Metal-doped Zeolites as Green Catalysts for Organic Synthesis

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Dedicated to Professor Willi Kantlehner for his achievements

Metal-doped zeolites prepared by vapor diffusion are excellent heterogeneous catalysts. Copper(I)-exchanged zeolites catalyze for example 1,3-dipolar reactions or Mannich condensation, whereas scandium(III)-exchanged zeolites catalyze the Mukaiyama-type aldolization. These catalysts are easily prepared, stable for months, conveniently recovered by filtration and recyclable. They can be used in safe solvents and even without solvent, and thus fully comply with the Green Chemistry principles. Their ease of handling and their large scope of applications enabled us to introduce the "zeo-click" concept for organic synthesis catalyzed by such green heterogeneous catalysts.

Key words: Heterogeneous Catalysis, Zeolite, Copper, Scandium, Click Chemistry

Introduction

With increasing environmental concerns, relayed by the United Nations [1], several tendencies [2] from the chemical community merged a decade ago into the concept of Green Chemistry [3]. Within this context, industrial and academic chemists are facing numerous challenges to discover and develop new synthetic methods towards cleaner syntheses and production processes.

Although the most creative, the fine chemicals and specialty industries as well as the pharmaceutical industry cause major environmental impacts, at least as judged from the so-called E-factor (Table 1) [4]. In contrast, petrochemical and bulk industries have a minor impact due to extensive use of heterogeneous catalysts, thereby improving selectivity and facilitating product and catalyst recovery, and thus minimizing energy and wastes.

Table 1. Environmental factors (E-factor) in the chemical industry [4].

Industry branch	Product tonnage	E-factor[a]
Pharmaceuticals	$10^1 – 10^3$	25 – 100
Fine Chemistry	$10^2 – 10^4$	5 – 50
Bulk Chemistry	$10^4 – 10^6$	$< 1 – 5$
Petrochemistry	$10^6 – 10^8$	< 0.1

[a] Expressed in kg of waste per kg of product.

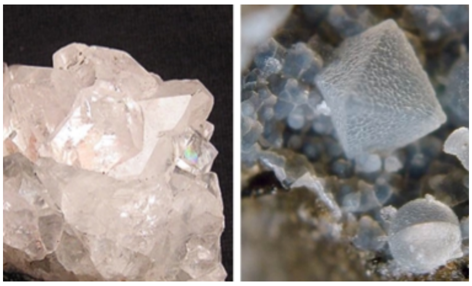


Fig. 1 (color online). Some natural macro- and microcristalline zeolites.

It is worth noting that the latter industries heavily rely on zeolites as heterogeneous catalysts. Zeolites are stable solid materials, widely found in nature as minerals and often as well-formed crystals usually in cavities of volcanic or metamorphic rocks (Fig. 1). Natural zeolites are hydrated alkaline or alkaline-earth aluminosilicates characterized by the general formula $(M^{n+})_{x/n}[(AlO_2)_x(SiO_2)_y]\cdot wH_2O$, discovered in 1756 by Cronstedt in Sweden, who coined their name from the Greek *zeo* (boil) and *lithos* (stone), due to their strange behavior upon heating in a flame [5, 6].

After his studies on the composition of natural alkaline silicates and aluminosilicates, the French chemist Sainte-Claire Deville found in 1862 that mixing sodium or potassium aluminate and silicate provided alkaline aluminosilicates analogous to natural zeolites [7]. This first zeolite synthesis was later taken over by Barrer, who prepared in 1948 an analog of mordenite [8], and then by Milton and Beck, who succeeded in synthesizing other zeolite types in 1959 [9]. Numerous non-natural zeolites have since been synthesized, some on a large scale for a variety of applications (adsorbents, additives, catalysts, *etc.*) [10].

From a structural point of view, zeolites are crystalline structures characterized by 3D networks of AlO_4 or SiO_4 tetrahedra linked together by a common oxygen atom, organized in cages or channels containing cations and water molecules. A large variety of structures is thus possible, all of them containing internal voids of different shapes [11]. From a chemical point of view, their internal shapes, different in each zeolite type, allow to modulate their reactivity and to exert discrimination, based on reactant sizes and, more interestingly, on shape and size of transition states. More importantly, their properties can also be tuned by modifying them through metal exchange.

Since numerous organic transformations are now often based on metal-catalyzed processes, usually under homogeneous conditions, it would be interesting to combine such metal-ion catalysis with the typical properties of zeolites. A homogeneous process could thus become heterogeneous by immobilizing the metal catalyst in zeolites, taking furthermore advantage of their size and shape selectivities. Moreover, the zeolite framework can act as a polydentate ligand toward the metal ion [12]. Distortion in coordination may occur, leading to a modification of the catalytic behavior. Therefore, new conditions and reactions could be achieved with such modified zeolites.

With the "greening" of organic synthesis as a goal, we thus aim to develop new classes of heterogeneous catalysts, easy to handle and if possible recyclable, which can be used for generating substances quickly and reliably by joining small units together. These criteria are close to the chemical "philosophy" introduced by Sharpless in 2001 under the name "click chemistry". Reactions, which are modular and wide in scope, regio- and stereospecific, which can be performed under simple conditions, giving in high yield a single reaction product easy to isolate, belong to this "click chemistry". Such criteria are those we are actually looking for but with catalysis by metal-doped zeolites. This led us to propose the term "zeo-click" synthesis for such chemistry (Fig. 2).

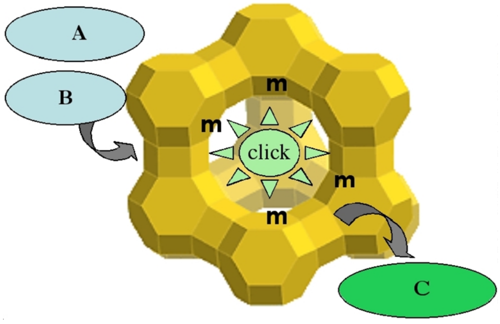


Fig. 2 (color online). The "zeo-click" concept.

In this context, we have started preparing various zeolites doped with different metals and exploring their behavior in organic synthesis. In the present report we give an overview of our selected recent results in this area.

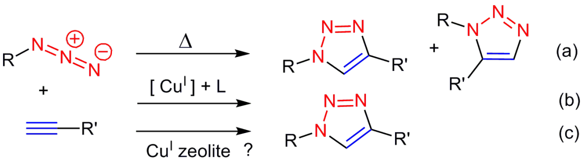
Results and Discussion

Cu^I-modified zeolites in organic synthesis

In 2002, Sharpless [13], concomitantly with Meldal [14], reported on a copper-catalyzed version of the thermal [3+2]-cycloaddition originally disclosed by Huisgen in the early sixties (see Scheme 3 (a – b)) [15]. This condensation between organic azides and terminal alkynes rapidly became the archetype of "click" reactions, and numerous applications have since been developed [16].

Due to similarities with our "zeo-click" concept, it was tempting to check if such catalyzed [3+2]-cycloaddition could be performed with copper(I)-modified zeolites (Scheme 1; (c)). Moreover, it is worth mentioning here that almost no heterogeneous version of this reaction was known when we started our investigations [17].

We thus looked for the preparation of copper(I) zeolites. Although known, such modified zeolites were



Scheme 1 (color online). The Sharpless-Meldal catalyzed Huisgen cycloaddition, (b) and (a), respectively; an alternative based on copper-modified zeolites (c).

$$(NH_4)^+_x\,[(AlO_2)_x(SiO_2)_y]^{x-} \xrightarrow{550\,^\circ C} (H^+)_x\,[(AlO_2)_x(SiO_2)_y]^{x-} \xrightarrow{\substack{CuCl\\350\,^\circ C}} (Cu^+)_x\,[(AlO_2)_x(SiO_2)_y]^{x-}$$

Scheme 2. Synthesis of Cu^I-modified zeolites.

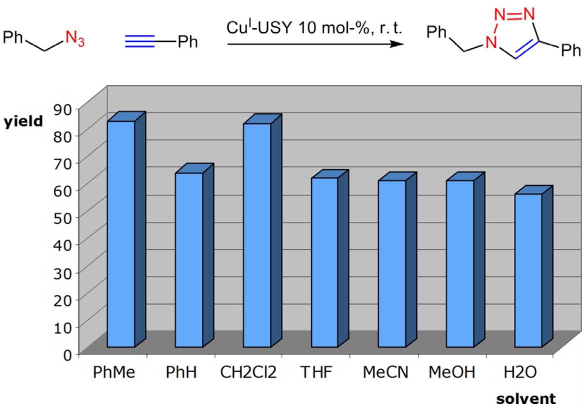


Fig. 3 (color online). Cu^I-USY-catalyzed cycloaddition of benzyl azide with phenylacetylene at r. t. in various solvents.

surprinsingly scarce, and only a few applications, mostly to redox processes for depollution, have been reported [18]. Interestingly, no application to organic synthesis could be found in the literature. On these grounds, we prepared a series of copper(I) zeolites through the doping of the corresponding acid zeolites, easily obtained by heating the corresponding commercially available ammonium zeolites (Scheme 2).

All of them proved to be efficient catalysts at r. t. for the Huisgen cycloaddition, but with variable yields depending on their structure (see below). These Cu^I-modified zeolites act as true catalysts, since only 10 mol-% was used (corresponding to approximately 10 mol-% of active Cu^I species based on the number of acidic sites in the native H-zeolite) [19]. Interestingly enough, a single triazole regioisomer was always formed, whatever the zeolite used. Moreover, all examined solvents including protic solvents proved suitable for this reaction, but toluene was the most effective and the cleanest at r. t. (Fig. 3) [20].

Among the zeolites examined, Cu^I-USY proved to be the best (Fig. 4), giving the highest yields at room as well as at higher temperatures in various solvents. In contrast, no reaction took place at room temperature without catalyst or with the precursor acidic zeolite (H-USY in Fig. 4), and almost no reaction occured at room temperature with copper chloride alone. Under these conditions, heating restores the classical thermal Huisgen reaction, and a mixture of regioisomeric triazoles are produced in ∼70 % yield (labeled red bars in Fig. 4). Increasing the temperature raised the yields, leveling differences between the Cu^I zeolites used as catalysts. At r. t., the channel-type zeolites (β, ZSM5, MOR) proved significantly less efficient than their cage counterparts (Y, USY). These differences could be ascribed to the volume required for the transition state of the cycloaddition, a spherical and large volume is probably better than a small and tube-like volume (Table 2).

As expected, the catalyst can be easily recovered through filtration and recycled four times without any significant change in yield and conversion [21]. Copper(I) leaching could have been an issue, and this has thus been investigated, revealing that leaching did not account for more than 5 % of the transformation.

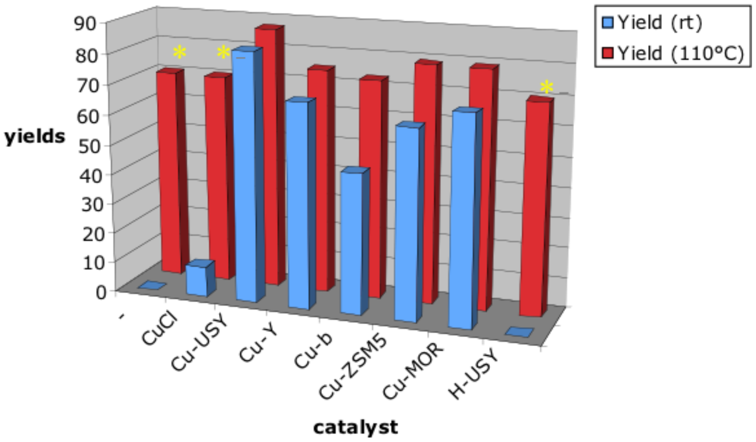
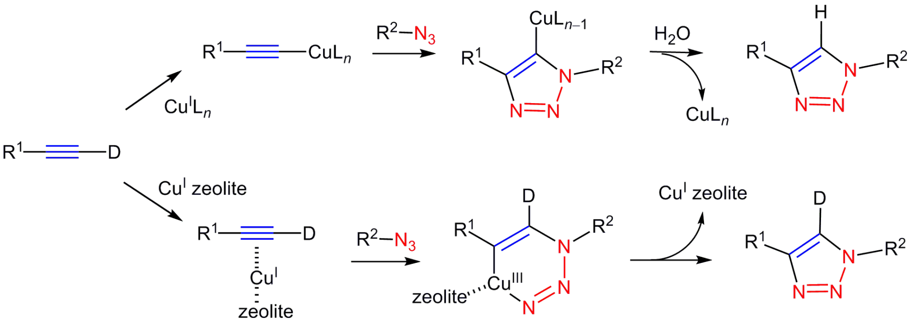


Fig. 4 (color online). Cycloaddition of benzyl azide with phenyl acetylene in toluene at r. t. (15 h) or in refluxing toluene (5 h) in the presence or not of various catalysts (yellow stars indicate conditions in which a mixture of regioisomers is formed).



Scheme 3 (color online). Possible mechanisms of the cycloaddition of alkynes and azides, catalyzed either by soluble Cu^I complexes (top) or by Cu^I zeolites (bottom).

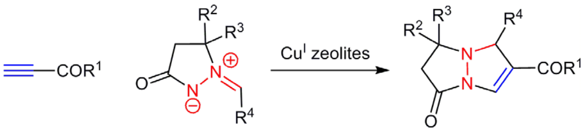
Table 2. Properties of native acid zeolites used in the course of our studies.

H-Zeolite	H-USY	H-Y	H-β	H-ZSM5	H-MOR
Topology	cage	cage	channel	channel	channel
Pore diameter, Å^2	7.4×7.4	7.4×7.4	7.6×6.4 5.5×5.5	5.1×5.5 5.3×5.6	6.5×7.0 3.4×3.8
Si/Al ratio	2.8	1.5	12.5 – 17.5	15	10.3
Acidic sites number, mmol g^{-1}	4.39	6.67	0.90 – 1.23	1.04	1.48

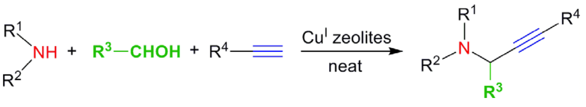
We have thus set up a novel and efficient heterogeneous ligand-free catalyst for the "click" cycloaddition of alkynes and azides. High yields of triazoles were routinely obtained with a wide variety of starting materials. The reaction scope indeed proved as large as the one of the Sharpless-Meldal version [21]. However, the mechanism seems to be different (Scheme 3). Investigations with deuterated substrates and zeolites suggested that no acetylide is formed within the Cu^I zeolites while it has been shown that such intermediates are produced in the Sharpless-Meldal version [21].

The "zeo-click" concept could be extended to other cycloadditions, as demonstrated by our recent report on an efficient and regioselective Cu^I zeolite-catalyzed [3+2]-cycloaddition of azomethine imines with terminal alkynes (Scheme 4). This Cu^I zeolite-catalyzed reaction provided a rapid, regio- and stereoselective access to complex pyrazolidinone derivatives [22].

Catalysis with Cu^I zeolites is even more general and not limited to cycloadditions. Various other reactions could indeed also be promoted with a catalytic amount of Cu^I zeolites. Among them, multicomponent reactions are particularly interesting. Such reactions allow combining several starting materials into usually a single compound and in a one-flask operation, exhibiting economy of steps as well as atom economy. Therefore, multicomponent reactions have become an intense research area [23, 24].



Scheme 4 (color online). Cu^I zeolite-catalyzed synthesis of pyrazolidinone derivatives.



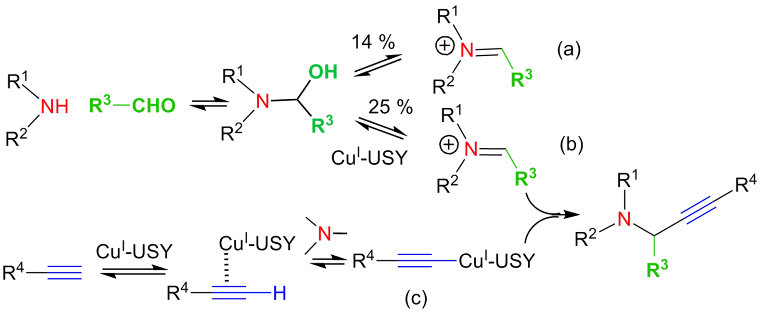
Scheme 5 (color online). Cu^I zeolite-catalyzed three-component condensation leading to propargylamines.

An archetype of such reactions is the Mannich-type condensation of alkynes and imines *in situ* produced from aldehydes and amines. As for the Huisgen cycloaddition, we thus looked for a Cu^I zeolite-catalyzed version [25]. After screening of zeolites and conditions, we found that Cu^I-USY was again the most efficient catalyst for this three-component reaction, and that the condensation was best achieved *without solvent* in a fully green process, although moderate heating was required (60 – 80 °C) (Scheme 5). Nevertheless, the reaction worked well either in toluene, THF or acetonitrile, but again at 80 °C.

Under such conditions, the produced propargylamines as well as the catalyst could easily be recovered by simple filtration. The latter could be recycled up to 4 times without decrease in efficiency.

The scope of this Cu^I zeolite-catalyzed synthesis of propargylamines by three-component condensation proved quite large. Deactivated amines, including aniline derivatives, and formyl, aryl or aliphatic aldehydes reacted under these conditions, giving the corresponding propargylamines in good to excellent yields.

Mechanistic studies have revealed that an iminium ion is produced during this reaction as expected, but more interestingly, that its formation is increased in the presence of Cu^I zeolites (Scheme 6; (b) *vs.* (a)).



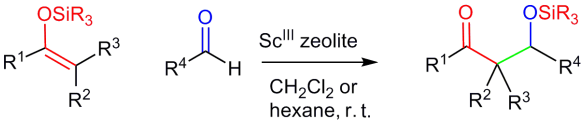
Scheme 6 (color online). Proposed mechanism of the Cu^I zeolite-catalyzed three-component synthesis of propargylamines.

In analogy with the mechanism of the Cu^I zeolite-catalyzed [3+2]-cycloaddition of azomethine imines with terminal alkynes (Scheme 4), established through labeled substrates and zeolites [22], the *in situ* formation of acetylides can be envisaged due to the presence of amino derivatives, which may act as bases toward the alkynes coordinated to Cu^I zeolites (Scheme 6; (c)). These results have thus demonstrated that Cu^I zeolites act as dual catalysts in such multicomponent reactions.

Sc^{III}-modified zeolites in organic synthesis

The "zeo-click" concept proved to be not limited to Cu^I zeolites. Indeed, zeolites doped with other metals could also be produced by ion exchange techniques, and depending on the latter, these metallated zeolites act as catalysts. Among other metals, we are currently evaluating the possibilities with scandium. Scandium ions are strong Lewis acids able to promote various organic reactions rendering this element a useful tool in chemistry [26]. Therefore, a recyclable scandium-based catalyst would be particularly useful. It is worth mentioning here that a silica-supported scandium catalyst has been described and applied to a few organic reactions [27].

In this context, it seemed obvious to try to sequester scandium ions in zeolites and look for their catalytic performance. We thus embarked on this project, although the main problem appeared to be the introduction of scandium ions into zeolites since only a handful of reports mentioned Sc zeolites. Simple ion exchange [28] as well as the substitution sol-gel method [29] were tested but did not yield active catalysts for our organic synthesis purposes. The slow vapor diffusion which proved efficient for preparing Cu^I zeolite catalysts require salts with relatively low melting and boiling points, but those of the scandium salts are usually high. Fortunately, both parameters are in the lower range for scandium triflate, and this salt proved "volatile" enough to diffuse into zeolites upon heating at 450 °C during 2 days. Rewardingly, this method provided us with active and useful catalysts.



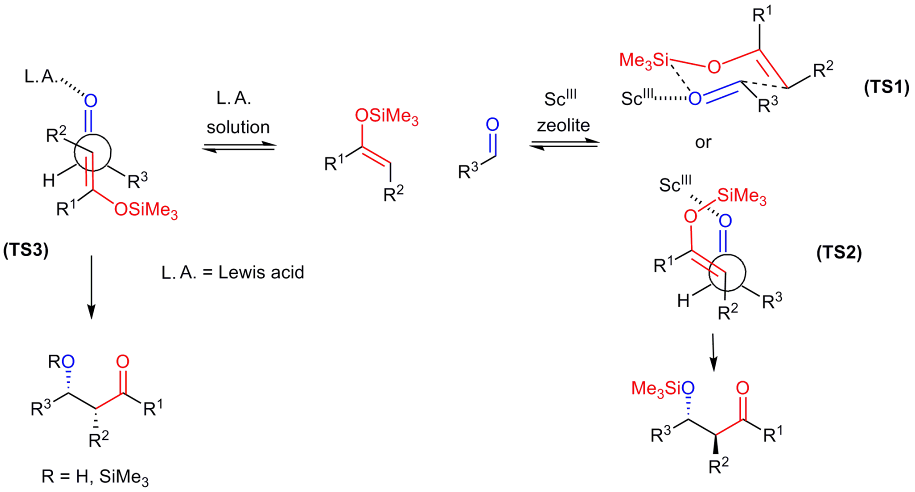
Scheme 7 (color online). Sc^{III} zeolite-catalyzed Mukaiyama aldol reaction.

Among the organic reactions promoted by scandium salts, the Mukaiyama aldol condensation is one of the most interesting, allowing to form a new C–C bond in a regio- and stereo-controlled manner. We thus first examined the behavior of Sc^{III} zeolites in this reaction with various silyl enolethers and aldehydes (Scheme 7) [30].

In sharp contrast to Cu^I zeolite-catalyzed reactions, this reaction proved only efficient in apolar and non-aromatic solvents (Table 3). However, the yield was excellent (quantitative), and the catalyst could be reused three times while still being fully effective (quantitative yield), and three more times with some decrease in yield (around 70 %). As for Cu^I zeolite-catalyzed reactions, no leaching of the active metal species occurred.

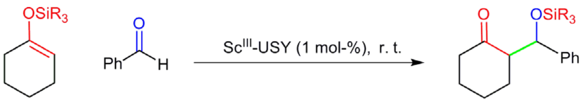
Unexpectedly, the recovered product was fully silylated, in contrast to the classical Mukaiyama aldol reaction which usually gives a mixture of silylated and non-silylated products. This behavior is highly interesting in synthesis, since further modifications on the aldol product could directly be performed without re-protecting the aldol hydroxy group.

As for other Mukaiyama aldolizations, mixtures of diastereoisomers were also produced here. However, a 30 : 70 ratio in favor of the *anti* isomer was usually observed under the Sc^{III} zeolite catalysis, while the reverse *syn*-*anti* ratio is usually achieved under more conventional conditions.



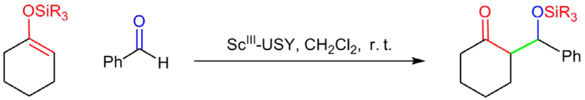
Scheme 8 (color online). Proposed mechanisms for the Sc^{III}-USY-catalyzed aldol reaction (TS1-2) compared to the classical mechanism of the Mukaiyama aldolization (TS3).

Table 3 (color online). Sc^{III}-USY-catalyzed condensation of 1-(trimethylsilyloxy)cyclohexene and benzaldehyde at r. t. in various solvents.



Solvent	Time (h)	yield (%)
toluene	16	0
hexane	30 min	100
CH_2Cl_2	4	100
THF	16	traces
DMF	16	traces
H_2O	16	traces

Table 4 (color online). Correlation between Sc^{III} zeolite loading and reaction time of the reaction of 1-(trimethylsilyloxy)cyclohexene with benzaldehyde at r. t. in dichloromethane.



Sc loading (mol-%)	Time (min)	Yield (%)
1	240	100
2	30	100
5	10	100
10	1	100

Interestingly, even a small amount of Sc^{III}-USY was still efficient, the only difference being the reaction time which is clearly correlated to the catalyst loading (Table 4).

This Sc^{III}-USY-catalyzed aldolization proved quite general, accepting aliphatic, cyclic or aromatic silyl enol ethers as well as aryl or conjugated aldehydes.

The fact that the aldol product is still silylated in this Sc^{III}-USY-catalyzed aldolization, combined with *syn-anti* ratios different from those observed in conventional Mukaiyama conditions, suggests a specific role of the zeolites in the reaction mechanism. It seems that the typical super-cage of USY constrains the transition state and forces the reagents to adopt either a chair-like transition state (Scheme 8, TS1) or a skew open transition state (TS2), instead of the classical open transition state (TS3).

Conclusion

Metal-doped zeolites can act as efficient catalysts in organic synthesis, as demonstrated by cycloadditions, multicomponent reactions and Mukaiyama-type aldolizations catalyzed by Cu^{I}- or Sc^{III}-modified zeolites.

Interestingly enough, the structural features associated with zeolites appear to lead to unusual mechanisms in the reactions investigated, and further studies are required to better understand and interpret these advantageous differences.

From a technical point of view, these heterogeneous catalysts are very attractive because they are easy to handle and can be recycled several times. They proved very effective in generating substances quickly and reliably, with low catalyst loading and usually at room temperature. These heterogeneous catalysts proved also to be general, accepting a large variety of substrates and even allowing to combine several components.

These interesting features led us to coin the term “zeo-click” organic synthesis for such catalyses.

Acknowledgements

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