 1 bar, aldehyde/ketone = 0.25, WHSV = 1.6 h^{-1}	419
0.5%Pd/MnAPSO-31	acetaldehyde + acetone	pentan-2-one	20	89	150 °C, 1 bar, aldehyde/ketone = 0.25, WHSV = 1.6 h^{-1}	419

Scheme 99. One-Pot Synthesis of MIBK from Acetone



have been carried out in the gas phase by using fixed-bed reactors. The best results obtained (considering both gas and liquid phase studies) varied between 30−40% acetone conversion with 90% selectivity to MIBK.[421−427] Some examples are summarized in Table 18. The main byproducts formed in this process are propane and 2-methylpentane resulting from three-step transformation (C═O hydrogenation, dehydration and C═C hydrogenation) of acetone and MIBK, respectively (Scheme 99). For this reason, the preferred metal catalyst is Pd which is more selective for the hydrogenation of the C═C bond rather than the carbonyl group. On the other hand, DIBK which was shown to be responsible for catalyst deactivation,[428] can also be formed from trimeric condensation of acetone. However, the formation of this byproduct can be minimized using MFI zeolites where the diameter of the channels avoids further acetone condensations.

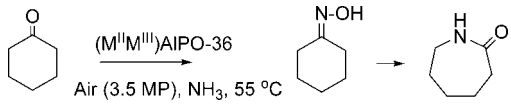
Cyclohexylcyclohexanone, which is a precursor of *o*-phenylphenol (a wide spectrum preservative) and 1,3-diphenylbutan-1-one (an ingredient for plastifying agents), can be obtained from cyclohexanone[429] and acetophenone,[430] respectively, in vapor phase using Pd supported on acid zeolites. For these bulky ketones, Pd/H-FAU with a three-dimensional large pore system was more active and selective than those based on mordenite (unidimensional large pore) or MFI (medium size pore) zeolites. With 0.2% Pd/H-FAU, a selectivity to cyclohexylcyclohexanone of 75% at a cyclohexanone conversion of 30% is obtained.

Crossed aldol condensations between acetone and aldehydes such as butyraldehyde and acetaldehyde have been carried out using Pd-containing aluminophosphate molecular sieves. Reactions performed in a vapor phase fixed bed reactor using 0.5% Pd/MnAPSO-31 yield the desired product in high selectivity, 70% of heptan-2-one (from butyraldehyde and acetone) and 89% of pentan-2-one (from acetaldehyde and acetone). The main byproduct was, in both cases, MIBK from acetone self-condensation.

2.4.13. Oxime Formation Followed by Beckmann Rearrangement: One-Pot Synthesis of ε-Caprolactam

The conversion of cyclohexanone to the corresponding oxime and subsequent Beckmann rearrangement to ε-caprolactam is an important industrial reaction for the manufacture of Nylon-6. On an industrial scale, cyclohexanone is converted into its oxime using hydroxylamine sulfate, while the Beckmann rearrangement is performed by using a strong mineral acid such as concentrated sulfuric acid. Main disadvantages of this process are the use of strong and corrosive sulfuric acid along with the production of large quantities of ammonium sulfate (low value) from the neutralization of the sulfuric acid from ammonia. Owing to these problems, more friendly alternatives for the production of ε-caprolactam have been developed, as for instance the use of titanosilicalite molecular sieve TS-1 developed by Enichem Co.[431] for the production of cyclohexanone oxime from cyclohexanone, ammonia, and H_2O_2 as oxidant, or the direct gas-phase conversion of cyclohexanone to ε-caprolactam using a variety of silicas and aluminas as acid catalyst.[432] More recently, Raja et al.[433] have developed a one-pot, solvent-free transformation of cyclohexanone to

Scheme 100. One-Pot Synthesis of ε-Caprolactam



ε-caprolactam, in liquid phase using oxygen (as air) and ammonia in the presence of a bifunctional transition-metal ion(framework)-substituted such as (M^{II}M^{III})AlPO-36 (M = Co, Mn) (Scheme 100). In these systems, M(II) ions have a proton associated with an adjacent framework oxygen atom showing Bronsted acidity, while M(III) ions are redox active sites.

The bifunctional acid-metal catalyst (M^{II}M^{III})AlPO-36 performs the consecutive steps converting cyclohexanone into cyclohexanone oxime and the later into ε-caprolactam. In this process, hydroxylamine (NH_2OH) is formed in situ inside the pores from NH_3 and O_2 at the M^{III} active sites. NH_2OH in the presence of cyclohexanone is converted to cyclohexanone oxime inside and outside the pores, and the oxime is isomerized into ε-caprolactam at the Bronsted acid sites within the pores of the molecular sieve catalyst. For instance, using (Co^{II}Co^{III})AlPO-36, 20% conversion of cyclohexanone is achieved after 20 h reaction time with selectivities to oxime and ε-caprolactam of 54.2 and 21.1%, respectively.

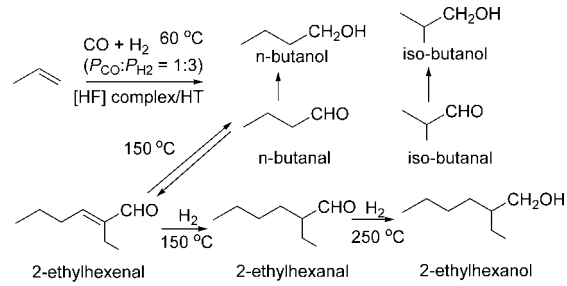
2.5. Multistep Sequential Processes on Basic-Metal Bifunctional Catalysts

2.5.1. Hydroformylation Followed by Aldol Condensation and Subsequent Hydrogenation

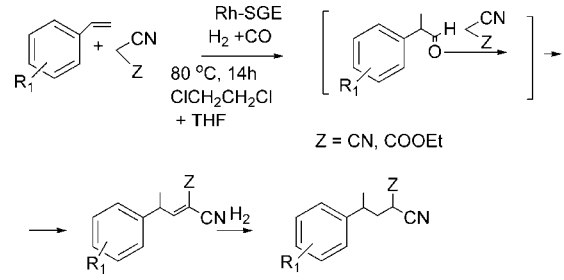
2.5.1.1. Synthesis of Aldehydes/Alcohols from Propylene. Catalytic hydroformylation of alkenes with synthesis gas is an industrial route to produce aldehydes and alcohols, hydroformylation of propylene to give butanals and butanols being one of the most important industrial processes. Butanal is largely used for the production of C_8-aldol products such as 2-ethylhexanal and 2-ethylhexanol, which are valuable intermediates for the synthesis of fine chemicals, alkyd resins, adhesives, and dioctylphthalate. The commercial strategy for the synthesis of C_8-aldol products from propylene involves a three-step process. In the first step, the hydroformylation of the propylene to produce the aldehyde is carried out using Rh or Co based catalysts.[434] The second step is the self-aldol condensation of the aldehydes in the presence of a stoichiometric amount of a strong base (KOH or NaOH) to produce unsaturated aldol derivatives[435] and finally the last step is the hydrogenation of unsaturated aldol derivatives using Ni or Pd catalysts. However, nowadays, new more environmental friendly catalytic processes have been developed. For instance, Shell and Exxon both have developed a single-step process (Aldox process), to produce ethylhexanol directly from propylene by adding cocatalyst based on Sn, Ti, Zn, Al, or Cu or NaOH to the hydroformylation catalyst. However, these proceses still require the use of strong base solutions for the aldol condensation of butanal, and they have low selectivity to the C_8 aldol derivatives and require relatively low liquid space velocity in the hydroformylation.[436]

Sharma et al.[437] have reported a novel approach for the one-pot synthesis of C_8 aldol derivatives (aldehydes or alcohols) from propylene using a multifunctional heterogeneous catalyst prepared by impregnation of a rhodium complex ($HRh(CO)(PPh_3)_3$) ([HF]) on the surface of a basic support such as an Al/Mg hydrotalcite. The [HF]/HT catalyst

Scheme 101. One-Pot Synthesis of 2-Ethylhexanal and 2-Ethylhexanol Starting from Propylene



Scheme 102. One-Pot Synthesis of Nitriles from Styrene



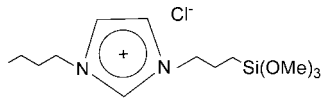
showed catalytic activity for hydroformylation of propylene, aldol condensation and hydrogenation in Scheme 101 are presented the different steps of the process, where the Rh complex plays a key role in the formylation step and in the hydrogenation reactions, while the basic sites of the hydrotalcite catalyze the aldol condensation of butanal.

The catalytic activity of [HF]/HT was studied in detail as a function of the Mg/Al molar ratio of the hydrotalcite (HT), amount of loaded [HF] complex, and reaction temperature. It was found that selectivity to 2-ethylhexanal increased with the Mg/Al molar ratio of HT achieving maximum selectivity (45%) at Al/Mg = 3.5 and working at 150 °C, while the highest selectivity to 2-ethylhexanol was achieved at hydrogenation temperature of 250 °C. The catalyst was stable after high temperature treatment (250 °C), and its reuse in four successive runs showed no changes in activity for the hydroformylation and hydrogenation steps. However, in the aldol condensation step, the selectivity to C_8 aldehydes/alcohols considerably decreased. This was attributed to the structural changes in the hydrotalcite support after the thermal treatment at high temperature.

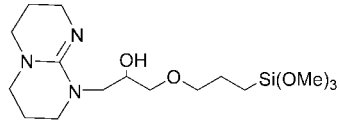
2.5.1.2. One-Pot Synthesis of Nitriles from Styrene. Using the same approach presented above, Hamza et al.[438] have prepared different nitrile derivatives through a one-pot multistep process in which styrene derivatives are selectively hydroformylated to give branched aldehydes, which subsequently are condensed with methylene compounds (malononitrile, ethyl cyanoacetate) and finally hydrogenated (Scheme 102). The process is performed in the presence of $[Rh(cod)Cl]_2$ and sulfonated triphenylphosphane (Na-[Ph_2-P-3-($C_6H_4SO_3$)]) which have been coentraped within ionic-liquid confined silica sol−gel with a separately encaged base (Rh-SGE).

The ionic liquid selected was 1-butyl-3-[3-(trimethoxysilyl)-propyl] imidazolium chloride (Scheme 103), which was chemically bound to the sol−gel backbone of the ceramic support that is entrapping the rhodium complex. The best results were obtained when the base was the sol gel bound 1,5,7-triazabicyclo[4.4.0]dec-5-ene modified with 3-(glycidoxypropyl)trimethoxysilane (Scheme 103).

Scheme 103. Ionic Liquid and Base Used for the One-Pot Synthesis of Nitriles from Styrene

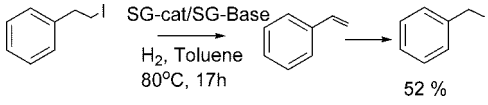


1-butyl-3-[3-(trimethoxysilyl)propyl] imidazolium chloride



1,5,7-triazabicyclo[4.4.0]dec-5-ene derivative

Scheme 104. Sequential Dehydrohalogenation Followed by Hydrogenation of the Alkene Intermediate

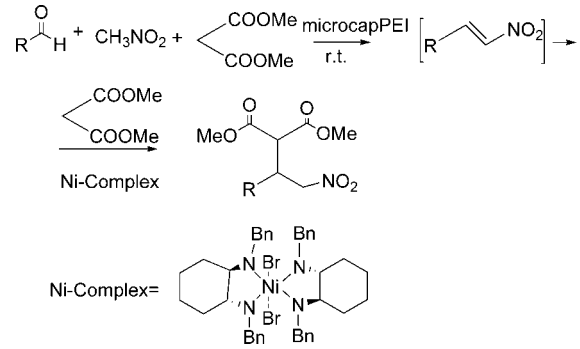


Using this catalytic system, different substituted styrenes were converted to the corresponding saturated nitriles in good overall yields (90%), while under homogeneous conditions, that is, when both rhodium catalyst and base, as well as the ionic liquid are not entrapped in the sol−gel, the multistep process does not take place at all. It is suggested that the imidazole derivative serves as carbene ligand of the rhodium complex and is responsible for the stereoselective hydroformylation. It is interesting to point out the preferential hydrogenation of the internal double bonds of the condensation products over the terminal one of the styrene derivatives, as well as over the easily reducible aldehydes groups. It is also remarkable that hydroformylation of the internal double bonds of the condensation product is not observed. Finally, it was shown that while the rhodium catalyst can be recycled, it was necessary to renew a part of the base after each run.

2.5.2. Dehydrohalogenation of Alkylhalides Followed by Hydrogenation of the Resulting Alkene

The sol−gel entrappement of incompatible catalysts is a versatile approach to perform one-pot processes, as reported by Gelman et al. in a series of publications.[439−443] One of these examples is the sequence of the base catalyzed dehydrohalogenation of 2-phenyl halides by an inmobilized diamine, followed by $RhCl[P(C_6H_5)_3]_3$ catalyzed hydrogenation of the resulting styrene.[439,442] The organometallic catalyst (Wilkinson catalyst) is a common alkene-hydrogenation catalyst, and was physically entrapped in a SiO_2 sol−gel matrix (SG-cat). The base catalyst, $NH_2(CH_2)_2NH(CH_2)_3$-, was covalently heterogeneized by copolymerizing the base-$Si(OCH_3)_3$ monomer with $Si(OCH_3)_4$ (SG-base). Thus, 2-phenylethyl iodide reacted in the presence of SG-cat and SG-base under 200 psi of H_2 in dry benzene at 80 °C (Scheme 104) achieving a maximum yield of 52% for ethylbenzene. Using 2-phenylethyl bromide as substrate, lower yield of ethylbenzene was obtained due to the competing polymerization of styrene, which was attributed to the lower rate of dehydrobromination compared with the dehydroiodination. It was confirmed that no leaching of the active species occurs during the reaction and no interferences between both catalysts exist. The Rh complex was completely deactivated (either in its homogeneous or immobilized form) in the presence of 2 equiv of the free diamine.

Scheme 105. One-Pot Synthesis of Nitrocompounds by Sequential Nitroaldol Condensation Followed by Michael Addition

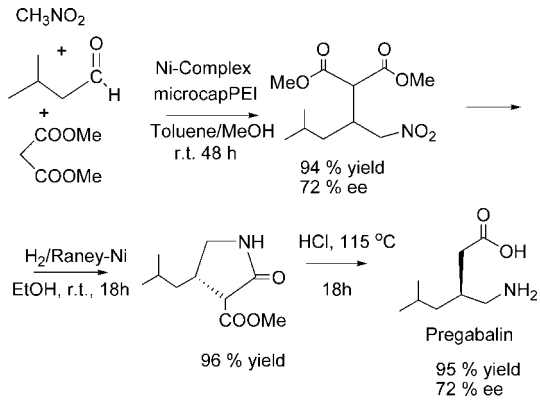


2.5.3. Nitroaldol Condensation Followed by Michael Addition: Synthesis of Nitrocompounds

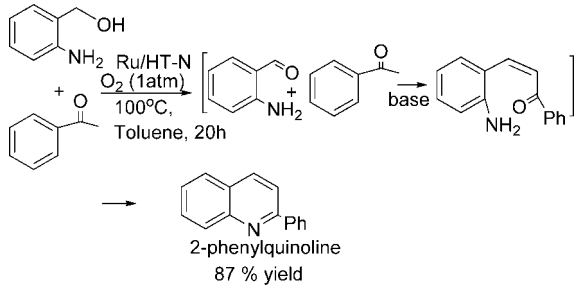
Following the concept of catalyst microencapsulation for the isolation of incompatible catalytic sites, Poe et al.[444,445] have reported the one-pot nitroaldol condensation between aldehydes and nitromethane catalyzed by a microencapsulated amine catalyst, followed by Michael addition to the resulting nitroalkene of a methylene active compound catalyzed by nickel based catalyst. Typically, amine catalysts and nickel complexes are incompatible due to their tendency to chelate and render each other inactive. However, it is shown that microencapsulation of amine catalyst allows to be used in conjuction with the Ni-complex for the tandem process (see Scheme 105). The microencapsulated catalyst was prepared starting from a poly ethylenediamine (PEI) which was treated with 2,4-tolylene diisocyanate to initiate cross-linking, and forming polyurea shells that contain free chains of PEI.

It is interesting to notice that when the reaction is performed in the absence of the Ni-complex, the nitroalkene intermediate reacts with another molecule of nitromethane forming the corresponding dinitro compound; however, in the presence of the second catalyst, the alkene intermediate can be trapped and the reaction is directed to a different reaction pathway giving the Michael addition with the methylene active compound. In addition, kinetic studies showed that the presence of the microcapsule shell not only provides site isolation but they also serve a second function by enhancing rate of the Michael addition (rate-determining step) promoted by the Ni-complex. This effect is attributed to the interaction of the nitro group with the urea moieties of the microcapsule shell, which activates the nitroalkene. The one-pot process was extended to a variety of aromatic and aliphatic aldehydes, giving from good to moderate yields of the target compound. Furthermore, the catalytic system was applied to the one-pot synthesis of pregabalin which is a γ-aminobutyric acid (GABA) analogue, approved for the treatment of both epilepsy and neuropathic pain. The three-step total synthesis of pregabalin is presented in Scheme 106 and involves the use of 3-methylbutyraldehyde as starting material and an enantioselective version of the Ni-complex catalyst. The one-pot reaction yields the Michael adduct in high yield and *ee*, and subsequent hydrogenation and hydrolysis gives 74% overall yield of pregabalin.

Scheme 106. Three-Step Total Synthesis of Pregabalin



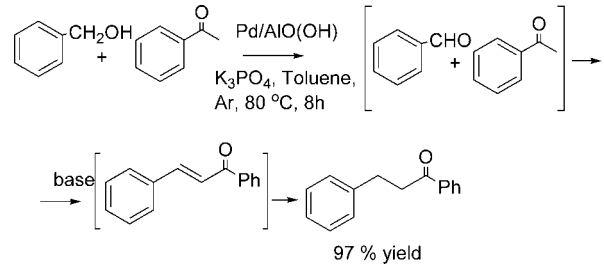
Scheme 107. One-Pot Synthesis of 2-Phenylquinoline



2.5.4. Oxidation of Alcohols Followed by Aldol Condensation and Subsequent Cyclization: Synthesis of Quinolines

Quinolines are important compounds as intermediates in the design of pharmacologically active compounds.[446] The traditional synthesis of quinolines is the Friedlander synthesis,[447] although many synthetic routes have been developed. For instance, the one-pot formation of quinolines from 2-aminobenzyl alcohol and ketones via hydrogen transfer reaction and cyclization mediated by a homogeneous Ru complex in the presence of a stoichiometric amount of KOH was reported by Cho et al.[448,449] The reaction involves the dehydrogenation of 2-aminobenzyl alcohol to 2-aminobenzaldehyde that in the presence of a base subsequently condenses with the ketone, giving an α,β-unsaturated carbonyl compound which spontaneously cyclize to quinoline (see Scheme 107). This is an interesting approach to the synthesis of quinolines since 2-aminobenzylalcohol is less expensive and more stable than 2-aminobenzaldehyde. On the basis of this route, Motokura and co-workers[450] reported for the first time a one-pot quinoline synthesis using heterogeneous catalysts, in the absence of a homogeneous base and using oxygen as an oxidant. A catalyst prepared by treating a non-calcined hydrotalcite (HT) sample ($Mg_6Al_2(OH)_{16}CO_3$) with $RuCl_3$ and triethylamine (Ru/HT-N) showed the highest catalytic activity performing the one-pot reaction between 2-aminobenzyl alcohol and acetophenone (Scheme 107), while other Ru supported catalysts such as Ru/Al_2O_3, Ru/MgO, $Ru/Mg(OH)_2$, and $Ru/Al(OH)_3$ were inactive for this quinoline synthesis. A Ru/HT sample nontreated with triethylamine gave only 61% yield of quinoline. The authors suggest that the role of triethylamine is the neutralization of HCl generated by the chemical adsorption of the Ru species onto the HT surface. The proposed mechanism for the one-pot process using the Ru/HT-N catalyst, involves the oxidation of 2-aminobenzylalcohol to 2-aminobenzylbenzaldehyde under an O_2 atmosphere on the Ru sites, followed by the aldol condensation with ketones catalyzed by the basic sites of the HT to yield the quinolines.

Scheme 108. One-Pot α-Alkylation of Acetophenone with Benzyl Alcohol



The Ru/HT-N catalysts could be reused with retention of its catalytic activity. Additionally, this catalyst system requires only a little excess of ketones (1.2 equiv) than the conventional synthesis method using hydrogen transfer to ketones from 2-aminobenzyl alcohol.

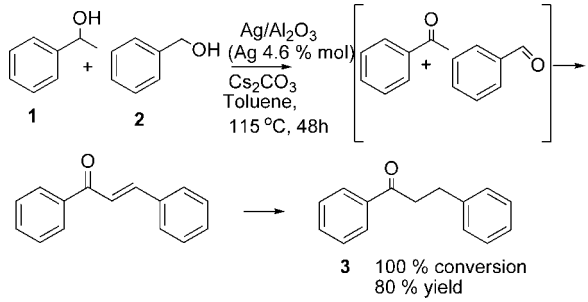
The synthesis was extended to several substituted and heteroaromatic substituted ketones, giving the corresponding quinoline derivatives in good to moderate yields (90−74%).

2.5.5. Oxidation of Primary Alcohols Followed by Aldol Condensation with Ketones: One-Pot Synthesis of α-Alkylated Ketones

The metal catalyzed α-alkylation of ketones with alcohols for the formation of C−C bonds is an attractive alternative to the conventional α-alkyation of enolates derived from ketones with electrophiles such as alkyl halides.[451] Kwon et al.[452] have reported that Pd/AlO(OH) catalyst (palladium nanoparticles entrapped in boehmite nanofibers) is very effective for the α-alkylation of ketones with primary alcohols. The catalyst is able to produce aldehydes from primary alcohols which in the presence of a base undergo the aldol condensation with ketones giving intermediate enones which are hydrogenated to the corresponding ketones. Taking as the model reaction the alkylation of acetophenone with benzaldehyde, the reaction conditions were optimized. Among the different bases tested, K_3PO_4 was found to be the best, while strong bases such as KOH, NaOH, and CaH_2 dissolved the aluminum hydroxide matrix, and weak bases such as K_2HPO_4, K_2CO_3, Na_2CO_3 and triethylamine were ineffective. Thus, in the presence of Pd/AlO(OH) (Pd 0.2% mol) and using 3 equiv of K_3PO_4 at 80 °C under argon atmosphere, the reaction beween benzyl alcohol and acetophenone afforded 1,3-diphenylpropan-1-one in 97% yield within 8 h (Scheme 108), while other commercial palladium catalysts (5% Pd/C, 5% Pd/Al_2O_3, 5% Pd $BaCO_3$) gave low selectivities (<70%) and yields (<55%). Interestingly, the ruthenium-grafted hydrotalcite[453] showed a better activity in the absence of an added base giving 85% yield of ketone. Nevertheless, higher temperature (180 °C) and reaction times were required.

The Pd/AlO(OH) catalyst could be reused up to five times with little loss of activity. The catalytic system was efficiently applied to a wide combination of ketones and alcohols giving always the corresponding α-alkylated ketones in excellent yields. On the other hand, when reactions were performed in the presence of O_2 (1 atm), *trans*-enones were produced selectively, although the reaction rates were relatively slow. For instance, the reaction between benzyl alcohol and

Scheme 109. One-Pot Synthesis of α-Alkylated Ketones Starting from Primary and Secondary Alcohols



acetophenone under aerobic conditions afforded 95% of chalcone in 20 h.

2.5.6. Oxidation of Secondary and Primary Alcohols Followed by Aldol Condensation: One-Pot Synthesis of α-Alkylated Ketones

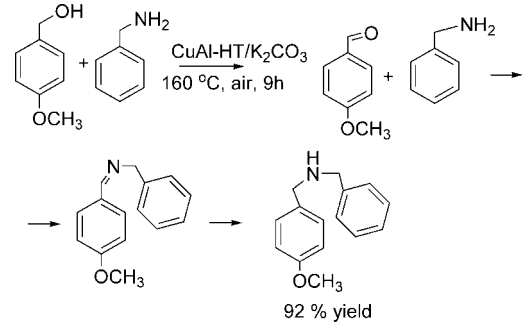
Direct cross coupling of secondary and primary alcohols is an interesting and environmentally friendly alternative for the production of C−C bonds. This one-pot process involves the oxidation of the primary and secondary alcohols to the corresponding aldehyde and ketone respectively catalyzed by metal sites (through the formation of a metal hydride species), followed by the base catalyzed aldol condensation of the carbonyl compounds formed giving an α,β-unsaturated ketone which is finally reduced to the corresponding ketone by the metal hydride. The β-alkylation of secondary alcohols with primary alcohols without requiring any hydrogen acceptor or donor has been achieved using Ru and Ir complexes as catalysts. However, large amounts of strong base is required (200−300% mol of KOH or NaOt-Bu), while the catalytic turnover numbers (TONs) are low. Cho and co-workers[454] showed that Pd/C can be used for this one-pot transformation, but the process requires a large amount of sacrificial hydrogen acceptor (500% mol of 1-dodecene). More recently Shimizu et al.[455] have showed that an alumina supported sub-nanometer-sized silver cluster (0.8 nm) acts as a recyclable heterogeneous catalyst for the one-pot C−C coupling reaction of secondary and primary alcohols without any sacrificial additives in the presence of catalytic amounts of a weak base (Cs_2CO_3). The C−C cross-coupling of 1-phenylethanol with benzyl alcohol was selected as a reaction model (Scheme 109), and while different metals supported on alumina such as Au, Ru, Pt, Pd, and Cu gave low activiy, the Ag/Al_2O_3 (Ag 4 mol %) catalyst gives a maximum yield of 80% of ketone (Table 19). It was found that varyng the basicity of the carbonate salt, the yield of ketone increased in the order $Li_2CO_3 < Na_2CO_3 < K_2CO_3 < Cs_2CO_3$, suggesting that the alcohol dehydrogenation and aldol condensation steps demand stronger basic sites. However, lower yields and lower conversion were achieved when stronger bases such as NaOH and KOH were used instead of Cs_2CO_3. It was determined that the reaction catalyzed by Ag/Al_2O_3 is a structure−sensitive reaction, while the acid−base character of the Al_2O_3 support plays an important role in the catalytic activity. Thus, the reaction proceeds by means of the cooperative action of the coordinatively unsaturated silver sites and acid−base sites on the Al_2O_3 support. The scope of the reaction was established with a series of secondary and primary alcohols achieving moderate to good yields of the corresponding α-alkylated ketones.

Table 19. Reaction of 1-Phenylethanol (1) with Benzyl Alcohol over Different Catalysts[a]

catalyst-x[b]	conversion of **1** (%)	yield of **3** (%)
Ag/Al_2O_3-1	98	72
Ag/Al_2O_3-3	100	78
Ag/Al_2O_3-5	100	80
Ag/Al_2O_3-10	100	68
Ag/Al_2O_3-50	100	49
Au/Al_2O_3-1	100	45
Pt/Al_2O_3-1	9	1
Rh/Al_2O_3-1[c]	91	17
Ru/Al_2O_3-5	100	19
Pd/Al_2O_3-3	100	36
Cu/Al_2O_3-8[c]	51	17
Pd/C-5	100	54

[a] Reaction conditions: **1** (1 mmol), **2** (1 mmol) in toluene (2 mL), catalyst (0.1 g), Cs_2CO_3(100 mol %), 48 h. [b] x is the metal loading (wt %). [c] 72 h.

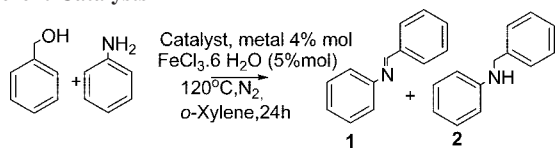
Scheme 110. One-Pot N-Monoalkylation of Amines with Alcohols



2.5.7. Oxidation of Alcohol to Aldehydes Followed by Condensation with Amines and Subsequent Reduction: One-Pot N-Monoalkylation of Amines with Alcohols and Synthesis of Piperazines

The direct alkylation of amines by alcohols yielding substituded amines is a reaction of interest in organic synthesis, because amines are versatile building blocks for various organic molecules. In addition, the catalytic amination of alcohols is an atom-economical and environmentally attractive method for the synthesis of amines which allows the replacement of aryl or alkyl halides by readily available alcohols as alkylating agents. The reaction involves the loss of one hydrogen from the alcohol to provide a carbonyl intermediate that reacts with amines to form imines or iminium species which are then reduced to amines with concomitant formation of water. This oxidation/imination/reduction sequence has been performed with Ru^{II} and Ir^{I} complexes under transfer hydrogenation conditions, requiring an excess of a soluble base,[456−459] the catalyst being difficult to recover. Recently, Likhar et al.[460] have reported the amination of alcohols with benzylamines using a Cu−Al hydrotalcite/K_2CO_3 catalytic system. Reactions were performed at 160 °C using a stoichiometric amount of K_2CO_3 and an excess of amine (Scheme 110). While benzyl alcohols with electron-donating substituents facilitate the amination reaction affording excellent yields to the amines (83−92%), with electron-withdrawing substituents the yields were lower (67−79%). Long-chain aliphatic alcohols were also aminated with benzylamine giving good results. However, the yields of amine decreased with increasing carbon chain length. It was showed that the Cu−Al−HT/K_2CO_3 catalytic system was also active for the amination of benzyl alcohols with primary and secondary amines, benzylamines, anilines, and

Table 20. N-Alkylation of Aniline with Benzyl Alcohol Using Different Catalysts[a]



catalyst-x[b]	D (nm)[c]	conv (%)	yield (%) **1**	yield (%) **2**
Au/Al_2O_3-1	1.9	99	12	29
Pt/Al_2O_3-1	1.3	100	24	1
Pd/Al_2O_3-1	1.5	99	17	3
Ag/Al_2O_3-1	0.73	100	1	67
Ag/Al_2O_3-3	0.78	100	1	72
Ag/Al_2O_3-5	0.84	100	1	94
Ag/Al_2O_3-5[d]	0.84	100	63	16
Ag/Al_2O_3-10	1.2	99	42	22
Ag/Al_2O_3-50	30	48	15	8

[a] Reaction conditions: benzyl alcohol (1 mmol), aniline (2 mmol), catalyst (0.1 g, 4 mol % of metal), *o*-xilene (2 mL), $FeCl_3 \cdot 6H_2O$ (5 mol %), at 120 °C, 24 h. [b] Metal loading. [c] Average particle size of the supported metal. [d] In absence of $FeCl_3 \cdot 6H_2O$.

long-chain aliphatic amines. After the reaction, the Cu−Al−HT catalyst was separated by filtration and reused up to five times showing consistent activity.

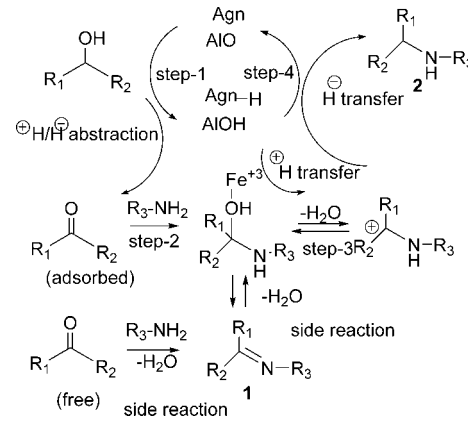
However, it was shown that in the absence of base no products were formed. The authors suggest a mechanism where the base promotes the abstraction of a proton from the alcohol giving a copper alkoxide which could be transformed into the aldehydes through β-hydride elimination, leaving a mono(hydrido)copper surface species. The condensation of the aldehyde with the amine yields an imine that can be reduced by the mono(hydrido)copper to form an (amido)copper species. Ligand exchange between the copper amide and alcoholic substrate (or alkoxide) could afford the desired amination product. Although the $CuAl\text{-}HT/K_2CO_3$ was an efficient catalyst, some drawbacks are associated with its use, mainly the requirement of a homogeneous base in stoichiometric amounts which cannot be recovered at the end of the reaction.

Shimizu et al.[461] have also reported the direct N-alkylation of anilines with alcohols using alumina supported subnanometer-sized silver cluster in the presence of a catalytic amount of Lewis acid such as Fe^{3+} salts (see Table 20).

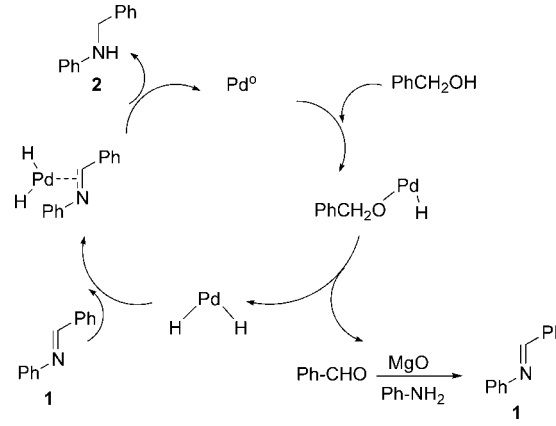
It is suggested that the Lewis sites of the additive enables faster hydride transfer from the metal to immonium cation intermediate, which results in the higher selectivity to amine (Scheme 111). This catalytic system was applied to the synthesis of different secondary amines starting from a variety of substituted anilines and benzyl alcohols with good to moderated yields (62−94%). When the Ag/Al_2O_3 catalyst was reused in a second cycle, slight loss of activity was detected, however further deactivation was not observed in subsequent runs.

In order to avoid the use of nonrecoverable components, a purelly heterogeneous catalytic system has been used with excellent success by Corma et al.[462] to perform the amination of alcohols. Thus, the authors have recently reported that by using a bifunctional solid catalyst bearing basic and metal sites such as Pd on MgO, it is possible to catalyze the monoalkylation of amines with high selectivity. The reaction involves the abstraction of hydrogen from the alcohol giving the corresponding metal hydride and carbonyl compound from the alcohol. The carbonyl compound condenses with the amine to give an imine, which is subsequently hydrogenated to the final monoalkylated amine by the Pd hydride (Scheme 112).

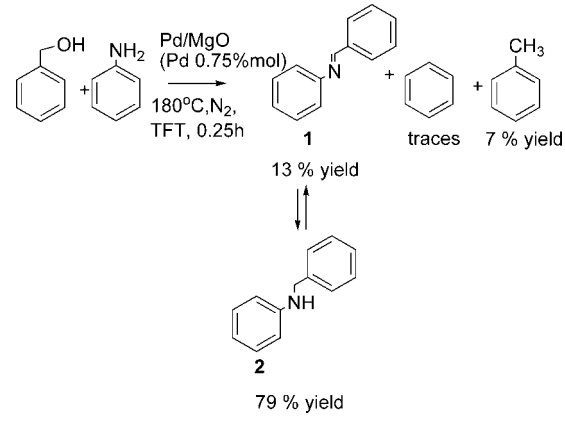
Scheme 111. Suggested Mechanism for the N-Alkylation of Alcohols with Amines Catalyzed by Ag/Al_2O_3 with $FeCl_3 \cdot 6H_2O$



Scheme 112. Proposed Reaction Mechanism for the Monoalkylation of Aniline with Benzyl Alcohol Catalyzed by Pd/MgO



Scheme 113. One-Pot N-Monoalkylation of Amines with Alcohols Using Pd/MgO as Bifunctional Catalyst



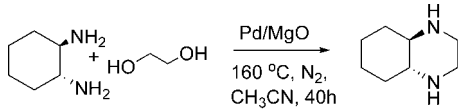
Selecting as a reaction model the N-alkylation of aniline with benzyl alcohol (Scheme 113), a series of bifunctional catalysts based on metals with different abilities to form hydrides and to give back the hydrogen (Pd, Pt, and Au) were supported on MgO and tested in the reaction at 180 °C, in trifluorotoluene (TFT) as a solvent under N_2 atmosphere (Table 21). It was found that the Pd/MgO catalyst was the most active and selective to perform the N-monoalkylation of amines, giving a turnover number about four times higher than that of the homogeneous Ru or Ir

Table 21. N-Alkylation of Aniline with Benzyl Alcohol Catalyzed with Diverse Bifunctional Solid Catalyst[a]

			yield (%)[c]					
entry	catalyst	C (%)[b]	**1**	**2**	benzene	toluene	T (h)	TON[d]
1	Pd-MgO (0.8%)	99	13	79	traces	7	0.25	192
2	Pd−C (5%)	91	23	28	3	16	23	198
3[f]	Pd-MgO (0.8%)	96	12	84	0	0	6	97[e]
4[g]	Pd-MgO (0.8%)	90	8	80	traces	1	0.8	172
5	Pd-HT (0.55%)	100	11	49	5	34	2	182
6	Pd-HAP (0.55%)	100	39	26	3	31	2	167
7	Au-MgO (1.0%)	93	49	38	3	2	5	156
8	Pt-MgO (1.0%)	98	21	61	6	11	1	145
9[h]	AuPd-MgO	76	7	59	2	7	2	123[e]
10[i]	AuPt-MgO	87	42	36	8	2	2	149[e]
11[i]	PdPt-MgO	100	10	80	3	7	0.75	149[e]
12	Pd-MgO (2.0%)	84	16	47	6	16	0.75	561
13	Pd-MgO (5.0%)	75	13	38	8	15	1	521
14	Pd-MgO (10.0%)	66	11	30	9	16	1	408

[a] Reaction conditions: benzyl alcohol (1 mmol), aniline (3 mmol), *n*-dodecane (0.1 mmol), catalyst (0.0075 mmol of Pd, or Pt, or Au), trifluorotoluene (1 mL), $T = 180$ °C. [b] Conversions were determined by GC on the basis of benzyl alcohol consumption. [c] Determined by GC. [d] Based on total metal atoms. [e] Based on surface Pd atoms. [f] After two uses. [g] Reaction conditions: benzyl alcohol (1 mmol), aniline (1 mmol), *n*-dodecane (0.1 mmol), catalyst (0.025 mmol Pd), trifluorotoluene (1 mL), $T = 110$ °C. [h] 0.0075 mmol of Pd. [i] 0.0075 mmol of Pt.

Scheme 114. One-Pot Synthesis of Piperazines



86 % yield

catalysts working under similar reaction conditions.[459] In addition, the catalyst could be used in a second run without loss of activity. When Pd was supported on two other basic supports such as Al/Mg hydrotalcite and hydroxyapatite the activity and selectivity were lower, and benzene and toluene were obtained as byproduct in significant amounts. On the other hand, Pd showed higher activity than Au and Pt for the N-monoalkylation reaction, following the order Pd > Pt > Au. Considering that the controlling reaction step is the hydrogenation of the imine through hydrogen transfer from the metal hydride, and that the surface hydride concentration and its ability to release the hydrogen will determine the activity and selectivity of the catalyst, the clear superiority of Pd for catalyzing this reaction can be explained taking into account that the stability of gold and platinum hydrides are too low or too high, respectively, for optimum hydride transfer.

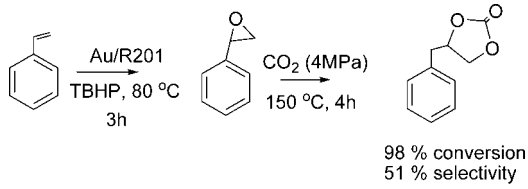
The metal crystallite size has an important impact on reactivity. It has been found that the hydride transfer to the imine as well as dehydrogenation of the alcohol are structure sensitive reactions;[463] that is, the initial reaction rates for amine formation as well as the formation of benzaldehyde increase exponentially as the Pd crystallite size decreases. Meanwhile, the initial rates for competing reactions that give toluene and benzene remain constant with the particle size. This means that selectivity to the target compound can be increased by controlling the crystal size of the metal. With a Pd/MgO in which the metal particle size was optimized (2.2 nm), the reaction was successfully extended to other alcohols and amines, and applied to one-pot synthesis of piperazines by reaction between different 1,2-diamines and diols (Scheme 114).

Kim et al.[464] have also reported the N-alkylation of aniline with benzyl alcohol using a supported ruthenium hydroxide on alumina ($Ru(OH)x/Al_2O_3$) as catalyst, which was prepared by treatment with NaOH of $RuClx/Al_2O_3$. It was shown that the generation of active ruthenium hydroxide species on the surface of Al_2O_3 was crucial in order to achieve high catalytic activity, while other ruthenium based materials (Ru/C, Ru supported on hydroxyapatite, RuO_2 anhydrous, $Ru(OH)x$, $RuClx/Al_2O_3$) showed poor activity. With $Ru(OH)x/Al_2O_3$ (5% mol of Ru), at 132 °C, under Ar atmosphere, the N-alkylation of aniline with benzyl alcohol gave 96% conversion after 5 h, with yields of secondary amine and imine of 78% and 18%, respectively. These results are similar to those reported by Corma et al.[462] using Pd/MgO bifunctional catalyst; however, the TON of $Ru(OH)x/Al_2O_3$ was 1 order of magnitude lower. Different aromatic amines were N-alkylated with various benzylic and aliphatic alcohols using the $Ru(OH)x/Al_2O_3$ catalyst with good to moderate yields, but long reaction times were required in all cases. The catalyst could be reused in a second run without appreciable loss of activity. A similar reaction mechanism than the one proposed for Pd/MgO is suggested, in which the N-alkylation proceeds via three sequential reactions: (a) oxidative dehydrogenation of an alcohol to a carbonyl compound with the transitory formation of the ruthenium hydride species; (b) reaction between the carbonyl compound and the amine to give the imine; and (c) the hydrogen transfer from the hydride species to the imine, affording the corresponding secondary amine.

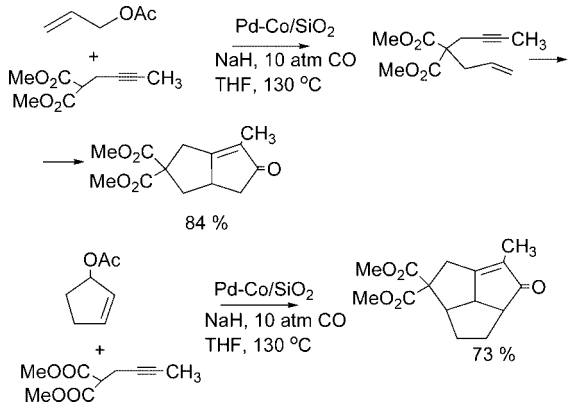
2.5.8. Epoxidation of Styrene Followed by Cycloaddition of CO_2: One-Pot Synthesis of Styrene Carbonate

Cyclic carbonates have found a variety of applications such as aprotic polar solvents, polymer precursors and intermediates in the production of pharmaceuticals and fine chemicals.[465] An attractive green route for the production of cyclic carbonates is the cycloaddition of CO_2 to epoxides.[466] However, as epoxides are mostly obtained from olefins, and olefins are cheaper and less toxic than epoxides, the one-pot synthesis of cyclic carbonates from olefins (direct oxidative carboxylation of olefins) could be a promising route for synthesizing this type of compounds. For instance, Aresta el al.[467,468] have reported the synthesis of styrene carbonate from styrene in the presence of CO_2 and O_2 at 135 °C using Nb_2O_5 and $Nb_2O_5 + NbCl_5$; however, poor yields of styrene carbonate were obtained (11%). More recently, Srivasta et al.[469] reported the synthesis of styrene carbonate from styrene by two steps in a single reactor using titanium silicalite in the presence of *N*,*N*-dimethylaminopyridine as cocatalyst. In this case, the yield of styrene carbonate was also low (33%), while high temperature, long reaction times, and toxic organic solvents were required. Sun et al.[470,471] found that the $ZnBr_2$/tetrabutylammonium bromide catalytic system had excellent activity and selectivity for the cyclocondensation of CO_2 with styrene oxide; then this catalytic system combined with a epoxidating catalyst such as silica supported nanogold particles was utilized to perform the direct oxidative carboxylation of styrene. Reactions performed in the absence of solvent at moderated temperature (60−80 °C) in the presence of *tert*-butyl hydroperoxide (TBHP) or cumene hydroperoxide and 1 MPa CO_2 pressure, afforded styrene carbonate in moderate yields (20−45%). More recently, Sun et al.[472] have reported that Au supported basic resin R201, whose functional group is quaternary ammonium hydroxide ((poly-

Scheme 115. Direct Oxidative Carboxylation of Styrene



Scheme 116. One-Pot Synthesis of Bicyclic and Tricyclic Enones



styrylmethyl)trimethyl ammonium)), was active in both the epoxidation reaction of styrene and cycloaddition reaction of CO_2 to epoxide. Then, using this catalyst the direct oxidative carboxylation of styrene to styrene carbonate was performed over Au/R201. The reaction performed under optimized conditions and in the absence of ZnBr, using TBHP as oxidant, gave 51% selectivity at 100% conversion of styrene (Scheme 115). The authors suggest that styrene epoxidation proceeds over the gold nanoparticles and carbon dioxide is activated by quaternary ammonium cation of the basic R201 resin. The catalyst was reused in a second run without any loss of activity.

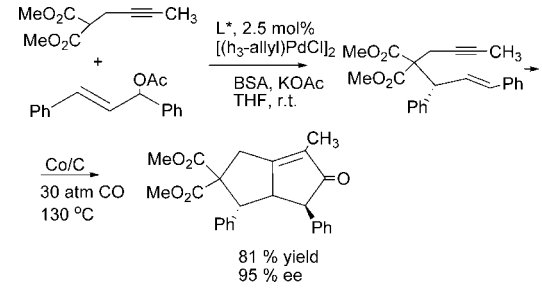
2.6. Mutistep Sequential Processes on Bi- and Multimetallic Catalysts

2.6.1. Allylic Alkylation Followed by a Pauson−Khand Reaction: Synthesis of Bicyclic and Tricyclic Enones

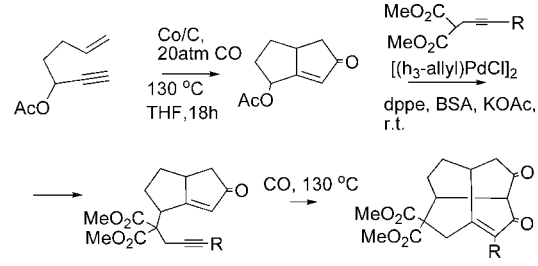
Park and co-workers[473] reported the one-pot synthesis of bicyclic and tricyclic enones through the sequential allylic alkylation of propargyl malonates followed by Pauson-Khand cyclization[474] using palladium and cobalt nanoparticles (44% mol Co, 1.7 mol % Pd) supported on silica as a catalyst (Scheme 116). The process is performed in THF solution at 130 °C, giving from good to moderate yields of the corresponding enones (68−88%). The study of the catalyst stability by means of several reuses showed that significant leaching of Pd nanoparticles occurs during the reaction, while the leaching of Co was negligible. This results in a low recyclability of the catalyst, which could only be reused three times with moderate to high yields.

Following a similar approach, the same authors have reported the asymmetric synthesis of bicyclopentenones and tricyclopentenones by successive action of homogeneous Pd(II) and a heterogeneous Co/C catalysts in a two-step reaction (Scheme 117).[475] High overall yields of the cyclopentenones were achieved; however, the enantiomeric excess of the product depends on the optical purity of the in situ generated enyne.

Scheme 117. One-Pot Synthesis of Asymmetric Synthesis of Bicyclopentenones



Scheme 118. One-Pot Synthesis of Fenestranes

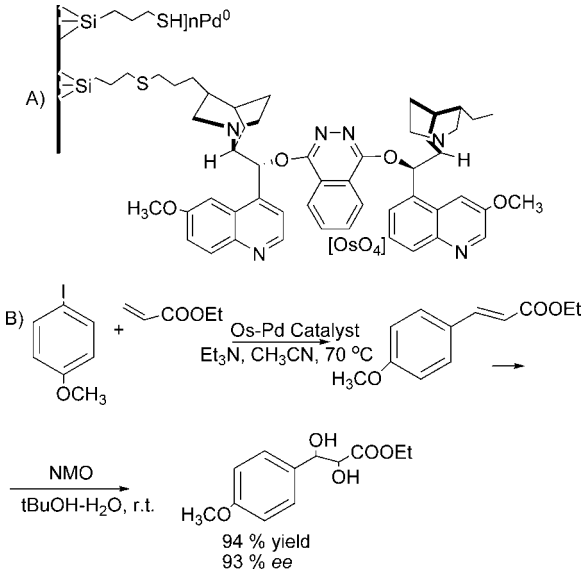


The authors applied this approach to the synthesis of fenestranes, a tetracyclic structure with a complex synthesis involving multiple steps and separation problems.[476] Thus, fenestranes were prepared from readily available chemicals in a three-step reaction using heterogeneous Co/C and homogeneous Pd(II)[477] (Scheme 118). The first step is a Co catalyzed Pauson-Khand reaction of an enyne leading to bicyclopentenone; after this, Pd (II) catalyst and an alkyne diester are added leading to the Pd catalyzed allylic alkylation; and finally the third step is another Co catalyzed Pauson-Khand reaction which leads to the fenestrane structure. Depending on the enyne and alkyne diester structure, moderate to good overall yields (54−84%) of fenestrane compounds were obtained.

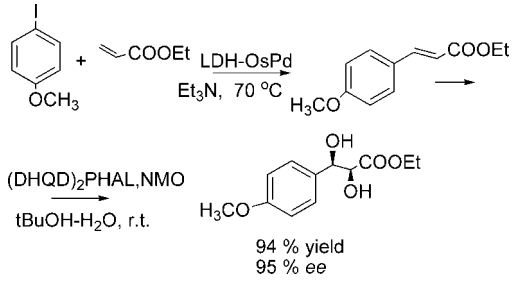
2.6.2. Heck Coupling followed by Asymmetric Dihydroxyalkylation of Double Bond: Synthesis of Vicinal Diols

Chiral vicinal diols are structures playing important roles in biological systems, and they are also used as starting materials for enantiospecific synthesis of several drugs such as diltiazem (calcium channel blocker), taxol side chain, chloramphenical (broad spectrum antibiotic), macrocyclic antitumor drugs and β-lactams. One of the most efficient methods for the preparation of chiral vicinal diols is the Sharpless asymmetric dihydroxyalkylation.[478] Choudary et al. have studied the tandem Heck/asymmetric dihydroxyalkylation of olefins using different heterogeneous bimetallic catalysts.[479−486] They reported the preparation of a Pd-thiol and osmium-cinchona alkaloid complexes covalently anchored on silica (Scheme 119A) to perform the Heck vinylation of aryl halides to obtain the desired prochiral olefin, which is subsequently dihydroxyalkylated in situ to afford chiral diols in a process (Scheme 119B).[479] The Heck reaction step was performed at 70 °C in acetonitrile as a solvent, and after the reaction was completed, solvent was removed and a cooxidant ($K_3Fe(CN)_6$ or *N*-methylmorpholine oxide (NMO) in *t*BuOH-H_2O was added and stirred at room temperature. The catalyst (1 mol % Pd and Os) showed excellent catalytic activity achieving overall yields and enantiomeric excess (*ee*) of 89−99% and 88−99% respec-

Scheme 119. (A) Pd-thiol and Osmium-Cinchona Complexe Anchored on Silica and (B) One-Pot Synthesis of Vicinal Diols



Scheme 120. One-Pot Synthesis of Vicinal Diols Using LDH Exchanged with OsO_4^{2-} and $PdCl_4^{2-}$

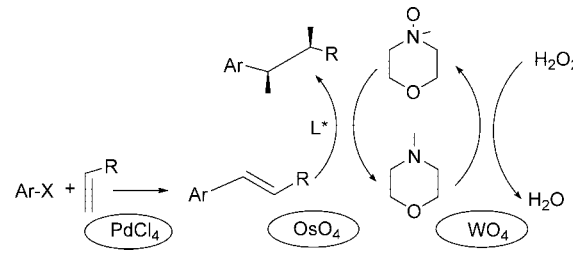


tively. The catalyst recovered by simple filtration and reused in a second cycle exhibited the same catalytic activity for the Heck coupling; however, a drop in activity and *ee* was noticed for the dihydroxyalkylation reaction. This was attributed to the leaching of osmium into solution during the process. When the reused catalyst was loaded with 0.3% mol OsO_4, the activity in dihydroxyalkylation reaction was restored.

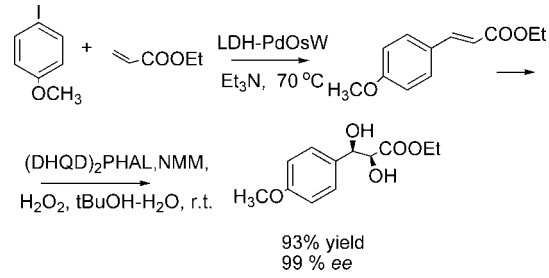
In order to suppress the leaching of metals and particularly toxic osmium, the authors prepared a new catalyst by exchanging bivalent anions OsO_4^{2-} and $PdCl_4^{2-}$ onto a chloride-saturated Mg−Al layered double hydroxide (LDH).[480,482] LDH are a class of layered solids with positive charged layers balanced by anions located in the interlayer spacing that can be easily exchanged. The catalytic activity of the LDH-PdOs (1% mol Pd and Os) was evaluated in tandem Heck-asymmetric dihydroxylation of olefins (Scheme 120). The Heck coupling was performed at 70 °C, in the absence of solvent and using Et_3N as a base. After completion of the first step, the Sharpless chiral ligand, 1,4-bis(9-O-dihydroquinidyl)phthalazine ($(DHQD)_2PHAL$), 1% mol), and NMO in *t*BuOH/H_2O were added and stirred at room temperature. Under these conditions, the diols were obtained with excellent yields and enantiomeric excess.

An interesting achievement of this study was to avoid the use of the hygroscopic and expensive NMO in stoichiometric quantities. Thus, the authors designed a LDH-PdOsW trifunctional catalyst able to perform the in situ oxidation of

Scheme 121. In Situ Oxidation of *N*-Methyl Morpholine (NMM) to NMO



Scheme 122. One-Pot Synthesis of Vicinal Diols Using LDH-PdOsW Trifunctional Catalyst



N-methyl morpholine to NMO in catalytic amounts using H_2O_2 as oxidant[480] (Scheme 121).

With this trifunctional catalyst, excellent yields and enantioselectivities of the glycols were obtained (Scheme 122). The catalyst was recovered quantitatively by filtration, whereas the chiral ligand was recovered by acid−base extraction. The recovered catalyst was reused at least for five cycles showing consistent activity which indicates that the metal leaching during the process is low.

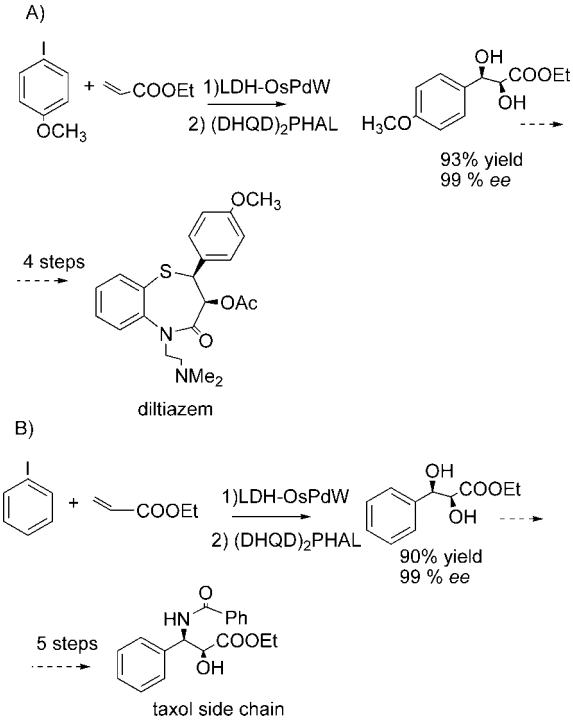
The superior performance for yield and enantioselectivity of LDH-PdOs and LDH-PdOsW was ascribed to the presence of $Et_3N{\cdot}HI$ generated during the Heck coupling and to the basic character of the support, which facilitates the hydrolysis of osmium monoglycolate. The excellent results obtained with the trifunctional catalyst allowed the preparation in one-pot of chiral diols of cinnamates with high *ee* (99%) and free from osmium. The products were directly used to make diltiazem (Scheme 123A) and taxol side chain[482] (Scheme 123B).

The authors reported the use of other supports such as nanocrystalline MgO for the preparation of MgO-PdOs and MgO-PdMgOs catalyst[486] and polymeric support such as a PdOs-resin prepared by ion exchange of quaternary ammonium salts covalently bound to resin.[485] The PdOs-resin exhibited similar catalytic activity in terms of yield and enantioselectivity that LDH-PdOs, while MgO-PdOs were less active than LDH-PdOs.

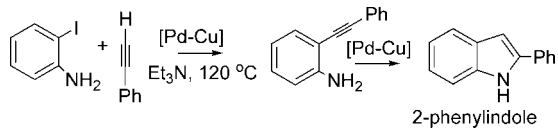
2.6.3. Sonogashira Coupling Followed by Heteroannulation: One-Pot Synthesis of Indoles

The indole ring is an important substructure of numerous natural and pharmacologically active compounds[487] and synthesis can be performed through many methods.[488,489] Generally, the indole synthesis through the Sonogashira reaction is performed in two steps: the first one involves the Pd−Cu catalyzed Sonogashira cross-coupling between a 2-aminoaryl halide and a substituted 1-alkyne and the second step is a Cu(I) or Pd(II) catalyzed ring-closure by hydroamination/cyclization giving the indole. This step requires stronger reaction conditions (higher temperature, stronger bases) than the first step in order to achieve high conversions.

Scheme 123. One-Pot Synthesis of Vicinal Diols of Cinnamates As Intermediates in the Synthesis of (A) Diltiazem and (B) Taxol Side Chain



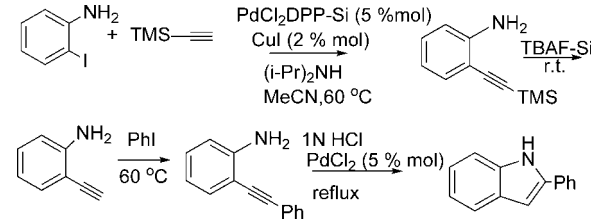
Scheme 124. One-Pot Synthesis of 2-Phenylindole



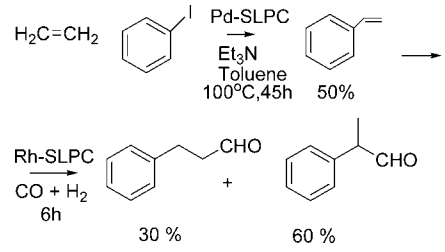
Gruber et al.[195] reported the synthesis of 2-phenylindole in one-pot process by reacting 2-iodoaniline with phenylacetylene in the presence of 1 mol % Pd^{II}/C and 1 mol % CuI at 120 °C using DMF/H_2O = 1:1 as a solvent. After 6 h, 100% conversion with 72% yield of 2-phenyl indole was achieved (Scheme 124). The intermediate compound resulting from the Sonogashira coupling between 2-iodoaniline and phenylacetylene was not detected in the reaction media, indicating that heteroannulation is very fast under these reaction conditions. It was determined that the presence of CuI as cocatalysts is relevant in order to achieve high performances in the process. Recycling experiments of the catalyst showed that a strong deactivation of the catalyst occurred during the first run which decreased considerably the initial activity in the subsequent runs; however, selectivity to 2-phenylindole was retained over four recycling cycles.

Following the same approach, the authors also reported the excellent activity for the synthesis of 2-phenylindole (100% yield) of a bimetallic heterogeneous (Pd−Cu) catalyst based on Pd and Cu complexes entrapped into NaY zeolite.[490] It was found that leaching of the metals to the reaction media was negligible, and the catalyst was active for several reaction cycles. 2-Functionalyzed indoles have also been prepared through this one-pot approach over $[Pd(NH_3)_4]^{+2}$/NaY (obtained by ion exchange method) and [Pd]SBA-15 (obtained by grafting a Pd complex). Reactions performed in DMF/H_2O at 80 °C give the corresponding indole derivatives with selectivities of 75−95% at 100% conversion; however, long reaction times were required (1−8 days).[491]

Scheme 125. One-Pot Four-Step Process for the Synthesis of Indole Derivatives



Scheme 126. One-Pot Heck Coupling Followed by Hydroformylation



Recently, Sakai et al.[492] reported a one-pot four-step process for the synthesis of indole derivatives using a combination of a heterogeneous and homogeneous catalyst system (Scheme 125).

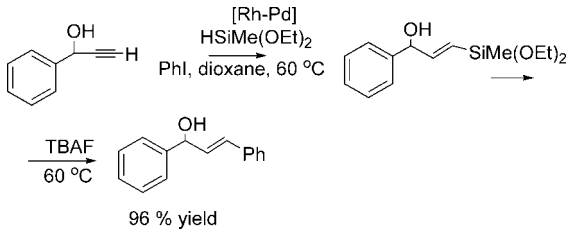
The process involves as the first step the Sonogashira coupling between 2-iodo aniline with trimethylsilylacetylene giving the TMS alkyne derivative. The heterogeneous catalyst for this step was a silica supported Pd catalyst ($PdCl_2$DPP-Si) prepared from $PdCl_2(PPh_3)_2$ and the commercially available silica bonded diphenylphosphine and CuI as cocatalyst. Subsequent addition of tetrabutylammonium fluoride supported on silica (TBAF-Si) gives the 2-amino acetylene derivative which subsequently undergoes the Sonogashira coupling with iodobenzene giving the phenylacetylene derivative. The fourth step is the heteroannulation of the phenylacetylene derivative homogeneously catalyzed by $PdCl_2$. The average yield of each independent step was about 90%, and the total yield to 2-phenylindole was 64%. In addition, the silica supported palladium catalyst was reused effectively in the third step. The authors showed the scope of this one-pot process by preparing different indole derivatives with different functionalized iodides. The methodology has remarkable features, such as many functionalized indoles can be synthesized in a one-pot reaction and it avoids the preparation of the corresponding substituted 1-alkyne.

2.6.4. Heck Coupling Followed by Hydroformylation: One-Pot Synthesis of Aldehydes

Supported liquid-phase catalysts (SLPC) are constituted by a thin hydrophilic film containing organometallic complexes supported on the surface of a high surface area solid. They were proposed by Davis et al.[493] to overcome the drawbacks in separation and recycling of homogeneous metal complexes. SLPC have been used by Bhanage et al.[494] as multifunctional catalysts in simultaneous hydrogenation reactions and sequential reactions involving Heck coupling followed by hydroformilation (Scheme 126).

The one-pot process was performed using a mixture of a supported Pd-complex and a Rh-complex in water film on silicagel (Pd-SLPC and Rh-SLPC). Thus, the Heck coupling between iodobenzene and ethylene catalyzed by the Pd-complex gives styrene in the first step which is subsequently

Scheme 127. One-Pot Hydrosilylation of Alkynes Followed by Hiyama Cross-Coupling



converted into 3-phenylpropionaldehyde and 2-phenyl-propionaldehyde by the Rh-complex, by introducing syngas (CO + H_2) into the reaction system. It was observed that yields of both aldehydes considerably decreased when using (Pd + Rh)-SLPC instead of the mixture (Pd-SLPC + Rh-SLPC), although the yield for the Heck reaction was not affected, indicating that the hydroformylation activity of the Rh-complex is notably changed by the presence of the Pd-complex in the same hydrophilic film.

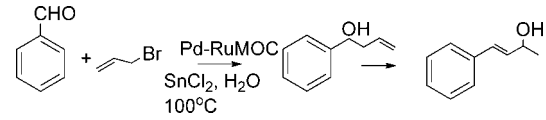
2.6.5. Hydrosilylation of Alkynes Followed by Hiyama Cross-Coupling: Synthesis of Disubsituted (E)-Alkenes

Recently, Thiot et al.[495] reported the use of polyionic gels as an efficient heterogeneous media for metal scavenging. They exploited their properties for preparing a bimetallic catalyst able to perform sequential hydrosilylation−Hiyama cross-coupling leading to *E*-alkenes.[496] The bimetallic [Rh−Pd] catalyst was easily prepared by soaking into an iodide ionic gel an equimolar solution of [$RhCl(PPh_3)_3$] and $Pd(OAc)_2$ in CH_2Cl_2. The catalyst showed excellent stereo- and chemoselectivities leading to (*E*)-alkenes with good yields (Scheme 127). The remarkable stereocontrol is ascribed to a beneficial Pd-catalyzed isomerization from the mixture of stereoisomeric vinylsilanes obtained in the initial hydrosilylation step into the more stable (*E*)-isomer. When N-heterocyclic iodides were used, they had to be added sequentially after completion of hydrosilylation to avoid deactivation of the Rh species. Interestingly, the [Rh−Pd] heterogeneous catalyst also showed higher chemoselectivity than the homogeneous catalytic combination $Pd(OAc)_2$ and [$RhCl(PPh_3)_3$], and no formation of Sonogashira side product was observed. Several (*E*)-substituted and conjugated alkenes, such as hydroxycinnamaldehyde, dienes, and trienes, were synthesized in good overall yields. In addition, the catalyst could be reused displaying complete stereoselectivity to (*E*)-isomer; however, a gradual decrease in yield was observed.

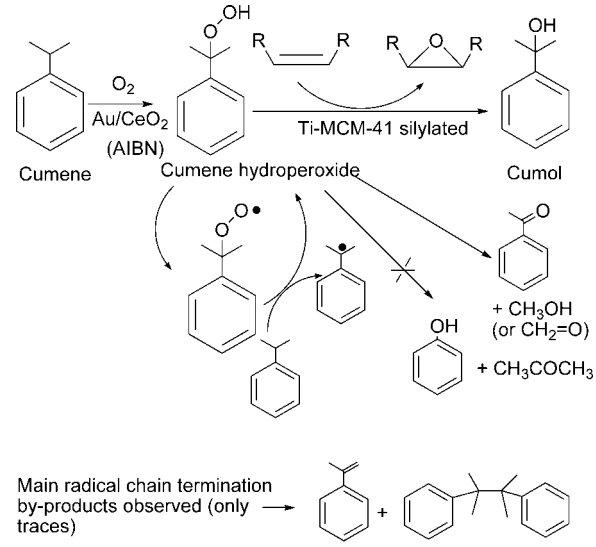
2.6.6. Barbier Reaction Followed by Homoallylic Isomerization: Synthesis of Allylic Alcohols

Recently, Zhang et al.[497,498] reported the preparation of mesoporous silica containing Pd and Ru organometallic active sites (MOC). The catalysts were synthesized using a traditional postsynthesis complexation of organometallic centers to mesoporous silica functionalized with chelating agents and by a surfactant directed assembly approach of silicate clusters of Pd- and Ru-containing organometallic silanes. The catalysts were tested for a two-step cascade reaction which involves a Pd-catalyzed Barbier reaction between benzaldehyde and allyl bromide followed by a Ru-catalyzed homoallylic isomerization (Scheme 128). The reactions were performed at reflux of water and the corresponding allyl alcohol was obtained with moderated yield

Scheme 128. One-Pot Synthesis of Allylic Alcohols



Scheme 129. Alkane Hydroperoxide Formation Followed by Alkene Epoxidation: One-Pot Synthesis of Epoxides

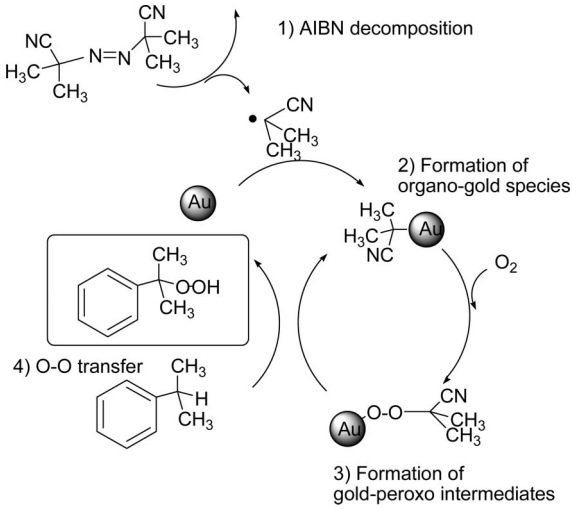


(67%) and selectivity (71%) using the assembled MOC catalyst, while the postsynthesis complexation MOC showed significantly lower catalytic activity. This was attributed to the distorted active site chemical environment during the postsynthesis complexation process. Additionally, the postsynthesis complexation MOC was much less stable than the assembled MOC catalyst, due to the leaching of active sites.

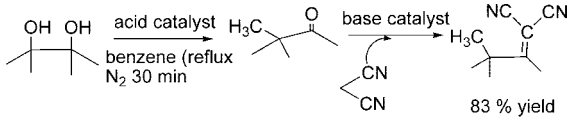
2.6.7. Alkane Hydroperoxide Formation Followed by Alkene Epoxidation: One-Pot Synthesis of Epoxides

Epoxidation of alkenes is an important reaction since epoxides are compounds with high versatility as intermediates in organic synthesis. The most important commercial routes for the synthesis of epoxides (for instance, to produce propylene oxide) involve the use of organic hydroperoxides (*ter*t-butyl, ethylbenzene, and cumene).[499−501] For instance, the production process of propylene oxide using *tert*-butyl hydroperoxide involves a first step in which iso-butane is oxidized with air in a thermal process giving *tert*-butyl hydroperoxide, which in a second step epoxidizes propene using a homogeneous Mo catalyst.[499] Corma et al.[502] have recently reported a new catalytic process in which the two reactions steps, that is, the formation of the peroxide and alkene epoxidation are coupled in a cascade-type reaction starting from the alkene, O_2 and hydrocarbons containing tertiary hydrogen. To do this, a combination of nanoparticulated Au/CeO_2 and silylated Ti-MCM-41 materials in the presence of a hydrocarbon (ethylbenzene, cumene, or 3-methylpentane), and azobis-iso-butyronitrile (AIBN) as a promoter, has been used. AIBN is able to form organo-gold species that promote the formation of hydrocarbon hydroperoxides which in the presence of Ti-MCM-41 epoxidize the alkene in good yields (Scheme 129). Thus, the epoxidation of 1-octene with molecular oxygen (PO_2 = 12 bar) at 90 °C over the AIBN-Au/CeO_2 + sylilated Ti-MCM-41 catalytic system gives an alkene conversion close to 40% of

Scheme 130. Proposed Mechanism for the Formation of Cumene Hydroperoxide



Scheme 131. Pinacol−Pinacolone Rearrangement Followed by Knoevenagel Type Condensation



the maximum conversion attainable, with 90% epoxide selectivity when working with cumene to form the cumene peroxide.

The formation of organo-gold species on Au/CeO_2 was evidenced by flash photolysis, while IR spectroscopy measurements showed the formation of gold-peroxo species as intermediates of cumene hydroperoxide. Taking into account the catalytic and spectroscopic results, the authors propose a mechanism for the formation of cumene hydroperoxide displayed in Scheme 130.

2.7. Multistep Sequential Processes on Acid−base Bifunctional Catalysts

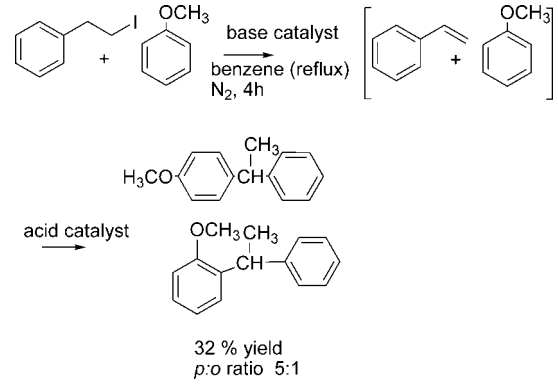
2.7.1. Pinacol−Pinacolone Rearrangement Followed by Knoevenagel Type Condensation

Following the separate entrapment in sol−gel matrices of incompatible catalysts approach for one-pot transformations, Gelman et al.[440] reported a one-pot process involving as a first step the acid catalyzed pinacol−pinacolone rearrangement of 2,3-dimethylbutane-2,3 diol into 2,2-dimethylbutan-2-one followed by base catalyzed condensation of the ketone with malononitrile (Scheme 131). Acid catalyst sol−gel entrapped Nafion was used while the basic catalyst was the organically modified silica sol−gel (Ormosil) carrying $NH_2(CH_2)_2NH(CH_2)_3$. The reaction was performed using a combination of both catalyst at reflux of toluene for 30 min, and after malononitrile was added to the reaction mixture. After 7 h reaction time 100% conversion of the pinacol was achieved with 83% yield of the target compound. The catalyst could be recovered and used in a second run with minimal loss of activity.

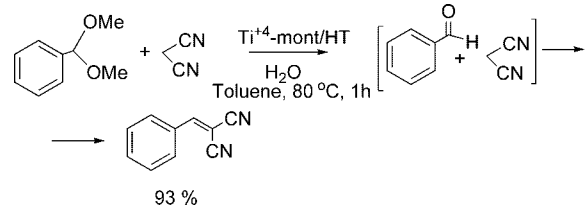
2.7.2. Dehydrohalogenation Followed by Aromatic Alkylation

Using the catalytic system described above, Gelman et al.[440] also performed another one-pot process involving the

Scheme 132. One-Pot Dehydrohalogenation Followed by Aromatic Alkylation



Scheme 133. One-Pot Hydrolysis of Acetal Followed by Knoevenagel Condensation



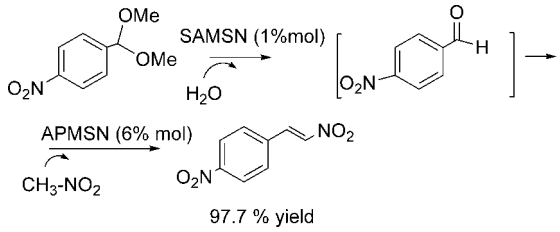
base catalyzed dehydrohalogenation of 2-iodoethylbenzene followed by the acid catalyzed alkylation of anisole (Scheme 132). In this case, all reactants were put together at the beginning of the reaction and 32% yield of the *o/p* isomers was obtained after 4 h reaction time. No reaction was observed when anisole and styrene were treated with entrapped Nafion and homogeneous base, indicating that the base totally quenched the acid.

2.7.3. Hydrolysis of Acetal Followed by Knoevenagel and Henry Condensation

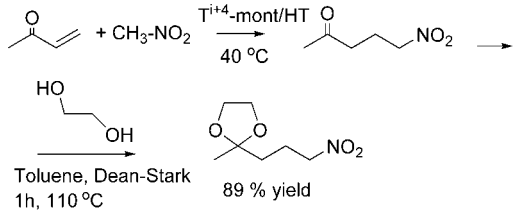
Synthesis of benzylidene malononitrile from benzaldehyde dimethyl acetal and malononitrile was performed in a one-pot procedure using a combination of Ti^{4+}-exchanged Montmorillonite bearing Bronsted acid sites and a non-calcined Al/Mg hydrotalcite (HT) as basic catalyst (Scheme 133).[503] In this process, the Bronsted acid sites catalyze the acetal hydrolysis while base sites in HT promote the Knoevenagel condensation between benzaldehyde and the methylene active compound. The system does not need the addition of water because the successive Knoevenagel condensation produces water which accelerates the deprotection of the dimethyl acetal.

It was shown that in the absence of HT, benzaldehyde was the only product detected while no reaction took place in the absence of Ti^{4+}-exchanged montmorillonite. When either Ti^{4+}-mont or HT was replaced by a homogeneous catalyst such as *p*-toluenesulfonic acid or piperidine, both deacetalization and Knoevenagel condensation scarcely occurred. The one-pot process was extended to other reactants such as methyl cyanoacetate and cyclic acetals bearing trimethylsily groups. In the last case, hydrolysis of acetal occurred without decomposition of the TMS group. Interestingly, when the reaction involves aldehydes having α-protons of carbonyl groups, this protocol depresses the competitive self-aldol condensation of the aldehydes because the concentration is maintained low during the process. Thus, by reacting hexanal dimethylacetal with phenylacetonitrile using

Scheme 134. One-Pot Hydrolysis of Acetal Followed by Nitroaldol Condensation



Scheme 135. One-Pot Michael Addition Followed by Acetalization



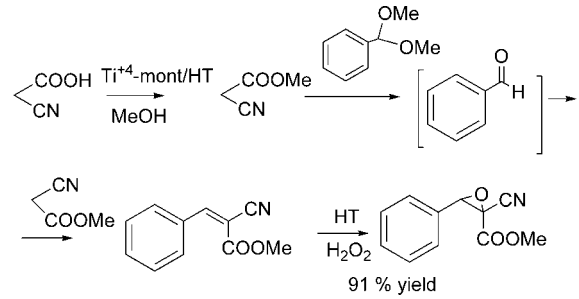
the Ti^{4+}-mont/HT catalytic system, 92% yield of the 2-phenyl-2-octenenitrile is obtained; when hexanal itself is used in place of hexanal dimethylacetal, 71% yield of the target compound along with 2-butyl-2-octenal is obtained. The catalyst mixture was easily recovered by filtration and reused five times with retention of high catalytic activity and selectivity.

Huang et al.[504] have reported the synthesis and characterization of two MCM-41 materials that were functionalized with 4-ethylphenylsulfonic acid (SAMSN) and an aminopropyl functionality (APMSN). Combination of both catalysts was used to perform a cascade reaction which involves acetal hydrolysis on the acid sites of SAMSN catalyst followed by Henry reaction on the basic sites of APMSN (Scheme 134). The acid deprotection of benzaldehyde dimethyl acetal was completed within 24 h in the presence of SAMSN (1 mol %) and APMSN (1−6 mol %), although the conversion of benzaldehyde to the Henry adduct was significantly increased from 43.5% to 97.7% as the amount of base catalyst increased from 1 to 6 mol %. These results suggest that the sulfonic acid functionality is not affected by the presence of APMSN. However, when the reaction was performed using the combination of SAMSN/*tert*-butyl amine or *para*-toluenesulfonic acid/APMSN, acid-basic neutralization occurs and the reaction does not occur.

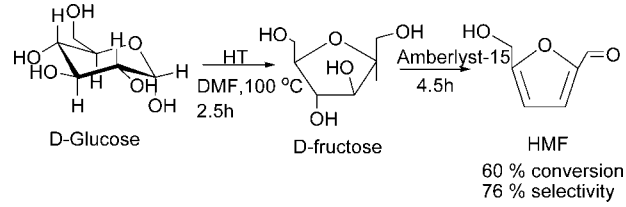
2.7.4. Michael Addition Followed by Acetalization

The Ti^{4+}-mont/HT catalytic system was also used for the tandem Michael addition followed by acetalization.[503] In this case, basic sites of HT promote the Michael addition, while acid sites of Ti^{4+}-mont play a role in the acetalization. Different Michael acceptors and donors where reacted under mild reaction conditions giving the desired Michael adduct. After completion of this first step, the alcohol, ethane 1,2-diol, was added to the reaction system and the corresponding cyclic acetals (1,3-dioxolanes) were obtained in good yields. For instance, nitromethane underwent the Michael reaction with methyl vinyl ketone, followed by acetalization with ethane 1,2-diol to afford 89% yield of 2-methyl-2-(3-nitropropyl)-1,3-dioxolane (Scheme 135). The two-step conventional method gave less than 70% yield.[505]

Scheme 136. One-Pot Esterification Followed by Deacetalization, Knoevenagel Condensation and Subsequent Epoxidation



Scheme 137. One-Pot Synthesis of 5-Hydroxymethylfurfural (HMF) Starting from Glucose



2.7.5. Esterification Followed by Deacetalization, Knoevenagel Condensation and Subsequent Epoxidation

Epoxinitrile, an intermediate for the synthesis of several heterocyclic compounds, was synthesized in high overall yield (91%) by coupling four sequential acid and base reactions (Scheme 136) using the Ti^{4+}-mont/HT catalytic system.[503]

The process involves as the first step the acid catalyzed esterification of cyanoacetic acid with methanol, giving methyl cyanoacetate which subsequently reacts with benzaldehyde (after dimethyl acetal hydrolysis), on the basic sites of the HT catalyst. This step yields the α,β-unsaturated nitrile that in the presence of HT catalyst and hydrogen peroxide affords the corresponding epoxide.

2.7.6. Isomerization of Glucose to Fructose Followed by Dehydration: One-Pot Synthesis of 5-Hydroxymethylfurfural (HMF)

HMF is an important biomass derived compound since it is a significant intermediate for the synthesis of a wide variety of chemicals and alternative fuels.[389,506] HMF is selectively formed from fructose dehydration using liquid[507] or solid acid catalysts.[508,509] While glucose is easily isomerized into fructose under basic catalysis, the reaction is more difficult in the presence of acid catalysts, and the direct production of HMF from glucose is ineffective because considerable amounts of byproduct such as levulinic acid and oligomers are produced.[389] Takagaki et al.[510] have recently reported a new strategy to obtain HMF from glucose which involves the one-pot isomerization of glucose into fructose catalyzed by a solid base followed by dehydration of fructose by a solid acid. An Al/Mg hydrotalcite (HT) consisting of layered clays with HCO_3^- groups on the surface was selected as a basic catalyst, while Amberlyst-15 was chosen as an acid catalyst (Scheme 137).

Reactions were performed using *N*,*N*-dimethylformamide as a solvent and in the presence of equal amounts of acid and base solids (0.1 g) at 100 °C. 64% conversion of glucose with 38% selectivity to HMF was achieved after a 3 h reaction time. The selectivity was increased up to 58% (at

Table 22. One-Pot Synthesis of 5-Hydroxymethylfurfural (HMF) from Mono- and Disaccharides Using HT and Amberlyst-15[a]

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

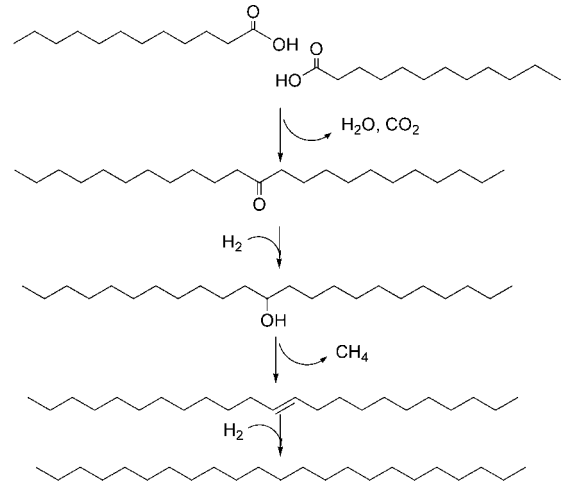
[a] Reaction conditions: substrate (0.1 g), HT (0.1 g), Amberlyst-15 (0.1 g), *N*,*N*-dimethylformamide (3 mL). [b] 100 °C, 3 h. [c] Using 0.2 g of HT, 80 °C, 9 h. [d] 120 °C, 3 h.

73% conversion) by lowering the temperature at 80 °C and increasing the amount of HT. When the reaction was performed in a sequential mode, that is, adding the Amberlyst-15 after 2.5 h reaction time, HMF selectivity was further increased up to 76% at 60% conversion (Scheme 137). The acid−base catalysts were recovered by decantation, washed with DMF, and reused in three consecutive cycles without loss of activity. Interestingly, this catalytic system was applied to the direct formation of HMF from disaccharides. Sucrose and cellobiose were also directly converted into HMF with high selectivity. In the case of sucrose, 93% selectivity at 58% conversion was achieved after 3 h at 120 °C (Table 22). These results indicate that sequential steps (including the hydrolysis of disaccharides by acid sites) isomerization of glucose by the base and dehydration of fructose by the acid sites are effectively achieved. The high selectivity to HMF from disaccharides was presumably attributed to the continuous formation of glucose from the disaccharide, which prevents side reactions.

2.7.7. Fatty Acids Coupling Followed by Hydrogenation: One-Pot Synthesis of Alkanes

Symmetrical ketones can be produced by coupling two carboxylic acid molecules in the presence of a base.[511] When the condensation occurs between two fatty acid molecules, fatty ketones with $2n - 1$ carbon atoms along with one molecule of water and one molecule of CO_2 are produced. In this reaction, 75% of the oxygen in carboxylic acids is eliminated, but if the ketone is subsequently hydrogenated followed by elimination of water and further hydrogenation of the resultant C=C, alkanes of interest as a dieselfuel or biolubricants can be synthesized. This reaction should allow production of liquid transportation fuels from biomass. The cascade process involving a condensation−hydrogenation−dehydration−hydrogenation sequence has been performed with a multifunctional catalyst (Scheme 138).[512] Initially, it was found that basic MgO was able to achieve the ketonization reaction of lauric acid ($C_{12}H_{24}O_2$) with an excellent selectivity to the corresponding ketone (97% at 95% conversion) working in a fixed-bed continuous reactor at 400 °C. In order to perform the cascade reaction, a bifunctional catalytic system bearing the hydrogenating function (Pt, Pd, Ru) and basic sites was designed. However, in order to minimize the reductive decarboxylation of the acid on the metal sites, the process was performed in a two-bed reactor in which the first catalytic bed contained MgO and the second bed contained either a metal/MgO or a metal/Al_2O_3 catalyst. Among the different catalytic systems tested, the highest yield was achieved with the MgO + Pt/MgO system, obtaining up to 70% selectivity to *n*-alkanes at 98.8% conversion. When alumina was used as Pt support, the hydrogenation activity was improved but owing to the acidity of alumina products containing 13−22 carbon atoms coming

Scheme 138. Formation of Tricosane from Two Molecules of Lauric Acid by Ketonic Decarboxylation−Hydrogenation−Dehydration−Hydrogenation Sequence



from the hydrocracking of the carbon chain were produced in larger amounts. With the MgO + Pt/Al_2O_3 system, the total yield of C_{10}-C_{23} *n*-alkanes was close 90%.

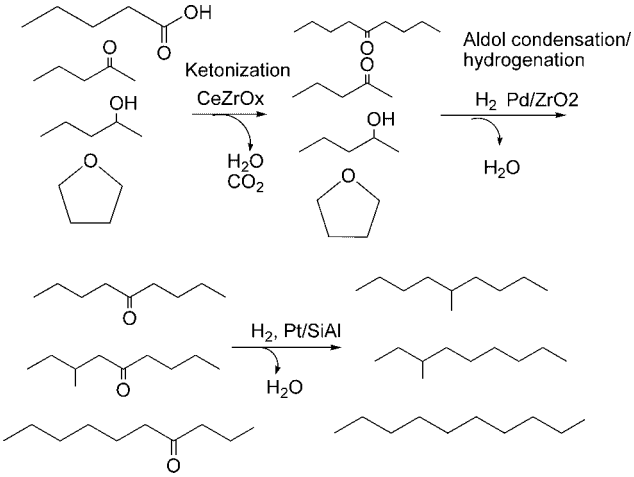
Recently, Dumesic et al.[513,514] have reported the integration in a single reactor the ketonization of carboxylic acids and aldol condensation/hydrogenation steps for the production of liquid fuels. For this integration, the catalyst for aldol condensation must be resistant to inhibition of CO_2 and water produced in the ketonization step. The authors found that Pd/ZrO_2 shows high activity for the aldol condensation, while it showed good resistance toward CO_2 and water inhibition. Then, they studied the feasibility of a double bed catalyst system using a mixture of a carboxylic acid and ketone as feed (20% mol butanoic acid in 2-hexanone) where the upstream catalysts bed (CeZrOx) is employed to carry out the ketonization of the carboxylic acid and the downstream catalyst bed (Pd/ZrO_2) is used to achieve the aldol condensation and hydrogenation of alcohols and ketones.[514] The reaction was performed at 350 °C and 5 bar, with H_2 and a liquid feed of 2-hexanone/butanoic acid. The main compounds obtained were C_{12} species (45% selectivity) which include 7-methyl-5-undecanone and 5-methyl undecane. The system was also applied to convert a feed composed by alcohols, ketones, carboxylic acids, and heterocyclic compounds coming from the catalytic conversion of sugars and polyols over Pt−Re/C catalysts. In this case, the high molecular weight ketones produced by C−C coupling reactions in the double catalytic bed system were subsequently converted to alkanes by dehydration/hydrogenation over a Pt/SiO_2−Al_2O_3 catalyst (Scheme 139). Thus, an aqueous feed containing 60 wt % sorbitol was transformed in liquid alkanes, containing 53% of C_{7+} hydrocarbons with minimal branching.[513]

2.8. Multistep Sequential Processes on Acid−base-Metal Trifunctional Catalysts

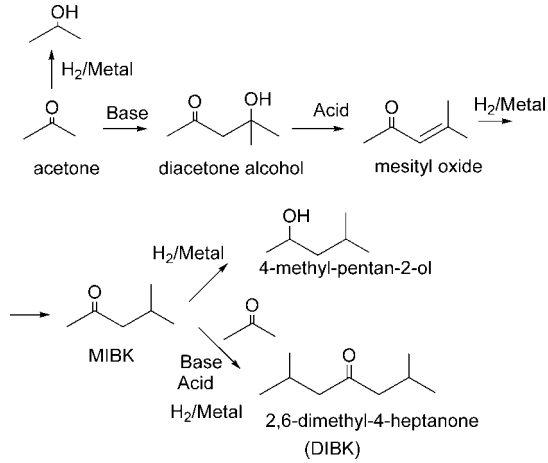
2.8.1. Aldol Condensation Followed by Dehydration and Subsequent Hydrogenation

The mechanism generally accepted for the base catalyzed aldol condensation of aldehydes and ketones involves as a first step a hydrogen abstraction by the basic site leading to the formation of an enolate type-species. Then the nucleophilic attack of the enolate species to the carbonyl group of

Scheme 139. Reaction Pathways for Ketonization, Aldol Condensation/Hydrogenation and Dehydration/ Hydrogenation for Representative C_5 Species



Scheme 140. One-Pot Synthesis of MIBK



another molecule leads to the formation of the aldol intermediate which subsequently dehydrates yielding an α,β-unsaturated carbonyl compound. This mechanism shows that besides the basic sites of adequate strength, acid sites are also required to stabilize the enolate species and for dehydration of the aldol intermediate,[515] though in most cases a weak acidity is sufficient for the dehydration step. Therefore, the preferred heterogeneous multifunctional catalysts for one-pot reactions involving aldol condensation−dehydration and hydrogenation steps are mainly based on metals (Pd, Pt, Ni, Cu) supported on metal oxides or metal mixed oxides, where the basic and acid sites are associated to M^{+n} O^{2-} acid−base pairs,[139] while the supported metal acts as hydrogenating function. Ni and Pd (better) are the preferred metals for the selective hydrogenation of C=C bond of the α,β-unsaturated carbonyl compounds. In this section, some relevant examples of cascade reactions performed with these catalytic multifunctional systems will be presented.

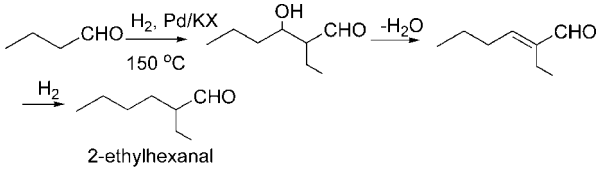
2.8.1.1. One-Pot Synthesis of Methyl Isobutyl Ketone. A variety of materials exhibiting acid/base and hydrogenating properties have been used as catalysts in the one-pot synthesis of MIBK. They include MgO supported Ni, Pd, and Cu,[516−518] Pd on ALPO and SAPO,[519] Pt supported on the basic CsX zeolite[520] and Pd, Ni, and Cu supported on Al/Mg mixed oxides (MgAlO) derived from hydrotalcites.[521−524] In Scheme 140, the main catalytic transformations of acetone using multifunctional acid/base/metal catalysts in the presence of hydrogen are presented. The byproduct affecting MIBK selectivity are the alcohols, 2-propanol, and 4-methyl-pentan-2-ol (produced by an excess of hydrogenating function), DIBK which is formed by successive overcondensation, and C_{9+} compounds which are generated by a stronger basicity of the support and/or a lack of sufficient hydrogenation activity. In general, the best results achieved in terms of conversion and selectivity are similar to those obtained using bifunctional acid/metal catalysts. For instance, using Pd, Ni; Cu and PdCu supported on MgAlO it is generally found that optimum MIBK selectivity is obtained at medium acetone conversion (30−50%) since at higher conversions consecutive reactions occur (Scheme 140).

The adequate balance between the basic and hydrogenating functions plays an important role in the activity and selectivity of the catalyst.[521,523,524] For instance, it has been demonstrated that using Pd/MgAlO with a deficit of hydrogenating function (0.05% Pd), consecutive aldol condensation to C_{9+} and cyclic ketones are the main reactions. However, an excess of hydrogenating function leads to isopropyl alcohol and 4-methyl-pentan-2-ol. It was also found that the particle size of Pd plays a role in selectivity. Thus, the activity of Pd for the hydrogenation of the C=C bond of the mesityl oxide increases when increasing the particle size in the range 1−5 nm, but this increase was much larger for hydrogenating the C=O bonds of acetone and MIBK. That means that C=O hydrogenation is a much more structure sensitive reaction than the hydrogenation of C=C bond. Therefore, an optimum of Pd particle size should exist for which the hydrogenation of the C=C bond in mesityl oxide was fast enough on the one hand while, on the other hand, the hydrogenation of C=O bond in saturated ketones still remains slow. The good balance was achieved with 0.2 wt % Pd/MgAlO with 2−4 nm Pd nanoclusters.[523]

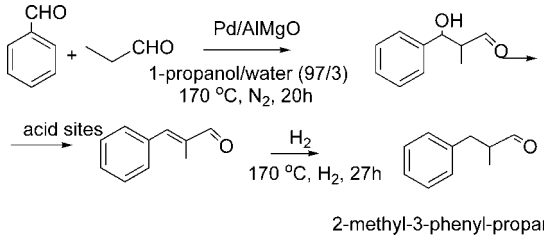
An alternative route to produce MIBK in one-pot using multifunctional catalysts starts from 2-propanol instead of acetone. This has been achieved using Cu^0 loaded on MgAlO.[525,526] The Cu atoms promote the 2-propanol dehydrogenation to acetone which is transformed according to Scheme 140. The initial dehydrogenation of 2-propanol to acetone generates H_2 which is sufficient to hydrogenate the mesityl oxide produced by aldol condensation. By operating at 260 °C in N_2, the Cu/MgAlO catalyst with 6.4% Cu yields 27% MIBK, which is on the order of the better yields obtained with a multifunctional catalyst starting from acetone.

2.8.1.2. One-Pot Synthesis of 2-Ethylhexanal. 2-Ethylhexanal is a raw material for producing octanoic acid and perfumes. This is conventionally obtained through two separate steps which involve the base catalyzed self-aldol condensation of butyraldehyde[527] in the presence of stoichiometric amounts of a strong base (KOH or NaOH) to give 2-ethyl-2-hexenal, which is subsequently hydrogenated to 2-ethylhexanal. During the self-aldol condensation, different byproducts coming from consecutive aldol reactions can be produced depending on the type of base used,[528] while in the hydrogenation step, depending on the hydrogenating catalyst used, different amounts of 2-ethylhexanol are obtained. For instance, using Pd supported on Al_2O_3[529] or on SiO_2,[530] 2-ethylhexanal is formed almost exclusively; however, with Ni Raney both 2-ethylhexanal and 2-ethylhexanol are formed. However, the one-pot synthesis of 2-ethylhexanal from *n*-butyraldehyde in the presence of hydrogen on Pd/KX zeolite gives excellent selectivity to the target compound (Scheme 141).[531−533]

Scheme 141. One-Pot Synthesis of 2-Ethylhexanal



Scheme 142. One-Pot Synthesis of 2-Methyl-3-phenyl-propanal

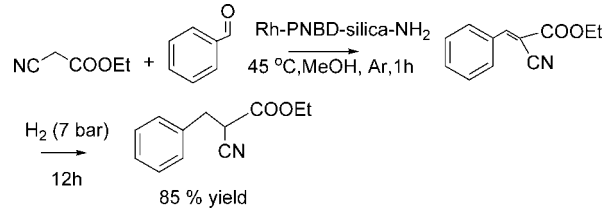


Reactions performed under 1 bar of hydrogen and 150 °C in a fixed-bed reactor with 0.5% Pd/KX zeolite, yielded 2-ethylhexanal in 92−96% selectivity, while the main byproduct obtained was 1-butanol coming from the hydrogenation of butyraldehyde.

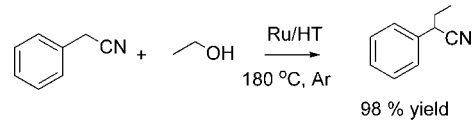
2.8.1.3. One-Pot synthesis of 2-Methyl-3-phenyl-propanal. Following the same approach, 2-methyl-3-phenyl-propanal, a compound widely used as a fragrance[534] was prepared in a procedure starting from benzaldehyde and propanal. In this case, an Al/Mg mixed oxide obtained from hydrotalcite precursor bearing acid and base sites and able to catalyze the consecutive aldol condensation and subsequent dehydration was used as support. Thus, the multifunctional catalyst prepared by supporting 0.2 wt % Pd on the AlMgO was used to perform the reaction between benzaldehyde and propanal under 1 MPa of hydrogen at 130 °C. Benzaldehyde conversion reached 43% after 24 h with 45% selectivity to 2-methyl-3-phenyl-propanal,[535] benzyl alcohol being the main byproduct from the hydrogenation of benzaldehyde. In order to decrease the hydrogenation of benzaldehyde, the one-pot synthesis was performed in a sequential mode, first performing the aldol condensation and dehydration steps under N_2 atmosphere during 20 h, and then introducing hydrogen (Scheme 142).[536] In this case, an optimization of the acid and basic properties of the support was performed. Thus, the best result for the one-pot process was achieved using a Pd/AlMgO sample prepared from Pd nanocolloids. Reactions performed in 1-propanol as a solvent gave also as a main byproduct benzyl alcohol which can account for both hydrogenation of the remaining benzaldehyde and hydrogen transfer on basic sites of AlMgO by the Meerwein−Ponndorf−Verley (MPV) reaction. The addition of water in the reaction medium produces the reconstruction of the Al/Mg mixed oxide into the lamellar hydrotalcite structure which contains Bronsted basic sites. This improves the conversion and inhibits the MPV reaction between propanol and benzaldehyde on the Lewis basic sites of the Al/Mg mixed oxide. Under these reaction conditions, the selectivity to 2-methyl-3-phenyl-propanal was improved up to 77% at 64% benzaldehyde conversion.

2.8.1.4. One-Pot Synthesis of α-Alkylated Nitriles. α-Alkylated nitriles are important intermediates for synthesizing carboxylic acids, amides, ketones, and a variety of biologically active compounds.[537−539] The preferred method for the synthesis of α-alkylated nitriles is the nucleophilic substitution reaction of alkyl halides with nitriles using

Scheme 143. One-Pot Synthesis of α-Alkylated Nitriles



Scheme 144. One-Pot Synthesis of α-Alkylated Nitriles from Nitriles and Primary Alcohols



homogeneous inorganic bases such as NaH and $NaNH_2$ in stoichiometric amounts. However, the toxicity of halogenated substrates, along with the use of strong homogeneous bases, and production of large amounts of waste render this methodology unappropriated. Therefore, the catalytic α-alkylation of nitriles using alcohols or carbonyl compounds instead of halides is a more sustainable protocol. Thus, Goettmann et al.[540] have reported the use of 1-phosphanorbornadiene-rhodium complex (Rh-PNBD) anchored on a mesostructured porous silica matrix combined with additional grafted amino functions in the one-pot synthesis of the α-benzyl ethyl cyanoacetate from benzaldehyde and ethyl acetate. The reaction proceeds in two steps: in the first one the condensation occurs on the basic sites during 1 h under argon, and then the C═C double bond reduction is performed selectively on the metal sites by submitting the reaction mixture at 7 bar hydrogen during 12 h (Scheme 143).

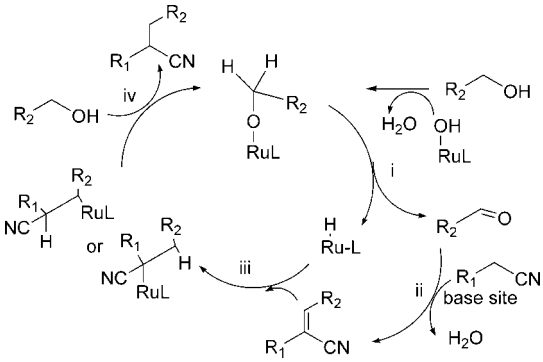
More recently, Motokura et al.[453,541,542] have reported the one-pot synthesis of α-alkylated nitriles starting from alcohols or carbonyl compounds using as catalysts Ru and Pd supported onto Al/Mg layered double hydroxides (hydrotalcites).

The alkylation of nitriles with primary alcohols was studied taking as a reaction model the alkylation of phenylacetonitrile with ethanol in the presence of various supported Ru catalysts.[542] Reactions performed at 180 °C under argon atmosphere using the alcohol also as a solvent showed that a Ru/HT was an active catalyst, giving the corresponding α-ethylated phenylacetonitrile in 98% yield after 20 h reaction (Scheme 144). Other solid base-supported Ru catalysts such as Ru/Al_2O_3, Ru/MgO, $Ru/Al(OH)$,[3] and $Ru/Mg(OH)_2$ gave poor activity.

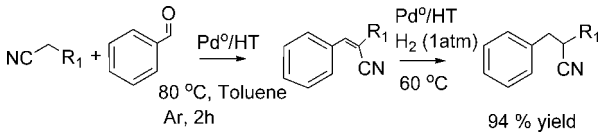
Mechanistic investigations of the process lead to the authors to propose a reaction pathway which involves three consecutive steps (Scheme 145): (i) the oxidative dehydrogenation of the alcohol to aldehyde with the formation of Ru−H species occurs on the metal sites, (ii) the aldol condensation of the nitrile with the aldehyde giving the α,β-unsaturated nitrile at the basic sites, and (iii) the hydrogenation of the α,β-unsaturated nitrile by the Ru−H giving the α-alkylated nitrile (iv).

This one-pot process has several advantages with respect to multistep procedures, for instance, the hydrogen transfer reaction using the Ru/HT under argon avoids the formation of overoxidation products, while the oxidation of primary alcohols using molecular oxygen or hydrogen peroxide often produces carboxylic acids as byproducts. Another important advantage is that when the cross-aldol condensation involves

Scheme 145. Reaction Pathway Involved in the One-Pot Synthesis of α-Alkylated Nitriles from Primary Alcohols and Nitriles



Scheme 146. One-Pot Synthesis of α-Alkylated Nitriles from Nitriles and Carbonyl Compounds



aryl acetonitriles and aldehydes bearing α-protons of the carbonyl group the self-aldol condensation of the aldehyde is suppressed since the concentration of the carbonyl compound is kept low during the reaction. Finally, this one-pot process gives the hydrogen-transfer reaction without any waste, since the aldehyde is consumed as alkylating reagent.

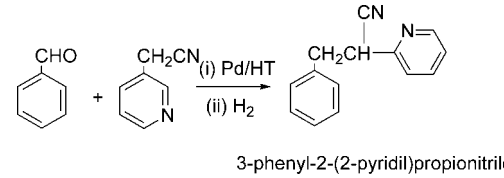
The synthetic scope of the process was extended using a variety of nitriles and primary alcohols, and it was found that while Ru/HT promotes efficiently the α-alkylation of aryl acetonitriles with primary alcohols, the reaction with nitriles of low pK_a values such as malononitrile, cyanoesters, and 2-pyridinylacetonitrile was practically suppressed due to strong coordination to the Ru species. Because of that, the authors developed an alternative route to produce α-alkylated nitriles in one-pot process using Pd supported on HT.[542] The process involves the aldol condensation between nitriles and carbonyl compounds on the basic sites, dehydration of the aldol intermediate on the acid sites giving the α,β-unsaturated nitrile, which is subsequently hydrogenated by the Pd species (Scheme 146).

A variety of substituted benzaldehydes were reacted with ethyl cyanoacetate using the Pd/HT catalyst system giving excellent yields of the corresponding α-benzylated ethyl cyanoacetates; however, chloro and nitro groups were reduced under the reaction conditions used. Also a variety of nitriles which were unreactive with the Ru/HT catalyst system could be used as donors, while the successive hydrogenation of the olefinic double bond occurs selectively leaving intact ester, cyano, amide, and sulfoxide groups. For instance, 3-phenyl-2-(2-pyridil)propionitrile, a precursor of antiarrhythmic agents, was obtained in 99% yield (Scheme 147).

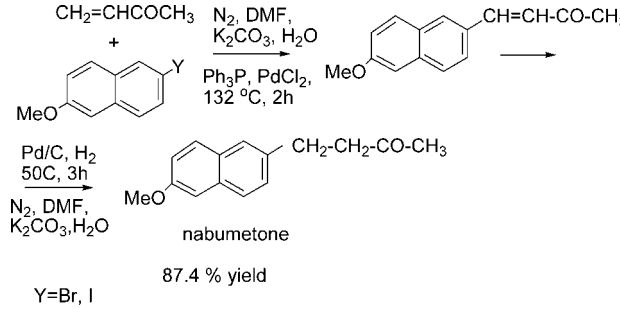
However, the noncalcined HT support was not basic enough to promote the aldol reaction with simple alkane nitriles with high Pka values (≈31).[543]

In addition, α-alkylation of ethyl cyanoacetate with linear and branched aliphatic aldehydes as well as ketones was also performed achieving good to moderate yields of the corresponding α-alkylated nitriles. Particularly, interesting was the alkylation of ethyl cyanoacetate with using an aqueous solution of formaldehyde (37%), giving 2-cyanopropionic

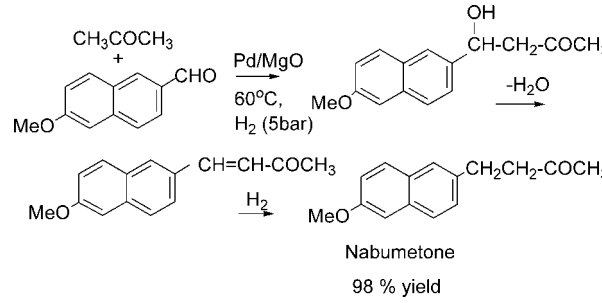
Scheme 147. One-Pot Synthesis of 3-Phenyl-2-(2-pyridil)propionitrile



Scheme 148. Conventional Synthesis of the Anti-Inflammatory Nabumetone



Scheme 149. One-Pot Synthesis of Nabumetone



acid ethyl ester in 91% yield, even in the presence of water. Finally, the Pd/HT catalyst was found to be recyclable with retention of its high catalytic activity and selectivity.

2.8.1.5. One-Pot Synthesis of Nabumetone (4-(6-Methoxy-2-naphthyl)-2-butanone). Nabumetone, 4-(6-methoxy-2-naphthyl)-2-butanone, is a nonsteroidal anti-inflammatory drug widely used as an analgesic in the treatment of several rheumatic and arthritic diseases.[544,545] The main commercial route to the synthesis of Nabumetone involves two steps: first the Heck coupling reaction of 2-methoxynaphthalene halide using homogeneous palladium catalysts[546,547] leading to the corresponding α,β- unsaturated ketone intermediate which is subsequently separated and hydrogenated in a second step to nabumetone using a typical C−C double bond hydrogenation catalyst such as Pd/C (Scheme 148). Yield of Nabumetone results in 87.4%, whereas a considerable amount of salts as well as byproduct are formed by consecutive Heck coupling of the α,β-unsaturated ketone intermediate.

As a green alternative to this process, Climent et al.[548] have proposed the synthesis of Nabumetone through a cascade reaction using a multifunctional heterogeneous catalyst bearing basic, acid, and metallic active sites. Thus, the cascade process involves the condensation of 6-methoxy-2-naphtaldehyde with acetone on a basic site giving the corresponding aldol condensation product, which is rapidly dehydrated on an acid site and the resulting double bond is hydrogenated on the metallic site, to give Nabumetone (Scheme 149). The synthesis of Nabumetone was performed using Pd loaded (1 wt %) over solid catalysts possessing

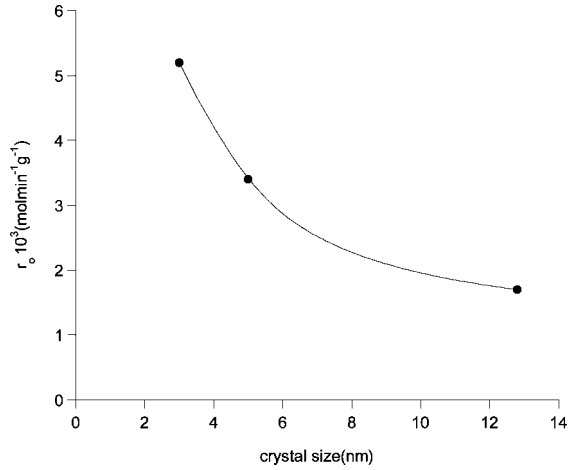


Figure 1. Initial reaction rates for the condensation step using MgO of different crystal sizes. Reaction conditions: molar ratio acetone/aldehyde = 10, 10 wt %, of catalyst with respect to the aldehyde, at 60 °C.

both Lewis acid and Lewis or Bronsted basic sites, that is, a calcined Al−Mg Hydrotalcite (HTc), MgO and a rehydrated Al−Mg mixed oxide (HTr). The results showed that Lewis bases (MgO and HTc) were more selective to Nabumetone than Bronsted bases (HTr). Moreover, MgO exhibited higher catalytic activity than HTc, being regenerated and recycled several times without loss of activity.

In addition the first reaction step, that is, the base catalyzed condensation, was studied, using three MgO samples with different crystallite sizes, and it was found that the initial reaction rate for the condensation step increases exponentially when decreasing the crystallite size of the MgO (see Figure 1). These results indicate that the reaction is structure sensitive;[463] that is, the basic sites associated with corners and edges, which are the most basic, are also the most active for the condensation.

The optimization of the crystal size of MgO allowed an increase in the yield of Nabumetone. Thus, when the one-pot reaction was carried out at 60 °C with the Pd-MgO (3 nm) sample, 98% yield of Nabumetone with 100% selectivity is obtained after 60 min reaction time, while Pd-MgO (13 nm) and Pd-MgO (5 nm) samples exhibited lower catalytic activity (Figure 2).

2.8.1.6. One-Pot Synthesis of Raspberry Scent Fragrance (4-(*p*-Methoxyphenyl)butan-2-one). As was presented above (see Scheme 31), the raspberry scent fragrance (4-(*p*-methoxyphenyl)butan-2-one) can be prepared in a one-pot process through the Heck coupling of iodoanisole with methyl vinyl ketone in the presence of a heterogeneous palladium catalyst (Pd/TiO_2), to yield the intermediate 4-(*p*-methoxyphenyl)buten-2-one which is subsequently hydrogenated to the final compound.[198] However, following the approach presented above for the synthesis of Nabumetone, Climent et al.[549] reported an alternative one-pot catalytic process to synthesize 4-(*p*-methoxyphenyl)butan-2-one (Scheme 150), which involves the aldol condensation between 4-methoxybenzaldehyde and acetone in the presence of PdMgO under hydrogen atmosphere. The condensation yields the corresponding α,β-unsaturated ketone, and the C=C bond is subsequently selectively hydrogenated to the target compound. Thus, when the reaction between 4-methoxybenzaldehyde and acetone was performed using 1 wt % of Pd loaded on the nanocrystalline MgO at 75 °C, 100% of conversion of 4-methoxybenzaldehyde with 99% selectivity

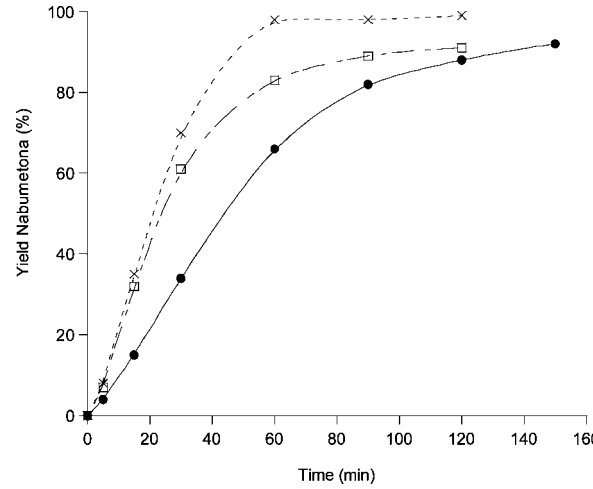


Figure 2. Results of synthesis of nabumetone using: (×) Pd-MgO(3 nm); (□) Pd-MgO(5 nm); (●) Pd-MgO(13 nm). Reaction conditions: molar ratio acetone/aldehyde = 10, 10 wt %, of catalyst with respect to the aldehyde, at 60 °C, at constant pressure of hydrogen (5 bar).

Scheme 150. One-Pot Synthesis of (4-(*p*-Methoxyphenyl)butan-2-one) (2)

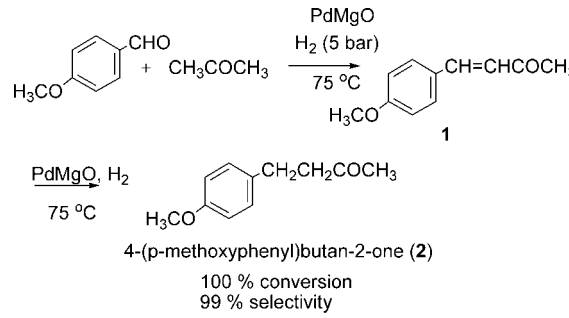


Table 23. Results for the Synthesis of 2 Using Different Multifunctional Catalysts[a]

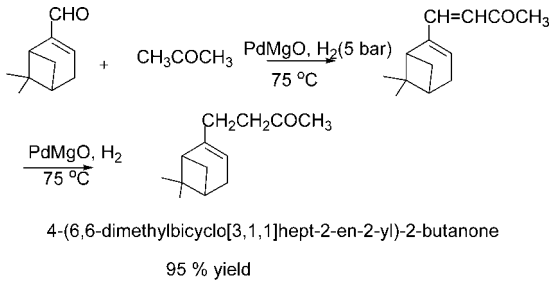
catalysts	r_o[b] 10^4 (mmolmin^{-1} g^{-1})	conversion (%)	yield **1** (%)	yield **2** (%)	selectivity **2** (%)
PdMgO	12.0	100	1	99	99
PdHTc[c]	5.0	89	25	62	68(2)
PdHTr[d]	9.7	95		95	100

[a] Reaction Cconditions: 4-methoxybenzaldehyde (3.8 mmol), acetone (37 mmol); 75 °C catalyst 38 wt % respect to 4-methoxybenzaldehyde. Conversion and yield at 75 min reaction time. In brackets is the percentage of Michael adduct. [b] r_o = rate of disappearance of 4-methoxybenzaldehyde. [c] Calcined hydrotalcite. [d] Calcined-rehydrated hydrotalcite.

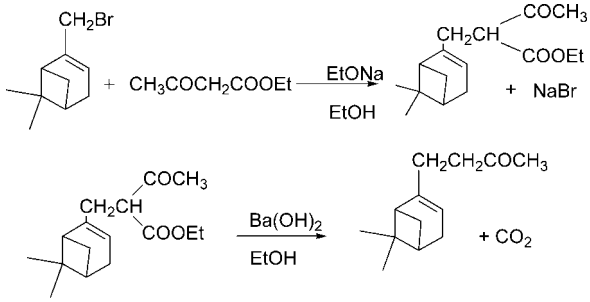
to 4-(*p*-methoxyphenyl)butan-2-one was obtained within 75 min (Table 23). Also Pd supported on calcined-rehydrated Al/Mg hydrotalcite catalyst (PdHTr) exhibited excellent activity and selectivity. However, an important decrease in activity upon regeneration was found with the PdHTr. In contrast, a Pd-MgO sample was subjected to four cycles of reaction-regeneration (calcinations)-reaction achieving in all cases 100% conversion and similar selectivity to 4-(*p*-methoxyphenyl)butan-2-one.

Interestingly, when the *E* factor ($kg_{waste}/kg_{product}$) for the global process that includes the manufacturing of the reactants was calculated, and compared with those obtained through the Heck route and by conventional methods using homogeneous catalysts, it was demonstrated that this new cascade process provides about 3 and 10 times less waste, respectively.

Scheme 151. One-Pot Synthesis of 4-(6,6-Dimethylbicyclo[3,1,1]hept-2-en-2-yl)-2-butanone



Scheme 152. Conventional Synthesis of 4-(6,6-Dimethylbicyclo[3,1,1]hept-2-en-2-yl)-2-butanone



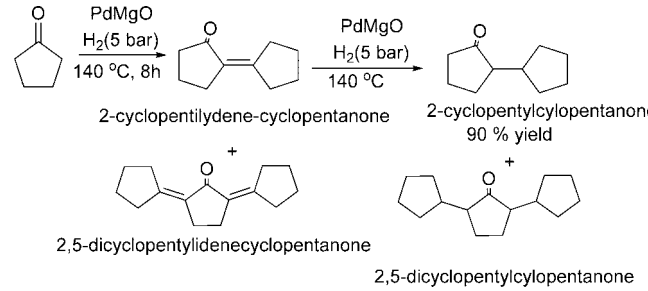
2.8.1.7. One-Pot Synthesis of 4-(6,6-Dimethylbicyclo[3,1,1]hept-2-en-2-yl)-2-butanone. Following the above methodology, 4-(6,6-dimethylbicyclo[3,1,1]hept-2-en-2-yl)-2-butanone, a terpenic compound used as a perfume and with activity as insect juvenile hormone,[550] was synthesized in a one-pot process using Pd supported on nanocrystalline MgO.[549] The reaction involves the aldol condensation between myrthenal and acetone, followed by dehydration of the aldol formed, and double bond selective hydrogenation. The reaction performed under mild reaction conditions gave the target compound in 95% yield (Scheme 151).

It is interesting to notice that the conventional preparation of 4-(6,6-dimethylbicyclo[3,1,1]hept-2-en-2-yl)-2-butanone is carried out through the acetoacetic reaction between the myrthenyl bromide and ethyl acetoacetate in the presence of stoichiometric amounts of sodium ethoxide at reflux temperature of ethanol yielding after 4 h 78% of ethyl 3-oxo-2-(2-pinen-10-yl) butyrate. Thus, in a second synthetic step, the keto-ester is decarboxylated by refluxing during 18 h with barium hydroxide in aqueous ethanol giving the target compound in 85% yield (Scheme 152).[551] This synthetic route generates 3.4 times more waste than the one-pot process, illustrating that process intensification by means of multifunctional solid catalysts can open new environmentally more benign routes for the synthesis of fine chemicals.

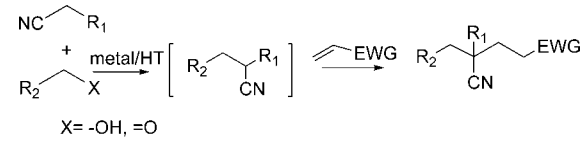
2.8.1.8. One-Pot Synthesis of 2-Cyclopentylcylopentanone. 2-Cyclopentylcylopentanone (Scheme 153) with a jasmine-like smell is a compound used for perfume or flavoring[552] and as a wood preservative.[553] The preferred method for the synthesis of 2-cyclopentylcylopentanone in terms of yield and availability of starting materials involves the condensation of cyclopentanone in the presence of a basic catalyst (NaOH, KOH, or sodium) followed by the hydrogenation of the resulting 2-cyclopentilydene-cyclopentanone in the presence of a hydrogenating catalysts such as Pd/C.[552]

It is interesting to point out that the main drawback associated with the self-condensation of cyclopentanone using homogeneous catalysts is, in general, the low yields of 2-cyclopentilydene−cyclopentanone achieved, because the self-condensation product can further condense with a second cyclopentanone molecule to form the highly conjugated trimer adduct (2,5-dicyclopentylidenecyclopentanone) that, after hydrogenation, is converted into 2,5-dicyclopentylcylopentanone. Because of the high thermodynamic stability of the conjugated trimmer adduct, this compound is formed in amounts between 30 and 50%[554] resulting in a very low selectivity to the target compound. However, when the reaction is performed through a cascade process (Scheme 152) using the Pd-MgO catalyst in the presence of hydrogen, higher selectivity to the 2-cyclopentylcylopentanone was achieved (91% selectivity at 98% cyclopentanone conversion),[549] demonstrating the advantage of the one-pot cascade process using PdMgO catalyst. In this case, it appears that the fast hydrogenation of the intermediary 2-cyclopentilydene-cyclopentanone diminishes the rate of the subsequent aldol condensation that leads to the undesired highly conjugated trimmer. The calculated *E* factor of the cascade process was 16 times lower than that of the conventional process, showing that the one-pot cascade reaction not only is a much more environmental benign route, but higher selectivities can be achieved with multifunctional catalysts, by adjusting the relative rates of the different consecutive steps.

Scheme 153. One-Pot Synthesis of 2-Cyclopentylcylopentanone



Scheme 154. Sequential α-Alkylation of Nitriles Followed by Michael Addition

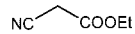
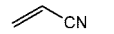
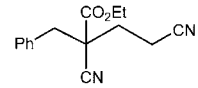
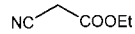
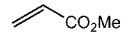
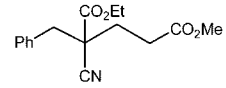
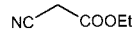
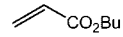
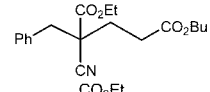
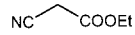
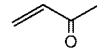
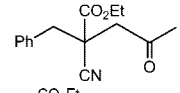
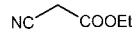
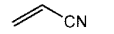
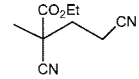
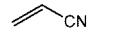
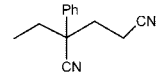
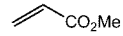
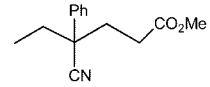
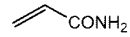
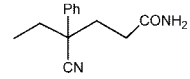


2.8.2. α-Alkylation of Nitriles Followed by Michael Addition: One-Pot Synthesis of α,α-Dialkylated Nitriles

As we have presented previously, Motokura et al.[542] showed that Ru/HT and Pd/HT multifunctional catalysts were active and selective for the synthesis of α-alkylated nitriles using alcohols or aldehydes as alkylating agents. With these catalytic systems, the authors performed the one-pot synthesis of glutaronitrile derivatives by the Michael reaction, catalyzed by the basic sites, of electron-deficient olefins with α-alkylated nitriles which were produced previously by the Metal/HT catalyzed α-alkylation (Scheme 154).[542]

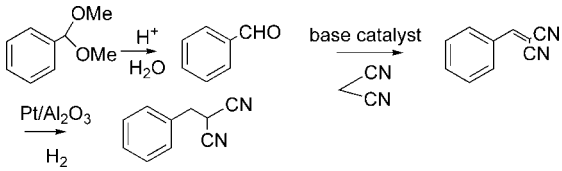
Table 24 shows the results of consecutive α-alkylation followed by the Michael reaction for various substrates using Pd/HT and Ru/HT catalysts. They are powerful multifunctional catalysts for the one-pot synthesis of highly substituted glutaronitrile derivatives.

Table 24. One-Pot α,α-Dialkylation of Nitriles using Metal/HTs[a]

Entry	Nitrile	Aldehyde or Alcohol	Olefin	Method	Product	Isolated Yield[b] (%)
1		PhCHO		A		94
2		PhCHO		A		98
3[c]		PhCHO		A		79
4[d]		PhCHO		A		79
5[e]		HCOH		A		63
6[f]		EtOH		B		93[g]
7		EtOH		B		80
8		EtOH		B		84[g]

[a] Reaction conditions: Method A: (i) nitrile (1 mmol) carbonyl compounds (1 mmol), Pd/HT (0.1 g; Pd 0.01 mmol), toluene (3 mL), 2 h, 80 °C, Ar. After completion of the aldol reaction, the reaction mixture was further treated at 60 °C for 1 h under H_2 (1 atm). (ii) Olefin (1.5 mmol), 5 h, 70 °C, Ar. Method B: (i) nitrile (1 mmol), alcohol (2 mL), Ru/HT (0.15 g; 0.0075 mmol), 180 °C, 20 h, Ar. (ii) Olefin (3 mmol), DMSO (2 mL), 150 °C, 1 h, Ar. [b] Overall yield based on nitrile. [c] At 110 °C, 12 h for Michael addition. [d] A solution of methyl vinyl ketone (1.5 mmol) in toluene (2 mL) was slowly added over 6 h and further reacted for 4 h. [e] DMF (3 mL) was used as solvent. [f] DMF (3 mL) was used as solvent for Michael addition. [g] Determined by GC by an internal standart.

Scheme 155. Sequential Acetal Hydrolysis Followed by Knoevenagel Condensation and Subsequent Hydrogenation

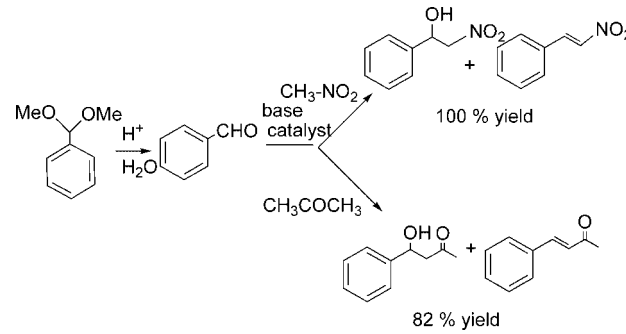


2.8.3. Acetal Hydrolysis Followed by Aldol Condensation and Subsequent Hydrogenation

The use of multiple combinations of catalysts instead of a single material bearing multifunctional sites to perform cascade reactions can be problematic from the point of view of recovering the pure form of each catalyst. Phan et al.[555] reported the possibility to separate the multiple catalysts used in one-pot cascade reactions in the pure form, by using magnetic, gravimetric, and membrane methods. This allows reusing the recovered catalyst in subsequent unrelated reactions. Superparamagnetic spinel ferrite nanoparticles functionalized with amino groups was used as a basic catalyst in combination with a sulfonic acid polymer resin and Pt/Al_2O_3 enclosed in a membrane in the three-step reaction sequence deacetalization-Knoevenagel condensation−hydrogenation (Scheme 155).

All components were added to the reactor at time zero, and the reaction was started at 1 atm total pressure; after 1 h reaction the hydrogen pressure was increased to 1000 psig to carry out the final step of the reaction. The overall yield of the final dinitrile was 78%, although 100% yield was obtained in the absence of membrane, indicating that

Scheme 156. Sequential Acetal Hydrolysis Followed by Aldol Type Condensations



the use of the membrane decreases the hydrogenation rate due to transport effects. The acid resin and the magnetic basic catalyst were recovered by affixing a small permanent magnet externally to one wall of the vessel. While the nonmagnetic acid catalyst was removed by decantation, the magnetic nanoparticle base catalyst was held stationary in the vessel by the magnet. Recovered catalysts were used in two other different one-pot reactions involving acetal hydrolysis and condensation (with acetone or nitromethane) with excellent results (Scheme 156).

3. Conclusions and Future Trends

It is apparent that intensification in chemical and most specifically in catalytic processes is of growing in interest among researchers. This is not only because of the potential economical impact if translated into industrial application,

but also because it is challenging and attractive to achieve the molecular design of a catalyst that allows cascade type reactions to be performed.

If multistep and cascade reactions have been widely performed with homogeneous catalysts, this is far more complicated when using solid catalysts. It has been presented that, either with mono- or multifunctional solid catalysts, it is mandatory to have well-defined uniform sites, for achieving selective multistep process. To do that, it is important to start from, as deep as possible, knowledge of the mechanism of the reactions involved. Only through this knowledge we will be able to rationalize the active sites required and to try to synthesize the corresponding solid catalyst.

This is so regardless whether catalytic sites for the multistep reaction will be acid (Bronsted or Lewis), basic (Bronsted or Lewis), metallic, oxides, or combination of the above. Furthermore, and even if we did not emphasize it in the review, selection or the design of the most appropriate reactor will help to achieve the maximum yield of the catalysts for the one-pot multistep reactions.

We believe that working in this field can be more satisfying if expertise from organic, physical chemistry, materials science, and engineering could be combined. If a symbiosis among the different disciplines is achieved, the reward will be not only to increase our fundamental knowledge of chemical reactivity and catalysis but to transfer that knowledge into industrial applications.

Process intensification and the use of ecofriendly, recoverable solid catalysts can help to achieve a more sustainable chemical process, with the corresponding positive impact of chemistry in our society.

4. Acknowledgments

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5.0. References

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