Green Chemistry

TUTORIAL REVIEW

Examples of heterogeneous catalytic processes for fine chemistry

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Fine chemicals are highly pure substances that are commercially produced by chemical reactions for highly specialized applications. In most cases, however, these reactions involve stoichiometric and highly polluting steps. A possible solution is the development of processes using enzymatic, homogeneous or heterogeneous catalysts. In this review, selected examples of clean heterogeneously-catalyzed reactions applied to the synthesis of fine chemicals are reported for the purpose of highlighting the growing need for more sustainable industrial processes, *i.e.*, processes that produce minimal waste and avoid as much as possible the use of toxic and/or hazardous reagents and solvents. A thorough knowledge of catalyst properties, reaction conditions and interactions with the reacting substrate are essential for optimizing the synthesis, thus making it possible to move on from laboratory to industrial production.

1. Fine and sustainable chemistry: a difficult marriage

The term "fine chemicals" is based on a three-tier segmentation of the world of chemicals into commodities, fine chemicals and speciality chemicals.[1,2] Commodities, for which the driving force is mainly the price, are large-volume, low-price, homogeneous and standardized chemicals produced in dedicated plants (Table 1). A further sub-category is represented where both price and end-use market must be considered.

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Fine chemicals are complex, pure chemical substances produced in limited quantities ($\leq 10\,000$ metric t y^{-1}) in multipurpose plants and by multistep batch processes; they are sold for more than 8 € kg^{-1} based on exacting specifications.[1] However, both of these numbers are somewhat arbitrary and controversial. Thus, key factors in fine chemistry are high market prices, with a corresponding high added value, and relatively low production volumes. Lastly, speciality chemicals are formulations of chemicals containing one or more fine chemicals as active ingredients, being mainly identified according to their performance. They are usually sold under brand names and suppliers have to provide product information. For example, in the life science industry, the active ingredients of drugs are fine chemicals, whereas the formulated drugs are specialities.

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Table 1 Main features of commodities, fine chemicals and specialties[1]

Commodities	Fine chemicals	Specialities
Single pure chemical substances	Single pure chemical substances	Mixtures
Produced in dedicated plants	Produced in multipurpose plants	Formulated
High volume/low price	Low volume (< 1000 t y^{-1}) and high price (> 8 € kg^{-1})	Undifferentiated
Many applications	Few applications	Undifferentiated
Sold on specification	Sold on specification: "what they are"	Sold on performance: "what they can do"

The concept of green chemistry was introduced in the early 1990s in the USA as a new philosophy in chemical research and engineering to encourage the design of products and processes that minimize the use and generation of hazardous substances.[3] Anastas and Warner[4] developed the 12 principles of green chemistry, which help to explain what the definition means in practice. However, it must be noted that many chemical industries had long previously followed such rules, and already by the beginning of the 1980s a lot of research in this field had been done and various processes commercialized.[5–17] About a decade ago, Hutzinger[18] discussed the topic of "green *versus* sustainable" chemistry, by pointing out that the meaning of the two terms is different: sustainable chemistry is the maintenance and continuation of an ecologically-sound development, whereas green chemistry focuses on the design, manufacture and use of chemicals and chemical processes that have little or no pollution potential or environmental risk, and are both economically and technologically feasible. Thus, sustainable chemistry proposes an integrated vision where chemistry, sustainability and innovation are three key components for the future of society. These concepts are an integral part of the strategy for the future F[3] (future, fast, flexible) factory, an innovative idea by the European Technology Platform on Sustainable Chemistry for the future of the chemical industry.[3]

Contrary to common belief, the production of fine chemicals does not generally fit the requirements of sustainable industrial chemistry because it generally involves multi-step syntheses and partly due to the widespread use of stoichiometric reagents with a consequent low atom economy (*i.e.*, the percentage of atoms in reagents that end up in the product) and a huge amount of by-products per weight unit of product (or *E*-factor value), which increases substantially going downstream from bulk to fine chemicals (Table 2).[19,20] Furthermore, it must be pointed out that process intensification in the synthesis of fine chemicals by using one-pot multistep processes with multifunctional solid catalysts allows the *E*-factor to be decreased by at least one order of magnitude.[21–24]

However, comparing alternative routes only on the basis of the amount of waste produced is an over-simplification, since a more accurate assessment has to take both the amount and the nature of the waste into account. Further refinement leads to the concept of environmental profile analysis, in which processes are assessed weighting against raw material and energy consumption, waste generation and safety aspects. More recently,[25,26] the concept of "production-integrated environmental protection" has been proposed for innovative chemical processes, taking both economic and ecological factors into account. The main aim of these technologies is the reduction or avoidance of waste by carrying out the integrated measure in production closely with waste management.

Also considering that its low product tonnage is conducive to high flexibility and availability for innovation, fine chemistry represents a promising subject for researchers to design and develop environmentally-friendly chemical processes. Therefore, it is not surprising that a relevant number of reviews are present in the literature concerning the application of heterogeneous catalysts for the sustainable production of intermediate and fine chemicals (see, for example, refs. 1, 3, 5–17, 21–29). In this review, selected examples of heterogeneous catalytic processes applied to the synthesis of fine chemicals are presented to show that a thorough knowledge of catalyst properties, reaction conditions and interactions with reacting substrates is not only fundamental for optimizing syntheses but is also essential for moving on from laboratory to industrial production. It is worth noting that several well known catalysts already applied in other reactions may have a new life in fine chemistry.

2. A new life for well known catalysts

Although clay minerals (or clays), acid-treated or pillared clays, and zeolites have already been applied in a large number of catalytic processes,[3,5–13,15–17,21,22,25–27,29–32] new and interesting applications also continue to be found in fine chemistry for materials developed for more trivial applications. In fact, increasingly stringent environmental issues and process optimization require the substitution of liquid acids with more friendly solid catalysts, because of their wide range of compositions, used in a catalytic amount (unlike AlCl$_3$ and with the possibility of recycling) with easily manipulated properties, low cost, *etc*. Cornelis and Laszlo,[32] stressing the advantages of Friedel–Crafts clay catalysts (high substrate selectivity, improved yield, conversion and reaction times, and a reduction in the amount of catalyst

Table 2 *E*-factor values for different chemical industries[19,20]

Industry segment	Production volume (t y^{-1})	*E*-factor value (kg$_{byproduct}$/kg$_{product}$)
Oil refining	10^6–10^8	*ca.* 0.1
Bulk chemicals	10^4–10^6	<1–5
Fine chemicals	10^2–10^4	5–50
Pharmaceuticals	10–10^2	>100

by up to a factor of 2000), claimed that their scientific work was the basis for the development of a commercial line of catalysts (Envirocats by Contract Chemical UK). Solid acids hold their acidity internally, and are thus easy and safe to handle, although their acidity level is very high, sometimes ten-fold higher than that of concentrated sulfuric acid. Lastly, being mainly derived from silicon and aluminum oxides, they can be disposed of easily and safely.

By replacing (for example in acylation reactions) a homogeneous AlCl₃ catalyst with solid acids, 100-times less aqueous discharge and 10-times less solid waste may be achieved, referring to the weight unit of the acylated product. Furthermore, solid acid catalysts considerably reduce the formation of by-products while operating with activated substrates (for example, thiophene, mesitylene, etc.).[11,31,33] Activated substrates give the best catalytic performance, although the results also depend on the strength and stability of the carbocations formed (Scheme 1). For the catalysts studied, the following scale of reactivity was detected: acid-treated clays > pillared clays > clays > zeolites, as a function of the accessibility and acidity of active sites, surface area and the nature of the constituent pillar.[11,33] The interesting behavior of commercial acid-treated clays was confirmed by the acylation of thiophene with *p*-fluorobenzoyl chloride using F-13 catalysts (Engelhard USA) with almost complete formation of the 2-isomer (yield = 91%), a useful intermediate of a pharmaceutical active ingredient, and only traces of the 3-isomer. The main by-product observed was *p*-fluorobenzoic acid due to hydrolysis of the acylating agent by residual water present on the catalyst, while other by-products due to side reactions of thiophene dimerization and/or polymerization did not seem to be formed, unlike that observed with AlCl₃.
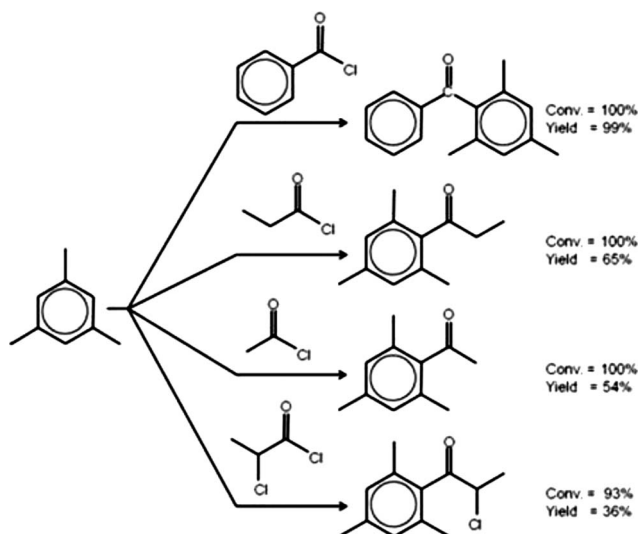
Scheme 1 The role of acyl chloride in the reaction with mesitylene using K10 (Süd–Chemie) as the catalyst (temperature = 473 K; time = 15 min). Conversion refers to the acyl chloride.[11,33]

Another interesting and new application is the environmentally friendly synthesis by the Fries rearrangement of hydroxyphenylalkylketones (useful intermediates in the synthesis of pharmaceuticals, speciality polymers, *etc.*) while operating in the vapor phase and with different catalysts (zeolites or

Nafion/silica).[8,9,11,34–39] The roles of both the reaction conditions and the behavior of different solid acid catalysts were first studied and correlated with the catalyst features.[34,35,38] High values of both phenylacetate feed conversion and, surprisingly, selectivity for 2-hydroxyacetophenone (2-HAP), together with a low amount of by-products [mainly phenol (PhOH) and 4-hydroxyacetophenone (4-HAP)] (unlike the previously reported high selectivity in 4-HAP[34,36,37]), were obtained by using a commercial pentasyl-type zeolite [T 4480, developed by Süd-Chemie (D) for the oligomerization of olefins], which also showed good catalytic performances with longer chain esters (Fig. 1) as well as a good regenerability (Fig. 2).[35,38]
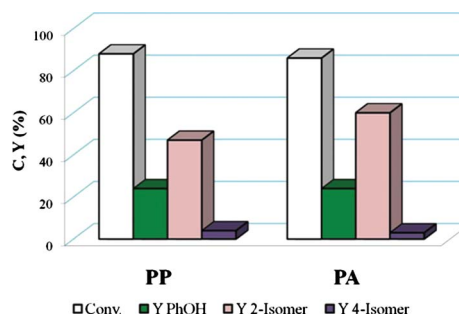

Fig. 1 Catalytic activity of the T 4480 zeolite (Süd-Chemie) in the conversion of phenylacetate (PA) and phenylpropionate (PP) (reaction time = 4 h; T = 583 K; WHSV = 0.50 h⁻¹; phenylester/He = 10:90 mol/mol).[38,39]
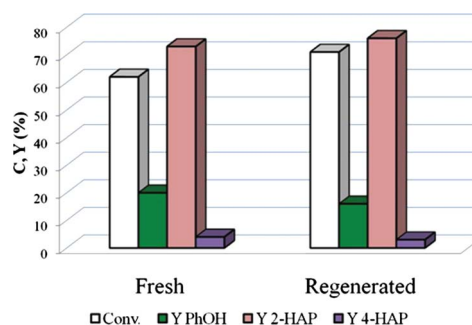

Fig. 2 Catalytic activity of the T 4480 zeolite (Süd-Chemie) before and after regeneration by calcination at 873 K for 4 h (reaction time = 4 h; T = 583 K; WHSV = 0.50 h⁻¹; phenylacetate (PA)/He = 10:90 mol/mol).[38,39]

This unusual behaviour, explained by FTIR spectroscopy[39] or by using probe molecules (acetonitrile and pivalonitrile) that evidenced the peculiar features of this modified H-ZSM5 zeolite, are probably related to its specific preparation from primary crystallites that are mutually joined by finely dispersed alumina that is obtainable by the hydrolysis of Al-organic compounds,[40] with a key role being played by the different binders used to prepare the extrudates (Table 3). It has been hypothesized[39] that in T-4480 zeolite, the reaction occurs on the external surface in the secondary porosity due to agglomerates, with partial coverage by a layer of terminal silanols, a lowering of the acidity and with the formation of a small amount of defects, represented by enlarged channels. The alumina binder did not hinder access to cavities but limited the number of defects and their availability.

On the other hand, many examples of the *O*-acetylation of different organic substrates have been reported in the literature

**Table 3** Activity of the T-4480 catalyst as a powder or extrudates[39]

Catalyst	PA conversion (%)	Selectivity (mol/mol%)		
		2-HPA	4-HPA	PhOH
T-4480	86	71	2	27
T-4480/Al$_2$O$_3$	75	45	4	23
T-4480/SiO$_2$	44	27	5	63

in the last few years using cheap and commercially available heterogeneous catalysts.[41–49] Hydroxyl group acetylation is an important step in the synthesis of fine chemicals, mainly for the protection of functional groups.[41,42] Acidic clays functionalized by gold nanoparticles show interesting results in *O*-acetylations of phenol and naphthol performed in water (yield > 90%), while the yield decreased for highly substituted phenols.[41] Shimizu *et al.*[43] showed the activity of acidic clay K-10 (Süd-Chemie D) exchanged with different cations in the *O*-acetylation of alcohols, with yields close to 100%.

Good results have also been obtained using a B-doped ZrO$_2$ catalyst in mild conditions to *O*-acetylate different aromatic alcohols.[42] Farhadi *et al.*[44] investigated a wide range of alcohols as possible substrates; spinel-type zinc ZnAl$_2$O$_4$ nanoparticles are very active towards linear, cyclic, aromatic and sterically-hindered alcohols, and the yields obtained were higher than 80% working in the absence of solvent. An interesting class of compounds to be used as renewable feeds are sugars, and many papers are present in the literature on the *O*-acetylation of sugars using heterogeneous catalysts. The already cited inexpensive solid acid K-10 has been shown to be an efficient catalyst for the per-*O*-acetylation of mono-, di- and trisaccharides. Pyranose forms accounted for yields of 75–100% in the *O*-acetylated products.[45] Similar results have also been observed using FeSO$_4$[46] operating in acetic anhydride. Finally, a further class of catalysts for *O*-acetylation is represented by acids immobilized on solid supports, like SiO$_2$; for example, interesting results have been obtained using immobilized HClO$_4$[47] and H$_2$SO$_4$.[48,49]

A further promising example of a novel clean technology using well known catalysts is the dehydration of 2,5-dimethyl-2,4-hexanediol (DMED) to 2,5-dimethyl-2,4-hexadiene (tetramethylbutadiene, TMBD). This technique—by a reaction with an appropriate diazo-acetic ester—gives rise to chrysanthemic acid, the main intermediate for the industrial production of pyrethroids, which, together with pyrethrins, represent the best known and safest classes of natural or synthetic insecticides, with wide domestic and agricultural applications. The most significant alternative for preparing TMBD is the vapor phase synthesis of *i*-butyraldehyde with *i*-butene according to the Prins reaction (Scheme 2) on different oxides; it, however, shows low conversion values and the formation of high amounts of by-products with rapid catalyst deactivation.[50]

The dehydration of DMED is a very promising alternative, considering that it is widely available on the market and has a significantly lower price than TMBD. However, in vapor phase synthesis, the surface acidity has to be finely tuned in order to prevent the formation of huge amounts of useless isomers. Preliminary screening tests[51] were performed on commercial acid catalysts (oxides, zeolites, clays and acid treated clays) by using the reaction conditions previously reported in literature[52]
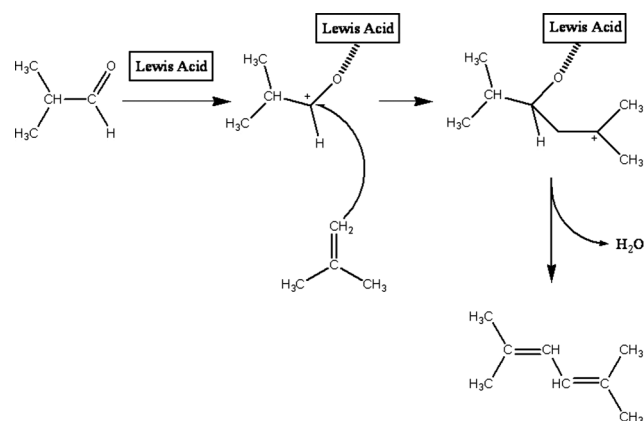
Scheme 2 The mechanism of TMBD synthesis by the Prins reaction.

(Fig. 3), with the following detailed set-up of reaction conditions (temperature, liquid hourly space velocity (LHSV) value and feed concentration).
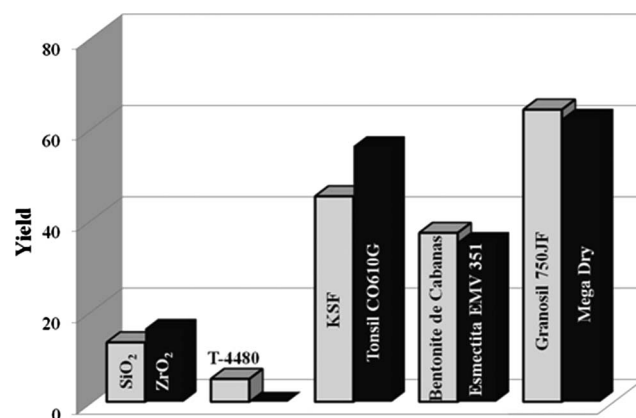
Fig. 3 Yield of tetramethylbutadiene (TMBD, preliminary screening tests) (catalyst = 9 g; *T* = 543 K; *P* = 0.1 MPa; feed = 2.8 M dimethyl-2,4-hexanediol (DMED)/CH$_3$OH solution in an N$_2$ flow; LHSV = 0.46 h^{-1}).[51]

In the best reaction conditions identified, yields higher than 80% were obtained by using some commercial and very inexpensive clay-based adsorbents or catalysts for the removal of olefins from jet fuel (Mega Dry and Granosil 750 JF, developed by Süd-Chemie), with a stable activity of up to 400 h time-on-stream (Fig. 4).[51,53] These results were significantly superior to those formerly claimed for a pure attapulgite clay.[52] Lastly, clay-based catalysts may be partially regenerated, making it possible to recover high amounts of isomers by converting them to TMBD.[51]

3. An example of multipurpose synthesis

An interesting example of multipurpose, environment-friendly synthesis giving rise to different products as a function of the feed, catalyst nature and reaction conditions is the vapor phase production of different classes of N-containing heterocyclic compounds using non-hazardous, commercially available and low-cost feeds.[54]

Alkylquinolines are an important class of heterocyclic compounds of high industrial interest that find applications in
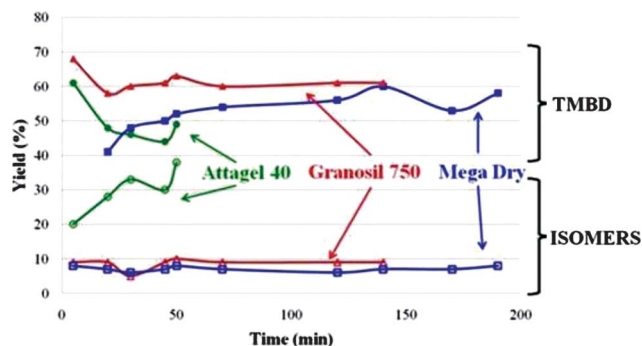
Fig. 4 Yield of tetramethylbutadiene (TMBD) and C_8H_{18} isomers with time-on-stream (catalyst = 9 g; T = 563 K; P = 0.1 MPa; feed = 2.8 M dimethyl-2,4-hexanediol (DMED)/CH_3OH solution in an N_2 flow; LHSV = 0.92 h^{-1}).[51,53]

the production of pharmaceuticals, herbicides, fungicides, acid-binding agents, corrosion or pickling inhibitors, *etc*. They are usually recovered from the methylnaphthalene fraction of coal tar by extraction with sulfuric acid, followed by precipitation with ammonia; however, today, this source no longer seems able to completely cover increasing market demand. Alternatively, quinolines may be obtained by different reactions that have many drawbacks. For example, the most widely employed method, Skraup's synthesis, like other similar methods, uses high amounts of sulfuric acid and temperatures higher than 423 K, with a significant violence in the initial reaction.[55] 2-Methyl-8-ethylquinoline (MEQUI) was synthesized from an excess of 2-ethylaniline (2-ETAN) and ethylene glycol (EG) or chloroethanol operating at 603 K, and using known solid acid catalysts such as acid-treated clays (K10 or $ZnCl_2$/K10 clay by Aldrich D) or zeolites.[31,54,56]

The synthesis of MEQUI is fostered by increasing both the reaction temperature and the amount of EG, operating in a partially reducing atmosphere and feeding small amounts of water into the feed. A possible reaction pathway was proposed (Scheme 3) and confirmed by feeding a 2-ETAN/crotonaldehyde mixture, observing similar yields of MEQUI regardless of the mixture fed.[56] However, it is not possible to exclude the possibility that a different and competitive reaction pathway may occur when other organic substrates and/or catalysts are employed.[57] Moreover, quinolines and/or

alkylquinolines may be synthesized with high selectivity and yield values, always operating in the vapour phase, but using zeolites as catalysts.[58]

On the other hand, *N*-(2-ethylphenyl)pyrrole (EPP) and *N*-(ethylphenyl)pyrrolidine (EPD) (intermediates for producing pharmaceuticals, fungicides, herbicides and dyes) were synthesized by using commercial copper chromite catalysts, and feeding 2-ETAN and 2,3-dihydrofuran (DHF), EPP being aided by the high temperature and the absence of water in the feed (Scheme 4).[54] It may be hypothesized that, in both cases, cyclization occurs directly on the nitrogen atom. The role of the temperature can be explained by considering that the dehydrogenation reaction to pyrrole was induced at higher temperatures than those required by the hydrogenation of the partially saturated intermediate.
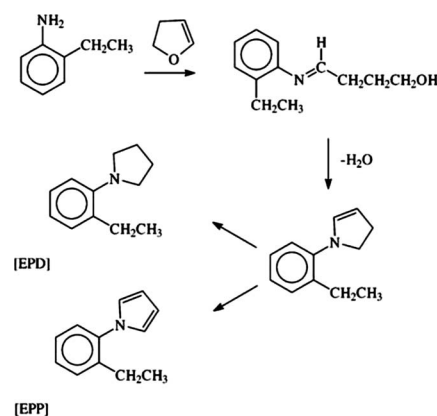
Scheme 4 Proposed reaction pathway for the synthesis of *N*-(2-ethylphenyl)pyrrole (EPP) and *N*-(2ethylphenyl)pyrrolidine (EPD) using copper chromite catalysts.[54]

Indole or alkylindoles are of considerable industrial interest, being applied as intermediates in the production of pharmaceuticals, herbicides, fungicides, dyes, *etc*.[59] Usually, they are recovered from the biphenyl-indole fraction obtained by coal tar distillation, although this source no longer seems able to cover the increasing market demand. Alternatively, they can be obtained in high yields from well known liquid phase reactions, which, however, present many drawbacks.[8,59–61] Thus, increasing interest has been focused on the vapour phase synthesis of these
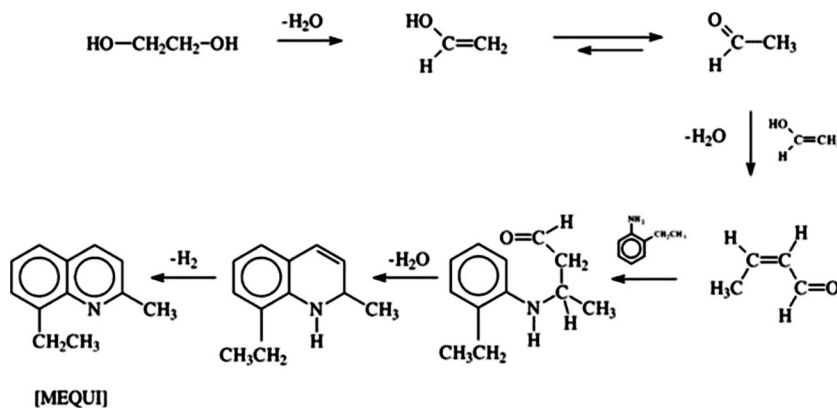
Scheme 3 Proposed reaction pathway for the synthesis of 2-methyl-8-ethylquinoline (MEQUI) using solid acid catalysts.[54,56]

molecules, since it exhibits many advantages in comparison with liquid phase synthesis.

Although there is patent literature that is rich in data regarding the nature and composition of catalysts, and the operating conditions for the synthesis of indole, few data have been reported for the synthesis of alkylindoles. Basically, two technologies may be identified: (i) the high temperature (773–973 K) dehydrocyclisation of dialkylanilines over oxides or chromites, followed by partial hydrogenation of the raw product;[62] (ii) lower temperature (453–623 K) reactions of anilines and glycols operating at a low LHSV.[63–68] However, in this latter case, many different catalysts have been claimed, making it difficult to identify the reaction requirements and optimum catalyst properties.

In preliminary work operating at lower temperatures, low LHSV values and using copper chromite catalysts, 7-ethylindole (7-ETI) was obtained by feeding 2-ETAN and EG; an excess of the aromatic amine was required to avoid the formation of polyalkylated by-products.[54,69] The best results were obtained by using a catalyst containing only promoters to improve the physical properties (BaO, CaO and SiO_2). Mixing SiO_2 with the best copper chromite made it possible to operate with high LHSV values, thus improving the hourly productivity, although with a corresponding increase in the volume of carrier gas to be recycled.[54,69,70]

Both the excess of aniline derivatives and the large volume of carried gas required to operate at high GHSV values were avoided by using novel ZrO_2/SiO_2 catalysts,[69,70] which were able to operate with almost stoichiometric aromatic amine/EG ratios using water as the main carrier gas, which may be condensed, separated from the organic stream and recycled, with significant environmental and economic advantages. Catalytic results better than those reported in the literature were obtained for a ZrO_2/SiO_2 ratio of 5 : 95 (wt%): an outcome that also evidenced a very good regenerability (Fig. 5).[70]
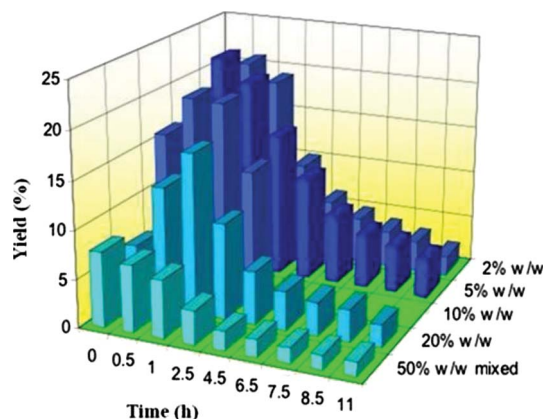

Fig. 5 Yield of 7-ethylindole (7-ETI) as a function of ZrO_2 content for catalysts prepared by incipient wetness impregnation (catalyst = 4 mL; 2-ethylaniline/ethylene glycol (2-ETAN/GE) = 1 : 1 mol/mol; H_2/H_2O = 2.8 v/v; T = 583 K; GHSV = 2900 h^{-1}; LHSV = 1.60 h^{-1}; yield values refer to the 2-ETAN feed).[54,69,70]

This synthesis can be applied to a wide number of substrates (anilines and/or diols) in order to obtain a wide number of alkylindoles operating in mild conditions and without the use of hazardous feeds.[70,81] In particular, while feeding EG, the best yield of the corresponding alkylindoles was obtained when a $C_2–C_3$ alkyl chain was located in the *ortho* position with respect to the amino group. The differences in reactivity between aniline and alkylanilines were significantly reduced when the length of the diol chain was increased and eliminated with 2,3-butanediol. On the basis of the above data and those collected by sharing the synthesis in single steps, a possible overall reaction pathway was proposed to design a better tailor-made catalyst (Scheme 5). It was also indicated that the formation of heavy compounds that are able to deactivate the catalyst was not derived from the reagents or from the following reactions
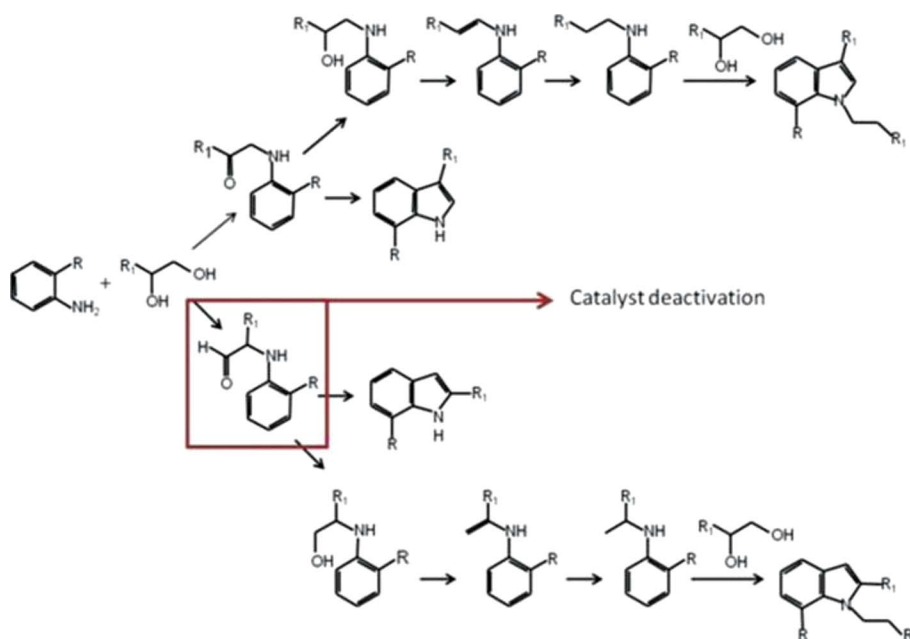
Scheme 5 Proposed reaction pathway for the vapor phase synthesis of indole and alkylindoles as a function of the aromatic amine and diol feed.[72]

of the indole formed, but may mainly be attributed to the polycondensation of an aldehyde intermediate.[71]

4. Promising scenarios for the catalysts obtained from hydrotalcite-type anionic clays

Clays are versatile materials, and hundreds of millions of tons currently find applications not only in ceramics and building materials, paper coatings and fillings, muds, foundry molds, pharmaceuticals, *etc.*, but also as adsorbents, catalysts or catalyst supports, ion exchangers, *etc.*, depending on their specific properties.[3,5,6,11,27,30–32] In particular, clays and catalysis seem to have a very promising future, and even if many catalytic applications have already been reported, more and more are being found day by day (in the laboratory and on an industrial scale), with a focus mainly towards establishing new environmentally-friendly technologies. The structure, main properties and preparation methods of clays have been previously reviewed in light of the high versatility and potential of these materials (see, for example, refs. 3,5,6,11,30–32,72–80).

Although it is not widely accepted, clays may be split in two classes: cationic and anionic, with complementary properties (acid and basic, respectively) and catalytic applications. In particular, over the past few years, hydrotalcite-type (HT) anionic clays (also called layered double hydroxides) have seen an exponential increase in their catalytic applications, as such or after controlled thermal decomposition. Even more will probably be seen in the future in unexpected areas, due to the possibility of designing catalysts tailored for specific reactions and/or substrates. The relatively simple and cheap preparation methods, the wide range of composition for both brucite-type layers and interlayers, the possibility to have more active species in the cationic layers (thus capitalizing on unusual synergistic effects), the high surface area and porosity values of the mixed oxides obtained by controlled thermal decomposition, and the very good dispersion and stability of the active species obtained following activation[3,11,72–74] are all promising factors for the promotion of their applications in catalysis (last but not least, in fine chemistry), with a very impressive increase in the number of references in the last few years (see, for example, refs. 3,6,11,17,73,76,77,81–92).

A few examples of recent applications of calcined HT precursors in which a multidisciplinary approach was required are: the synthesis of isobutyl alcohol (*i*-BuOH) from methanol (MeOH) and *n*-propanol (PrOH) through Guebert's condensation, the semi-continuous condensation of aromatic aldehydes with acetone, and Oppenauer's oxidation by paraformaldehyde (PFA) of the corresponding 3,4-(methylenedioxy)benzyl alcohol (or piperonyl alcohol, PAL) to 3,4-methylenedioxybenzaldehyde (also known as 1,3-benzodioxole-5-carboxaldehyde, piperonal or heliotropine, HEL).

In Guebert's condensation, calcined Mg/Al HT precursors were used together with pre-activated copper chromite (CuCr) to replace soluble sodium methoxide (MeONa) and develop fully heterogeneous two-component catalysts that are most suitable from industrial and environmental standpoints.[93] Unlike the CuCr/MeONa system, these catalysts were tolerant of the water co-produced in the condensation step and did not display any appreciable deactivation during the course of the reaction.

The catalyst productivity increased by reducing the Mg/Al ratio in the HT precursors, according to the increase of the fraction of medium-strong basic sites which speeded up the aldol condensation between the aldehydes derived from MeOH and PrOH. Considering the environmental constraints on the use of chromites, novel fully heterogeneous bifunctional catalysts were developed starting from bifunctional HT precursors also containing, together with basic sites, small amounts of a dehydrogenating/hydrogenating metal (Pd, Rh, Ni or Cu).[94] In particular, the Cu/Mg/Al mixed oxide catalysts offered the best results in terms of activity and selectivity. These systems were also tested in some preliminary experiments carried out in the gas-solid phase in a flow reactor, thus confirming their promising application perspectives.[94]

Considering the importance of the aldol condensation step in the synthesis of many intermediates or fine chemicals,[95,96] the factors affecting the reaction of some model aromatic aldehydes (benzaldehyde, the three isomers of F-benzaldehyde and 2-naphthaldehyde) with acetone were investigated by using heterogeneous catalysts obtained through the calcination of Mg/Al HT precursors at 773 K for 8 h and following rehydration at room temperature for 7 h under a flow of N_2 saturated with water vapor.[97] In order to evaluate the possible scale-up of the reaction, a significant improvement in the productivity per kg of catalyst was achieved by repeatedly adding new amounts of aromatic aldehyde to the reaction mixture when the conversion value was about 80%, thus developing a semi-continuous process.

HEL is the basis for heliotrope-type perfumes and is widely used for cosmetic preparations, with applications also as an intermediate for agrochemical and pharmaceutical products. Moreover, it is also a controlled substance, being the precursor of the hallucinogen 3,4-methylenedioxy-*N*-methylamphetamine (MDMA or Ecstasy). Currently, HEL is mainly produced by the isomerization of safrole, isolated from the essential oil of *Ocotea Cymbarum* and *Pretiosa* trees, following oxidation (chemical, electrochemical or by ozone). It is noteworthy that recently an environmentally benign route for the isomerization of safrole to isosafrole has been proposed using Mg/Al HT solid base catalysts.[98,99] However, the previously reported natural source is becoming less and less available, and consequently more expensive, because it contributes to the depletion of these perennial forests, thus boosting the demand for industrial alternatives for synthetic HEL. Since the price of natural safrole is about 5 € kg^{-1}, this prospect is starting to become commercially attractive.

Industrial processes for preparing HEL can be split into two groups: the first starting from 1,2-methylenedioxybenzene and the second from 3,4-dihydroxybenzaldehyde;[100–102] furthermore, a promising alternative is the production of HEL by oxidation of the corresponding PAL.[103,104] However, it is noteworthy that oxidation with air presents relevant safety drawbacks, since it operates with air in the presence of organic solvents at reflux temperature (*i.e.*, in the inflammability range). Thus, an interesting alternative may be Oppenauer's oxidation, which can be performed under safe and mild reaction conditions using either homogeneous or heterogeneous catalysts,[105–108] generally obtaining high selectivity values without the risk of oxidizing other functional groups. A further upgrading could be the

synthesis of HEL by Oppenauer's oxidation of the corresponding PAL using widely available and inexpensive commercial PFA as the hydrogen acceptor.[109,110] Among the heterogeneous catalysts studied (commercial ZrO_2 and calcined HT compounds), the best initial results were obtained by using commercial zirconia-type catalysts, with high yields being obtained regardless of the catalyst amount and reagent concentration, although these catalysts cannot be regenerated. Calcined Mg/Al commercial HT phases (by Sasol D and Süd-Chemie D) showed not only good catalytic results (having only a lower reaction rate than zirconia-type examples), but also an almost complete recovery of the initial activity after calcination at 823 K for 6 h (Fig. 6).
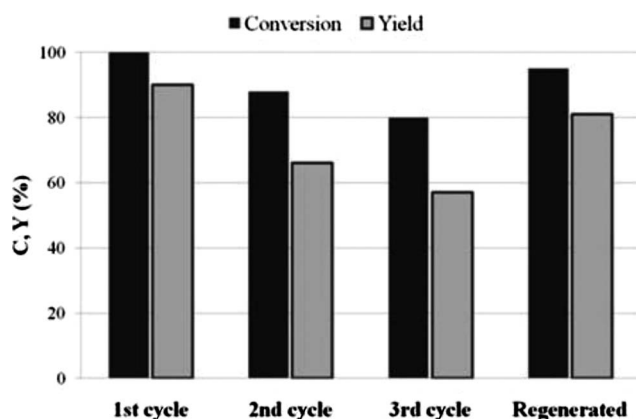

Fig. 6 Role of time-on-stream and regeneration in the Oppenauer's oxidation of piperonyl alcohol (PAL) by commercial paraformaldehyde (PFA) using calcined commercial Mg/Al hydrotalcite-type (HT) Sorbacid 696 (Süd-Chemie) (catalyst = 25 wt%, reaction time 6 h).[110]

5. Conclusions

Fine chemistry may be considered a promising "Eldorado" for both academic and industrial research in catalysis on account of its specific features (high added value, low production volumes, multistep syntheses, wide use of polluting stoichiometric reactions and the necessity for continuous innovation), as well as of increasing environmental constraints. Catalytic synthesis, mainly of the heterogeneous type, represents a promising alternative for developing economic and environmentally friendly processes, which may quickly move on from the laboratory to the industrial plant. Future prospects include the development of new catalysts and/or the tuning of their properties or shape in liquid phase reactions, or, even more of industrial interest, synthesis in the vapor phase, with continuous production and economic advantages. However, to exploit completely this potential cornucopia of catalytic applications, a multidisciplinary approach is required, in which researchers with very different backgrounds collaborate, each contributing their specific knowledge.

Acknowledgements

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