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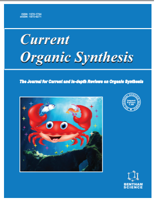
REVIEW ARTICLE



Organic Synthesis Using Environmentally Benign Acid Catalysis

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Abstract: Recent advances in the application of environmentally benign acid catalysts in organic synthesis are reviewed. The work includes three main parts; (i) description of environmentally benign acid catalysts, (ii) synthesis with heterogeneous and (iii) homogeneous catalysts. The first part provides a brief overview of acid catalysts, both solid acids (metal oxides, zeolites, clays, ion-exchange resins, metal-organic framework based catalysts) and those that are soluble in green solvents (water, alcohols) and at the same time could be regenerated after reactions (metal triflates, heteropoly acids, acidic organocatalysts *etc*.). The synthesis sections review a broad array of the most common and practical reactions such as Friedel-Crafts and related reactions (acylation, alkylations, hydroxyalkylations, halogenations, nitrations *etc*.), multicomponent reactions, rearrangements and ring transformations (cyclizations, ring opening). Both the heterogeneous and homogeneous catalytic synthesis parts include an overview of asymmetric acid catalysis with chiral Lewis and Brønsted acids. Although a broad array of catalytic processes are discussed, emphasis is placed on applications with commercially available catalysts as well as those of sustainable nature; thus individual examples are critically reviewed regarding their contribution to sustainable synthesis.

Keywords: Solid acid, heterogeneous catalysis, metal oxides, clay, zeolite, metal-organic-frameworks, heteropoly acids, ion-exchange resins, sulfated metal oxides.

1. INTRODUCTION

Acidity-basicity is one of the oldest concepts in the history of chemistry beginning with Lavoisier and Davy over two centuries ago [1]. While the first general description was developed by Arrhenius [2], it was later refined and replaced by the Brønsted-Lowry [3] and Lewis [4] concepts. Accordingly, acid catalysis has extensive history that covers a broad range of applications such as electrophilic addition, esterification, ester hydrolysis, aromatic electrophilic substitution or rearrangement reactions [5]. Conventional mineral acids, such as HCl, H_2SO_4 or HNO_3 were the traditional catalysts of choice for these transformations. Despite their usefulness, these acids are highly corrosive; many of them release gases that pose safety and health hazards. In addition, most of them are impossible to reuse. In short, their application is undesirable under the Green Chemistry principles [6]. Due to the importance of acid catalysis, significant efforts were made to address this problem. The two major ways to replace these harmful acids are the application of solid acids *via* heterogeneous catalytic reactions and the use of homogeneous (soluble) acid catalysts that do not undergo hydrolysis under aqueous conditions and can be recycled. The latter acids are soluble in water and several organic solvents thus acting as homogeneous catalysts. Both groups of catalysts are now frequently used in a broad variety of organic reactions, and are extensively reviewed [7].

In this account we will survey the applications of these catalysts in environmentally benign processes. Although we provide major sources of earlier reviews and books, the emphasis will be placed on recent advances, thus most of the original work reviewed in this article will cover the past decade between 2008 and 2018. Even with this limitation, due to the large number of papers published in this period and the page limitations of this work, the focus will be on providing a broad scope of reactions with representative examples.

2. ENVIRONMENTALLY BENIGN ACID CATALYSTS

Environmentally benign acid catalysts form two major groups depending on the type of catalysis they perform. Solid acids are not soluble in water or organic solvents and the reactions occur on the surface of these materials thus forming heterogeneous catalytic systems. In contrast, there are acids that, although solid under normal conditions, readily dissolve in water and many organic solvents thus performing homogeneous catalysis. In this part we summarize the most frequently used catalyst in both groups (Fig. **1**).

It is worth noting that there is a limited overlap between the two major groups. There are several acids, mainly inorganic acids and salts, such as heteropoly acids or metal triflates that are not soluble in certain organic solvents, thus with the appropriate selection of the solvent they can be used as either heterogeneous or homogeneous catalysts. Their water solubility and stability under aqueous conditions still aid their recycling during work up procedures.

2.1. Heterogeneous Catalysis - Solid Acids

Solid acid catalysts have been extensively used in organic synthesis as well as in the pharmaceutical industry [8]. Their advantages include their practical utility (durability, easy work-up by filtration), their potential recyclability, their low cost and overall their great green potential. These catalysts are of many types

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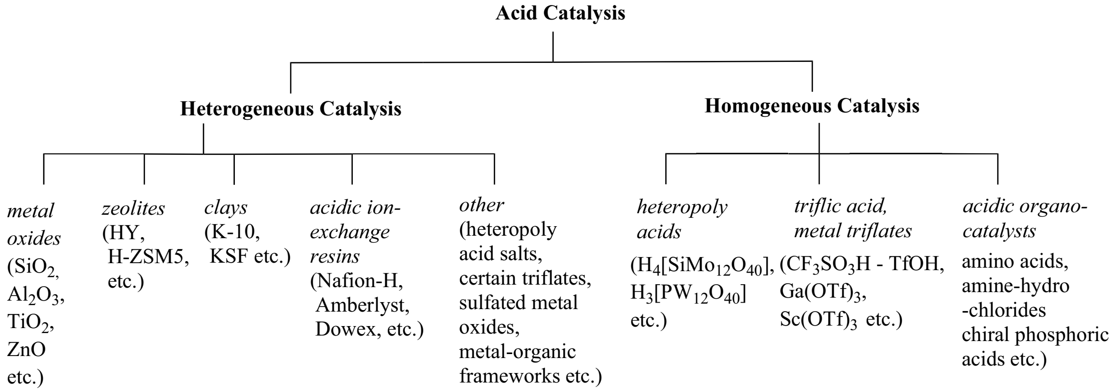


Fig. (1). Classification of green acid catalysts.

depending on the composition and the structure they possess. The aforementioned assets combined with various other specific properties attracted vast interest toward their applications. Due to the polar nature of these materials, most are excellent microwave absorbers thus can act as a catalyst as well as an internal heating medium for a broad array of transformations [9-11]. The main types of solid acid-catalysts; namely metal oxides, zeolites, clays, acidic ion exchange resins, heteropoly acid salts and metal organic frameworks and sulfated metal oxides; will be briefly described in this section.

The first large group of solid acids is based on metal oxides [12]. Although their acidity is relatively limited, due to their broad availability and low cost they represent a versatile group of weak acid catalysts for many transformations [13]. They include the common silica or acidic alumina catalysts. When metal oxides are treated with sulfuric acid they form a special group of catalysts named sulfated metal oxides [14]. The reaction with sulfuric acid appears to enhance the Lewis acid character and significantly strengthen acidity. Some of these materials, such as sulfated zirconia are commonly used Lewis acid catalysts in organic synthesis [15].

Probably the most utilized solid acid catalysts originate from natural aluminosilicates, zeolites and clays, although the success of the natural materials inspired extensive efforts in the preparation of semi-synthetic and synthetic alternatives.

Clays are aluminosilicates constituted of multiple layers of polyhedrons. Tetrahedral silicone oxides and octahedral hydrous alumina are their common building blocks [16]. Clays have demonstrated remarkable catalytic activity due to their porous structure that provides a unique environment in which molecules can interact in specific ways allowing reactions to take place. In other words, they act as a micro-reactor capable of initiating reactions on account of their inherent properties such as adsorption-, swelling- and ion-exchange capacities. Various types of clays exist; depending on their properties, they are suitable for catalyzing a broad scope of transformations [17]. Clays can be classified into two categories: the negatively charged clays that welcome balancing cations and the positively charged clays containing anions in their interlayer space [18]. The second class of clays is often synthesized while the first one is prepared from natural sources, most commonly montmorillonites. The natural clays can be used directly in their original form or after undergoing chemical treatments that enhance an existing characteristic or specifically introduce an extrinsic feature. An acidic activation method is often employed to enhance their acidic properties. To do so, several mineral acid solutions can be applied including phosphoric acid, sulfuric acid or nitric acid [19]. The resulting materials exhibit an increase in acidity and the number of active sites and surface area. The widespread montmorillonites are cationic clays, member of the smectite group [20], possess remarkable absorption capacity, high surface area as well as interesting acidic properties which altogether contribute to their success as catalysts in various reactions [21]. Montmorillonites K-10 and KSF, both acid treated montmorillonites, are the most widely used acidic clays in organic synthesis [22].

Zeolites are also aluminosilicates, however, in contrast to the layered structure of clays these highly porous, crystalline materials exhibiting a well-defined channel and cage-based structure [23] and less commonly a lamellar structure [24]. The molecular dimensions of their channels and cages contribute greatly to the catalytic potential of zeolitic materials [25]. Similarly to clays, the catalytic properties of zeolites are due in part to the exchangeable ions and water molecules trapped in their structure as well as their commonly high adsorption capacity [26]. It is important to mention that zeolites also offer the possibility to introduce specific active sites and to modulate the existing electronic features giving rise, for example, to zeolites with enhanced acidic properties. In catalysis, the most commonly used acidic zeolites are zeolites X and Y, employed in catalytic cracking, and zeolite ZSM-5, a fundamental catalysts in the petroleum industry [27]. In general, although zeolites are strong acids at high temperatures, their acidity is relatively modest at the common temperature range of organic synthesis [27]. Efforts to prepare zeolites with stronger acid sites by functionalizing them with organic moieties led to promising results; nonetheless, this issue still remains a challenge [26].

Acidic ion exchange resins are versatile materials used as catalysts for many organic transformations as well [28]. Their framework makes possible the synthesis of hybrid materials with tunable acidity. Depending upon their pore size, chemical structure and formulation, they are useful in a number of transformations. Ionic exchange resins exist as either cationic or anionic forms. The so-called acidic ionic exchange resins are typically of cationic type. Amberlyst and Nafion are two common sulfonic acid based-resins employed in numerous catalytic processes [29]. While the Amberlyst type is based on a polystyrene-sulfonic acid motif, Nafion possesses a perfluorinated backbone with sulfonic acid entities.

The high electron withdrawing character of fluorine in Nafion significantly enhances its acidity to the superacidic level. Amberlyts are able to catalyze the conversion of acetals and carbonyls to alcohols, the conversion of acids to esters, among others. Nafion has been successfully employed as solid-acid catalyst for several reaction types such as oxidation reactions, protection and deprotection of alcohols and carbonyl containing compounds, as well as rearrangements [30]. It is worth mentioning that their BET surface area, however, is rather low (~9 m^2/g) and they often suffer from a poor porosity. To address these issues and fully take advantage of the strong acidity of Nafion-H a Nafion-silica

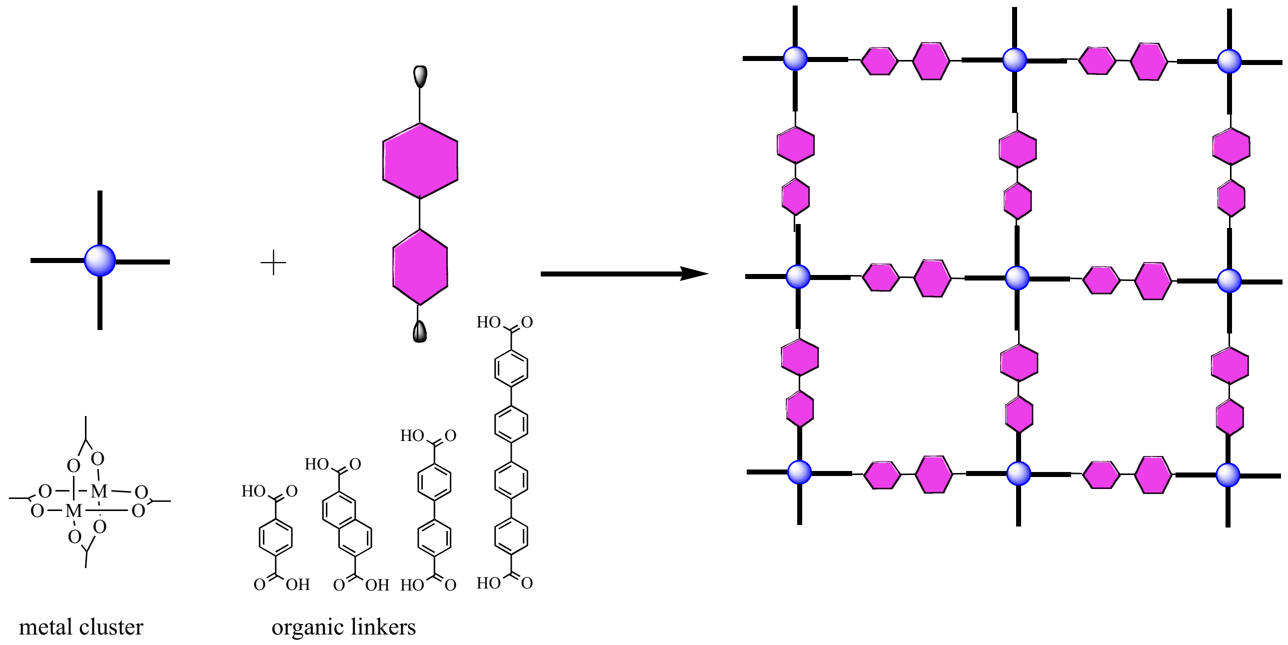


Fig. (2). Representation of the synthesis of a metal organic framework with examples of metal cluster/organic linkers [37].

nanocomposite material was developed, in which the small Nafion-H particles are trapped in a porous silica network significantly enhancing both the BET surface and available active centers [31].

Metal-organic frameworks (MOF) [32] constitute a highly porous class of materials possessing an important internal surface area; thus they have found applications as gas storage media, and as absorbents but they also appear to be excellent catalysts. They have the particularity to be composed of organic linkers and inorganic metal ions [33]. Unlike zeolites that have a restricted number of structures, the hybrid nature of MOFs allows multiple combinations of both components yielding practically infinite structural possibilities. Various synthetic methods exist to prepare MOFs. The self-assembly approach is likely the most common: two solutions containing the organic and inorganic components, respectively, are mixed, often under solvothermal conditions that result in a crystalline framework [34]. Clusters of metal-carboxylates are common secondary building blocks acting as nodes in the MOF architecture. They come together to form a network linked by organic ligands such as terephtalic acid (Fig. **2**). By selecting a particular ligands/metal cluster combination, the pore size as well as the flexibility of the material can be controlled and specific functionalizations can also be introduced. These easily tunable solid catalysts have therefore the potential to favor certain reactive intermediates and promote specific pathways, thus control the reactivity and selectivity of an organic reaction [35]. Moreover, the incorporation of chiral linkers extends the applications of the MOF to asymmetric catalysis [36].

Several *composite materials* are also often used solid acid catalysts. There are three major groups of catalysts that are particularly important in this area; the (i) carbon-, (ii) ionic liquid- and (iii) carbon silica composite based acids.

The first group is based on sulfonated carbon-based materials that were observed to be efficient and highly active solid Brønsted acid catalyst [38]. These catalysts resemble to graphite sheets that, after sulfonation, contain a high density of sulfonic acid groups. In fact the acid density of these materials surpasses that of Nafion-H by a factor of five. These materials are commonly prepared from susatinable sources, such as natural carbohydrates, *e.g*. starch, cellulose *etc*. by partial cabonization and sulfonation [39]. They are used in a broad variety of applications for example metal-doped alternatives were applied in the Suzuki coupling and oxidation [40].

The ionic liquid-base composites in which ionic liquids are immobilized on solid surfaces, *e.g.* sulfonated silica also attracted significant attention [41]. These materials, such as ionic liquid coated sulfonated carbon-silica composites were found to be novel solid acid catalyst for aqueous phase organic synthesis [42].

Sulfonated carbon-silica composites are also important catalytic materials [43]. These catalysts have been applied in a variety of transformations, such as the Hantzsch cyclization [44], multi-component synthesis of heterocycles [45], the Michael addition of indoles to α,β-unsaturated ketones [46], chemoselective protection of aldehydes, and C, N, O-acylations [47].

Another new emerging class of solid acid catalysts is the nanoscale version of the polymer-supported acid catalysts (PSAs). The so called “nanoacid” corresponds to polymer-based nanoparticles functionalized with sulfonic acid groups [48]. A synthetic method reported the use of emulsion polymerization technique in presence of a reactive surfactant to prepare such material [48]. The co-monomers, styrene and divinylbenzene, employed were crosslinked under specific conditions in order to form a backbone of nanoparticles that remains heterogeneous in solution. The surfactant, octylbenzene sulfonic acid, possessing a benzenesulfonate moiety was then reacted with the particles depositing the sulfonic acid groups at their surface. The resulting material showed good performance in catalyzing the formation of urethane from isocyanate and alcohol. While nanoacid catalysts offer a greater surface area than PSAs and therefore possess a high potential to perform acid-catalyzed organic reactions, their success remain to be demonstrated as very few examples are available in the literature. It is interesting to note that the term nanoacid has been used for other materials, such as heteropolyoxometallate-based materials that possess nanometer size as well as strong acidic properties [49].

The last solid acid catalyst type discussed in this section is heteropoly acid salts, fundamentally different from the other types described previously. Heteropoly acids are made of hydrogen, oxygen, heteroatoms, and metals often including tungsten or molybdenum. In other words, they can be considered special clusters of transition metal oxides [12]. Heteropoly acids are commonly soluble in water and many organic solvents. Their corresponding salts, obtained by replacing some or most of the hydrogens by large cations such as cesium, however, exhibit low solubility in both aqueous and organic media [50]. The resulting heteropoly acid salts have the potential to be recycled; they exhibit unique superacidic and multielectronic properties in addition to an important surface area when nanocrystallites are abundant within their structure. As a result they are interesting catalysts especially for acid or redox catalyzed reactions [51]. Their chemical composition can also be easily modified to adjust the desired redox and acid-base properties. The salts are often classified by the structure of the heteropolyanion that constitutes the fundamental unit called the primary structure. A secondary structure is generated by the connection of these heteropoly anions by hydrogen bonding. HPAs have been successfully used to promote alcohol dehydration, alkylation, esterification, polymerization and oxidation among other reactions [52, 53]. Despite their high acid strength however, some HPAs have a rather low surface area [54], which certainly is a drawback in heterogeneous applications.

The above short summary indicates that although the traditional solid acids, such as zeolites, clays or metal oxides (neat or sulfated) still dominate the field of solid acids, several new classes of these catalysts such as metal-organic frameworks, composite- materials and nanoacids have been developed to provide further variety and application possibilities for the traditional reactions and also allow the extension of the already broad scope applications.

2.2. Homogeneous Catalysis – Stable Soluble Acids

In its over two hundred years of history, homogeneous acid catalysis was successfully applied in a variety of transformations such as esterification, hydrolysis, aromatic electrophilic substitution and electrophilic addition, and many others. The traditional mineral acids, such as HCl or H_2SO_4 served as efficient catalysts for these reactions in the past. However, these acids are commonly highly corrosive, and many discharge poisonous fumes that represent safety and health hazards. The same is true for the conventional Lewis acids, such as aluminum chloride and bromide, or other metal-halogen compounds ($TiCl_4$, $SnCl_4$ *etc*.). These acids are all moisture sensitive, and decompose to metal oxides and hydrogen halides upon contact with water, whether it is during a reaction or a work-up procedure. In addition to the safety and health concerns this undesirable feature will also exclude the recycling of these catalysts and produce a significant amount of waste. Accordingly, significant effort has been made to replace these acids with greener alternatives both in industrial and laboratory applications. There are two major desired characteristics; (i) the acid should be stable under aqueous conditions and should not hydrolyze to allow recovery and recycling and (ii) it should have low vapor pressure in order to maintain a stable acid or catalyst concentration during a reaction and avoid toxic fumes. There have been several attempts on applying water soluble acids that do not hydrolyze under aqueous conditions and therefore are recyclable. The most typical examples are heteropoly acids [55] such as the commercially available $H_3[PMo_{12}O_{40}]$, $H_4[SiMo_{12}O_{40}]$, $H_4[SiW_{12}O_{40}]$, or $H_3[PW_{12}O_{40}]$. These Keggin-type HPAs are soluble in water as well as in several organic solvents, and readily promote the typical Brønsted acid catalyzed reactions. However, due to their moisture insensitivity they can be regenerated from the reaction mixture upon removal of the solvent. The practical usefulness of HPAs generated extensive efforts in their synthesis and a large number of polyoxometallates have been prepared and applied for various purposes [56]. Another important group is that of trifluoromethanesulfonic acid (triflic acid) and its triflates [57], common salts of various metals, such as copper, gallium, lanthanides *etc*. and triflic acid that function as Lewis acids. In contrast to the traditional Lewis acids (such as $AlCl_3$), these acids resist aqueous hydrolysis and can be recovered from such solutions. According to their properties, metal triflates are well-known for forming complexes with organic ligands, thus opening a way for a broad range of applications including asymmetric catalysis [58]. However, due to their considerable cost, their widespread applications, particularly at the industrial scale, are not yet established.

The third large group of potentially sustainable acid catalysts is the acidic organocatalysts. These materials are organic compounds that possess considerable acidity and thus are capable of promoting acid-catalyzed reactions. Most of them, although not soluble in aqueous medium, are water tolerant and would remain stable during aqueous workup conditions. The traditional examples are alkyl or aryl sulfonic acids, such as *para*-toluenesulfonic acid (*p*TSA), that catalyze a variety of transformations [59]. Another such example, camphor sulfonic acid (CSA) extends the application of these acids to asymmetric synthesis [60]. Although, amino acids also possess weak inherent acidity and are often used in organocatalysis, the focus of the applications is not in acid-catalyzed reactions unless they are used as chiral ligands.

A new class of acidic organocatalysts, chiral phosphoric acids, was first reported in 2004, involving asymmetric organocatalytic Mannich reactions catalyzed by 3,3'-disubstituted (BINOL)-derived phosphoric acids [61]. These pioneering studies initiated extensive interest on the application of these unique compounds. Since their introduction, a large variety of transformations were carried out by chiral phosphoric acids, including Kabachnik-Fields, Pictet-Spengler, Strecker, Friedel-Crafts or Biginelli reactions, just to name a few [62].

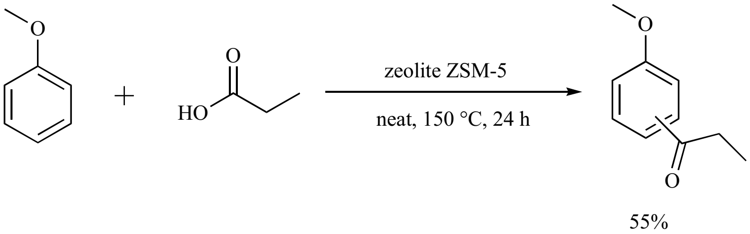
The field of green soluble acid catalysts has been dominated by triflates and heteopoly acids on the past two decades. More recently, acidic organocatalyst were introduced and found exceptionally active and selective in a number of applications, mostly in the field of asymmetric catalysis. Although organocatalysts are inherently green, their industrial applications are delayed by several factors. Among these, the often high cost (*e.g.* BINOL-based phosphoric acids), nearly stoichiometric amount required, and the difficult recyclability are the most detrimental issues that need to be addressed in future developments.

3. SYNTHETIC APPLICATIONS IN HETEROGENEOUS SYSTEMS

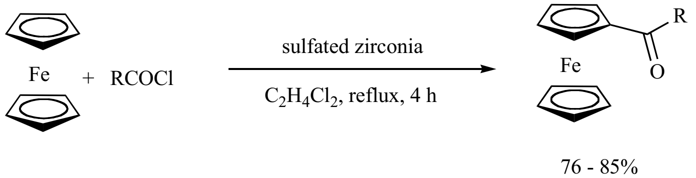
3.1. Friedel-Crafts and Related Reactions

The Friedel-Crafts reactions are one of the most fundamental transformations in organic chemistry. These processes are based on electrophilic aromatic substitutions and include acylation, alkylations, halogenation, nitration, sulfonation *etc*. Due to their practical importance the field has been the subject of numerous reviews and books, including Olah's extensive series [63]. Despite the nearly one and a half century old history, Friedel-Crafts reactions are widely used in organic synthesis to create carbon-carbon bonds and therefore prepare useful substituted aromatic compounds [64]. The catalysts that were conventionally employed to perform such reactions are traditional Lewis-acids such as $AlCl_3$ or BF_3. They are used in stoichiometric quantities and consequently generate a considerable amount of toxic waste. In addition, the regioselectivity when using these catalysts is often rather poor [65]. Solid acid catalysts offer many advantages over the traditional Lewis acid catalysts in a typical Friedel-Crafts reaction. Unlike conventional Lewis-acids, they have been shown to efficiently catalyze these reactions with good recyclability and interesting selectivity.

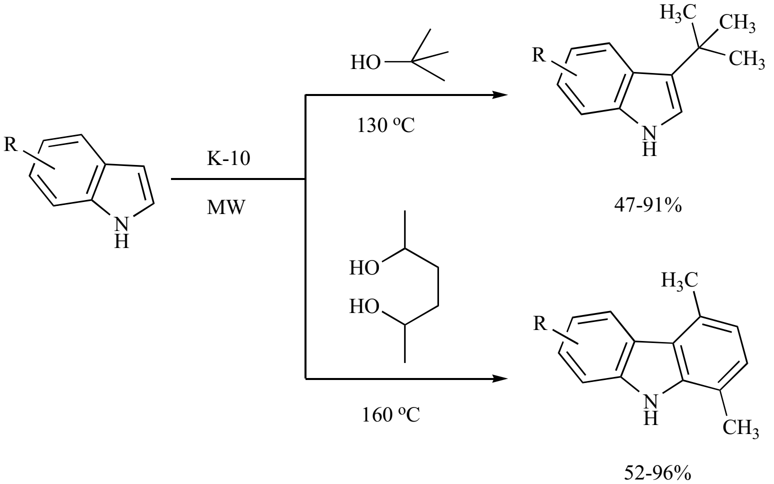
Acylation. The role of common zeolites and their metal-doped counterparts was studied for the acylation of anisole with propanoic acid under solvent-free conditions (Scheme **1**). The catalysts tested were ZSM-5 and BEA zeolites as well as their nickel, silver or iron-loaded derivatives [66]. Independently of the catalyst used, the



Scheme 1.



Scheme 2.



Scheme 3.

para- and *ortho*-products were predominant. The modified catalysts exhibited lower conversion compared to the original zeolites. This was explained by the replacement of Brønsted acid sites with Lewis acid sites that appeared to be detrimental for the reaction. The most efficient catalyst was found to be the pristine ZSM-5 zeolite yielding about 70% conversion and 80% selectivity. The same acylation could be carried out by MOF-based catalysts with high phosphotungstic acid loading [67].

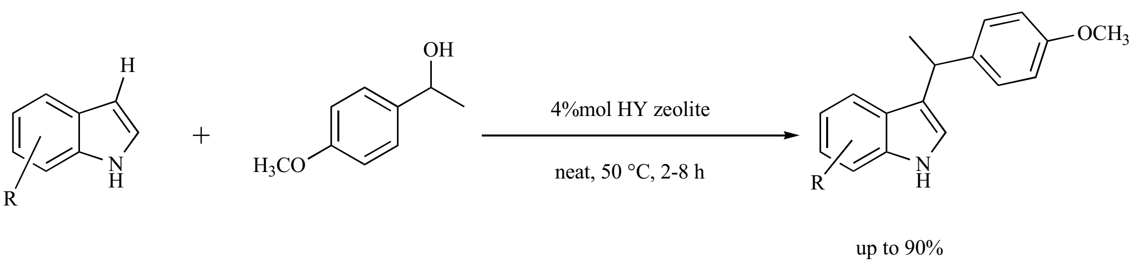
Yadav and Kamble developed a new solid superacidic mesoporous UDCat-5 catalyst for the similar acylation of toluene with propionic anhydride [68]. The reaction occurred at 180°C, with relatively moderate yield (68%), however, with exclusive regioselectivity. The reaction was carried out under solvent-free condition.

Sulfated zirconia was found to be an efficient catalyst for the acylation of ferrocene with acyl chlorides, including long chain compounds such as heptanoyl chloride (Scheme **2**). The reaction was carried out in dichloroethane under reflux conditions. The catalyst could be recycled in the reaction; five consecutive reactions resulted in no significant drop in activity and yields, in fact some activation (yield 88%) occurred during the subsequent reactions.

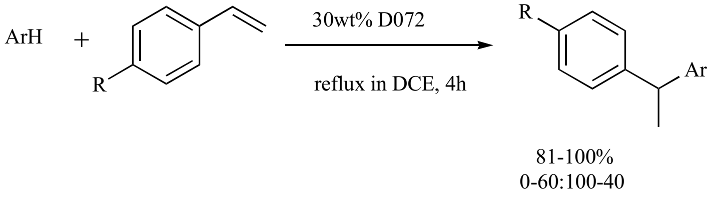
Alkylations. The microwave-assisted K-10-catalyzed alkylation and alkylation/electrophilic annulation of indoles were accomplished by using alcohols and diols as green alkylation reagents (Scheme **3**) [69]. The alkylation with *tert*-butyl alcohol occurred with moderate to high yields with high selectivity toward the C-3 position of indole. The solid acid appeared to show little sensitivity to the water that is eliminated during the reaction. Using 2,5-hexanediol the reaction occurred in a three steps sequence; alkylation, annulation and dehydrogenative aromatization to form 1,4-dimethylcarbazoles in good to excellent yields.

In a relevant extension, Cirujano *et al.* described a solvent-free Friedel-Crafts alkylation of indoles with alcohols (Scheme **4**), avoiding the use of the often required organic solvents [70]. In particular, the performance of ionic liquids and solid acid catalysts (metal organic frameworks and zeolites) were compared in terms of activity, selectivity and reusability. The major conclusion of the study was that the ionic liquids provide the best activity but the microporous frameworks provided better recyclability and better selectivity. Given the importance of lowering the environmental impact, the microporous solids are of great interests. They also showed improved selectivity towards small mono-alkylated products. HY zeolites were found to be the most attractive option in terms of yield, cost and recyclability for this reaction.

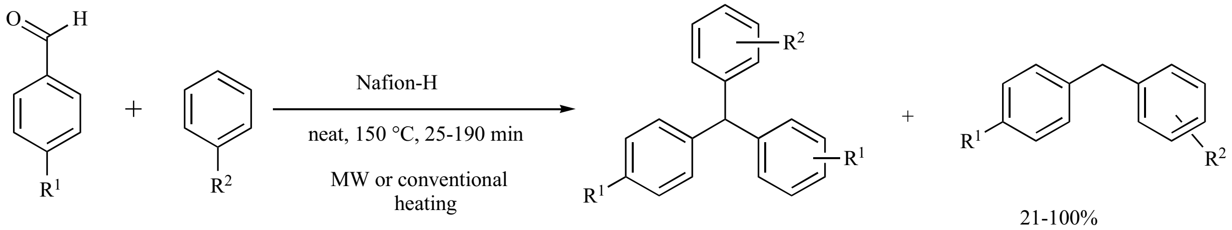
Acidic cation-exchange resins were also employed to catalyze Friedel-Crafts-type reactions [71]. Thanks to their inherent Brønsted acidity, they are capable of catalyzing the formation of carbocations or other electrophiles essential for the occurrence of an aromatic electrophilic substitution. The commercially available and low-cost sulfonic acid resin D072 was used for the hydroarylation of styrene-derivatives and electron-rich arenes (Scheme **5**). Under the optimized conditions the yields were close to quantitative with



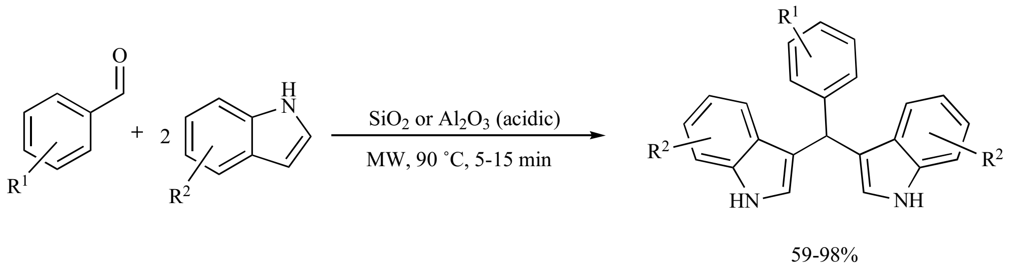
Scheme 4.



Scheme 5.



Scheme 6.



Scheme 7.

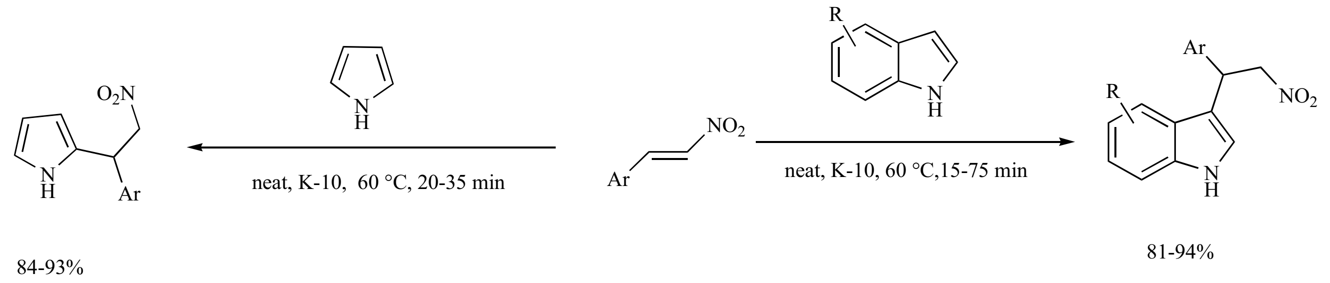
selectivity in favor of the main isomer reaching 100% for some reagents or as low as 60% for some others. The activity of the selected resin was also investigated in a fixed bed flow reactor in order to evaluate its potential use in large-scale applications. The activity was maintained and the selectivity was improved compared to the batch conditions. While dichloroethane is not a green solvent, 100% atom economy, the green alkylating agent and the recyclable catalyst substantially compensate this disadvantage.

The well-known, perfluoroalkyl-sulfonic acid resin Nafion-H served as a catalyst in the preparation of triarylmethanes from benzaldehydes and arenes under microwave irradiation and solvent-free conditions (Scheme **6**) [72]. The combination of the solid acid catalyst and the activation method proved to be effective to produce high yields in short reaction times. Different regioselectivities were obtained depending on the activation methods: microwave irradiation favored the formation of *ortho-ortho* products while conventional heating mostly yielded *para-para* products. The obvious advantages of the method lie mainly in the nature of the catalyst that is environmentally friendly and can be filtered off for an easier product separation, as well as in the use of a green alkylating agent, that only produces water as byproduct. However, the recyclability of the catalyst was not investigated.

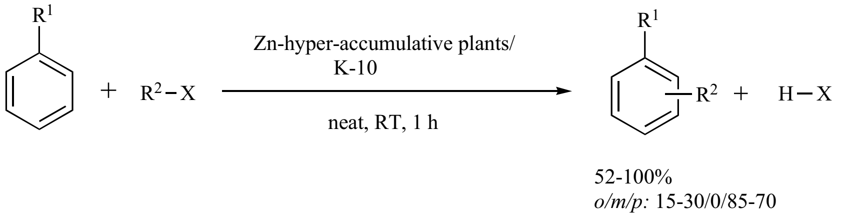
A similar process has been developed for the synthesis of bis(indolyl)methanes *via* the alkylation of indoles with aldehydes (Scheme **7**). According to the significantly enhanced reactivity of indoles, the inexpensive and abundant catalyst SiO_2 could be used under solvent-free conditions [73]. The reaction showed a broad substrate scope using a variety of aromatic aldehydes all providing high yields. Although the highest yields were obtained with silica as a catalyst, the reaction was not catalyst specific. The similarly abundant and inexpensive acidic Al_2O_3 was also found to be an effective catalyst for the reaction, however, resulting in slightly lower yields.

Due to its significant acidity and high surface area, K-10 montmorillonite is a widely used catalyst for various transformations including the Friedel-Crafts reaction. As shown in Scheme **8**, K-10 efficiently catalyzed the alkylation of indoles and pyrrole with nitroalkenes under solvent-free conditions at moderate temperature (60°C) providing high yields [74]. In addition to the low cost and environmentally benign nature of the catalyst, it appeared recyclable during three consecutive cycles.

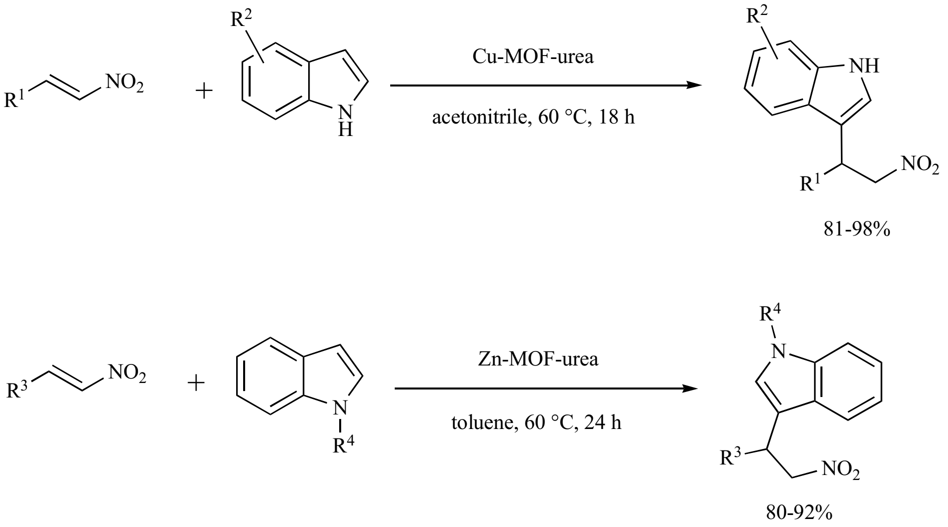
Several works have exploited the catalytic potential of non-conventional biomass, such as metal hyper-accumulator plants, in



Scheme 8.



Scheme 9.



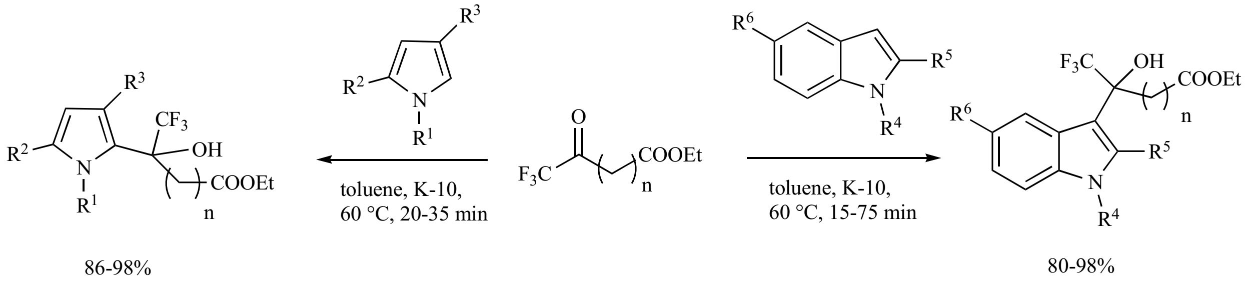
Scheme 10.

combination with the same common porous support, montmorillonite K-10 [75]. Grison *et al.* demonstrated the clear advantages of heterogeneous catalysts over their homogeneous counterparts [76]. The heterogeneous plant-based Lewis acids afforded high yields and good recyclability with consistent yields for up to four consecutive cycles. Two reactions were studied: the acylation of anisole with acetic anhydride and the alkylation of aromatics with alkyl halides (Scheme **9**). The combination of Zn hyper-accumulative plants supported on K-10 was demonstrated to be the most efficient catalyst providing yields ranging from 50% to 100% depending on the reactants. In addition, the results obtained with these ecocatalysts were considerably superior to the results obtained with the commercial Lewis-Acid $ZnCl_2$.

Numerous examples have shown the performance of metal organic frameworks in Friedel-Crafts reaction as well. They often are functionalized in order to improve their performance. Urea-containing MOF have recently attracted attention for the alkylation of indoles with nitroalkenes. Urea-based compounds are known for their capacity to participate in hydrogen-bonding and therefore act as organocatalysts. In traditional homogeneous systems, they undergo self-quenching and consequently require high catalyst loading. Functionalizing MOFs with urea moiety yielded interesting results. Luo *et al.* synthesized a MOF from V-shaped dicarboxylate ligands and dicopper units [77]. The obtained simple 2D structure was believed to ease the access of the substrates while stabilizing the urea moieties, previously attached to the building blocks. The resulting heterogeneous catalyst was highly active in the Friedel-Crafts alkylation of indoles with nitrostyrene (Scheme **10**); it was tolerant towards various substituents and exhibited good recyclability. Another similar study reported the alkylation of indoles with various nitroalkenes catalyzed by a zinc-based MOF containing ureylenic acid as the hydrogen-bond-donor [78]. The authors also observed a significant increase in activity upon heterogenization of the urea organocatalyst. When employed as catalysts for Friedel-Crafts reactions, the desired products were obtained in high yields in toluene at 60°C.

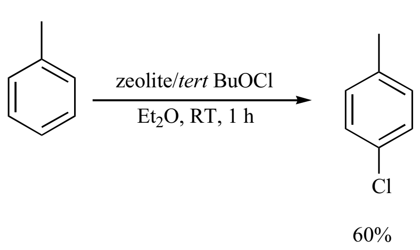
The synthesis of a large number of organofluorine indole and pyrrole derivatives was achieved by a K-10-catalyzed aromatic electrophilic hydroxyalkylation (Scheme **11**) [79]. Several of the synthesized products showed good to excellent activity in the inhibition of the fibril formation of Alzheimer's disease's amyloid beta peptide [80].

Halogenations. The chlorination of aromatic compounds was performed using various types of zeolites. One of them, the proton-



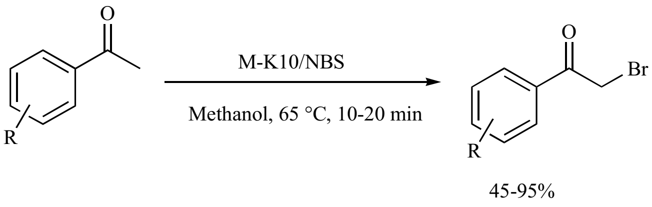
Scheme 11.

exchanged zeolite X, catalyzed the chlorination of toluene at ambient temperature in different solvents using *tert*-butyl hypochlorite (Scheme **12**) [81]. The solvent effect appeared to be an important factor for the selectivity as well as the conversion. The best results in terms of both yield and selectivity were obtained in ether, probably due to its polarity that is believed to stabilize the oxonium intermediate and aid the selectivity. Tetrachloromethane also provided high yields; however, both solvents cause many health and environmental issues.



Scheme 12.

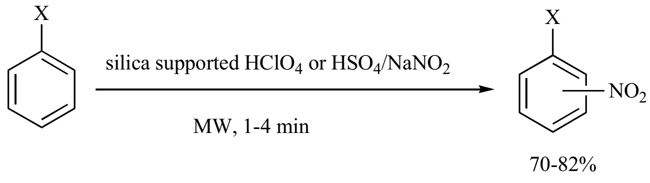
Mohan *et al.* reported a regioselective bromination reaction using the widely-used montmorillonite K-10 clay in presence of N-bromosuccinimide (Scheme **13**) [82]. Various aralkyl ketones were converted to α-monobrominated aralkyl ketones in methanol at mild temperature (65°C) with excellent yields and short reaction times. In addition to the simplicity and the efficiency of the method, the reusability of the catalyst is another benefit of the method surpassing other existing procedures that suffer from disadvantages such as the use of toxic brominating agents, long reaction times or tedious workup.



Scheme 13.

Nitration: Several works have reported successful nitration of aromatics over zeolites in attempts to substitute the concentrated acidic solution mixture (nitric and sulfuric acids) that is traditionally employed for this reaction type. For instance, the nitration of phenol over the acidic zeolite Hβ in ethanol resulted in a combined yield of 86% with a *para/ortho* ratio approaching 1 (Scheme **14**, **a**) [69]. Although the regioselectivity could be improved by using hexane instead of ethanol, selecting this solvent is not in favor of the environmental impact. In addition, the method doesn't completely eliminate the use of acidic solutions since a dilute solution of nitric acid was still used as the nitrating agent. Another work employed similar zeolites in dichloroethane under reflux for 48 h (Scheme **14**, **b**) [69]. It was observed that the best results were obtained when zeolites had large pores to optimize the reaction rate and restrictive channel structure to better control the regioselectivity. While the combined yield was lower than for the first method, the selectivity was higher. This method used isopropyl nitrate, another nitrating agent.

Kumar *et al.* reported the nitration of aromatics with silica supported perchloric acid or bisulfate under solvent-free microwave-driven conditions (Scheme **15**) [83]. The green nitrating agent $NaNO_2$ in combination with the supported acidic catalyst yielded excellent results in short reaction times. Perchloric acid was preferred over bisulfate due to its low nucleophilicity and higher acidity. The catalyst was easily prepared and could be reused for four consecutive cycles.

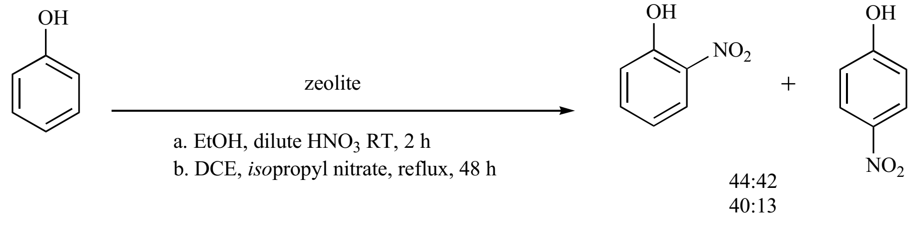


Scheme 15.

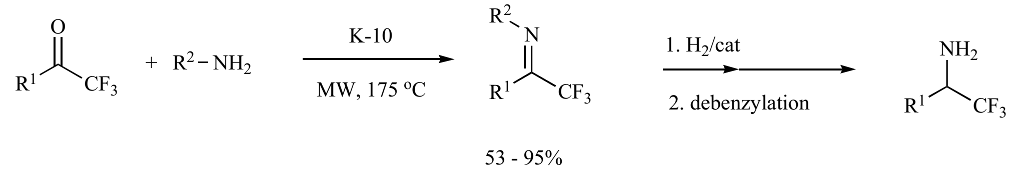
3.2. Condensations

Condensation reactions, an acid or base-catalyzed sequence of an addition and an elimination reactions, are versatile and constitute a broad scope of transformations that enable the synthesis of a wide range of products [84].

The K-10–catalyzed microwave-assisted condensation of substituted aryl trifluoromethyl ketones and different primary amines yielded the corresponding trifluoromethyl imines (Scheme **16**) in good to excellent yields. Although most of the reaction conditions qualify as green, high temperature (175°C) and somewhat long reaction times (45-60 min) were required even with



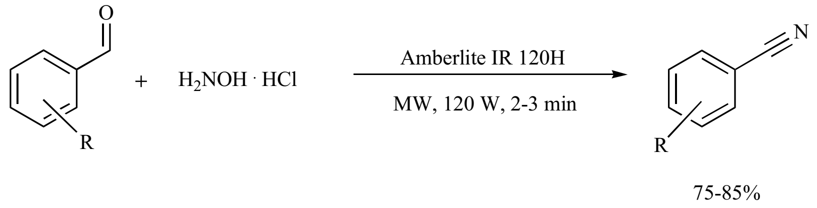
Scheme 14.



Scheme 16.

Method A	$B(OH)_3$ (20mol%) MW, 160 °C, 40 min	58-75%
Method B	KSF montmorillonite, MW, 150 °C, 60 min	43-97%

Scheme 17.



Scheme 18.

microwave activation to counter the low reactivity of the trifluoromethyl ketones. Despite the relatively harsh conditions the K-10/microwave protocol was still significantly greener than a similar, conventionally heated process that was catalyzed by PTSA; for some reactants as long as 7 days of heating at 175°C was needed to achieve 70-80% yields. The K-10 catalyst could be reused without any loss of activity [85]. The method could be successfully extended for the synthesis of chiral amines by carrying out the condensation with enantiomeric methyl-benzyl amines and hydrogenate the imines to secondary amines and finally remove the benzyl group by hydrogenolysis [86].

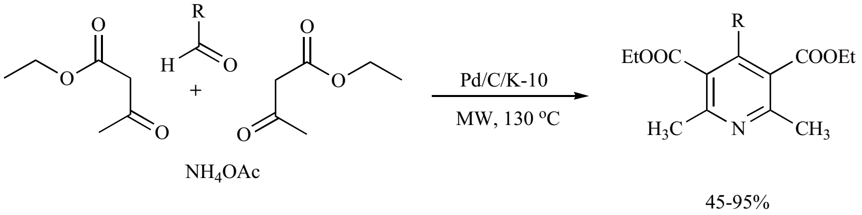
Chalcone derivatives were synthesized *via* the aldol condensation of acetophenones and benzaldehydes. The process was catalyzed by boric acid and was carried out under microwave-assisted solvent-free conditions (Method A) [87]. Due to the low solubility of boric acid, the reaction occurred in a rather heterogeneous system and the products were obtained in medium to good yields. The chalcones were obtained as the *E* stereoisomer with almost exclusive selectivity and were isolated in a pure form after a simple extraction of the product mixture (Scheme **17**, Method A). In a very similar approach (Method B) KSF montmorillonite was used as a catalyst [88]. The products were obtained in medium to good yields. Electron withdrawing substituents appeared to negatively affect the yield. (Scheme **17**, Method B).

Acidic ion exchange resins, such as Amberlite IR 120H, were also found to be excellent catalysts for the condensation reaction of aryl aldehydes and hydroxylamines (Scheme **18**) [89]. The solvent-free reactions provided high yields in short reaction times. The ion exchange resin could be readily recycled with only a negligible drop in activity even after the fourth consecutive run. The reaction appeared to be surprisingly substrate tolerant; a broad group of benzaldehydes was subjected to the experimental conditions without significant changes in yield.

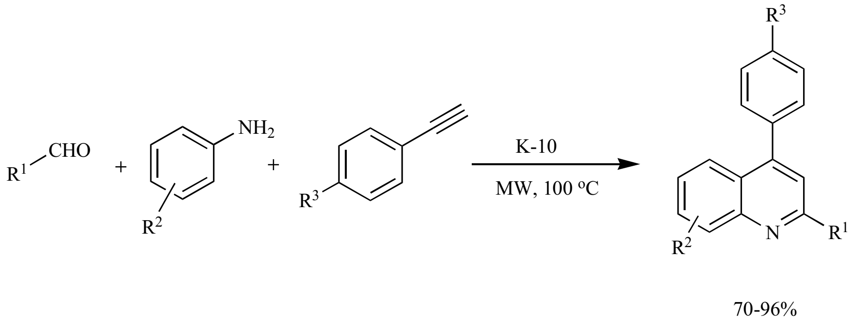
3.3. Multicomponent Reactions

The concept of multicomponent reactions is very simple; a cascade of reactions occurs in a specific order in one pot by simply adding the reactants to the reaction mixture at the beginning of the reaction producing a well-defined product selectively. This way, large compounds of complex structure can be prepared without the need of several purification steps of intermediates thus saving time, energy and effort, while also avoiding the formation of a potentially large amount of chemical waste. Therefore, multicomponent reactions are particularly attractive for green synthesis [90]. Given their attractive features these reactions have a long history dating back to the classic Hantzsch or Biginelli reactions from the late 1800s. Newer applications such as the Ugi reaction reinvigorated this field in the late 1950s.

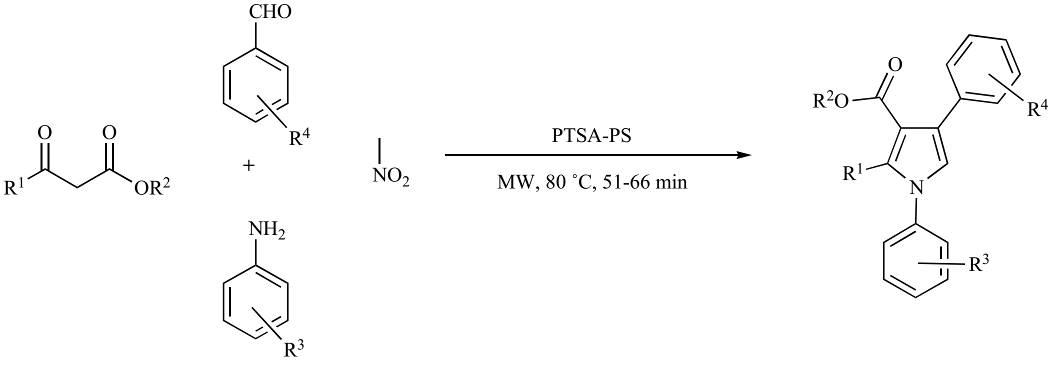
The traditional Hantzsch synthesis was successfully modified to an even greener heterogeneous catalytic approach by using a simple physical mixture of Pd/C and K-10 montmorillonite. The use of this catalyst mixture is a typical example of bifunctional catalysis. The solid acid K-10 efficiently catalyzed the condensation and cyclization of aldehyde, ethyl acetoacetate and ammonium acetate to result in typical Hantzsch esters. The successive dehydrogenative aromatization of the intermediate was catalyzed by the noble metal component to yield pyridine derivatives in moderate to excellent yields (Scheme **19**) [91].



Scheme 19.



Scheme 20.



Scheme 21.

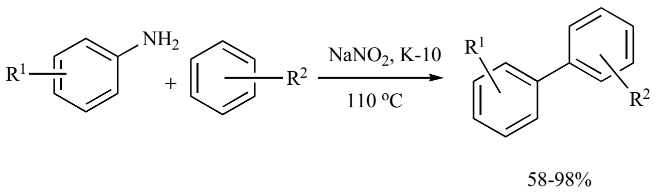
A similar, K-10-catalyzed microwave-assisted approach was developed for the synthesis of quinolones by a three component reaction using anilines, aldehydes and terminal aryl alkynes (Scheme **20**) [92]. The reaction pathway is of domino nature; the first step is the formation of an imine between the aldehyde and the aniline, which is immediately followed by the intermolecular addition of the triple bond to the imine. This intermediate then undergoes cyclization. Although the above steps are catalyzed by the strong acid centers of K-10, the last step, the oxidative aromatization, is due to the mild oxidative properties of this catalyst that is common to other montmorillonites as well.

The preparation of substituted pyrroles was achieved by Jeong *et al.* using a four-component reaction [93]. The authors reacted a β-ketoester, an amine, an aldehyde and nitromethane in the presence of catalytic amount of *p*-toluenesulfonic acid doped polystyrene (PTSA-PS) (Scheme **21**). The microwave irradiation resulted in high yields in short reaction times as compared to conventional heating. The catalyst was reused in seven consecutive reactions with only a negligible loss in activity.

3.4. Couplings

The traditional coupling reactions, such as the Heck, Suzuki or Negishi couplings are typical metal-catalyzed reactions [94]. Since their original discoveries the field has enjoyed considerable success [95] resulting in the Nobel Prize for the three scientists [96]. Thus acid-catalyzed approaches are relatively rare and occur through a different mechanism.

An environmentally benign metal-free, K-10 montmorillonite catalyzed domino-style approach was developed for the direct synthesis of biaryls by solid phase diazotization of anilines and successive nucleophilic attack by aromatic hydrocarbons that led to C-C bond formation (Scheme **22**) [97]. The reaction provided excellent yields using a broad range of substituted anilines and a variety of aromatic nucleophiles. The catalyst was found to be recyclable five times without a notable loss of activity.

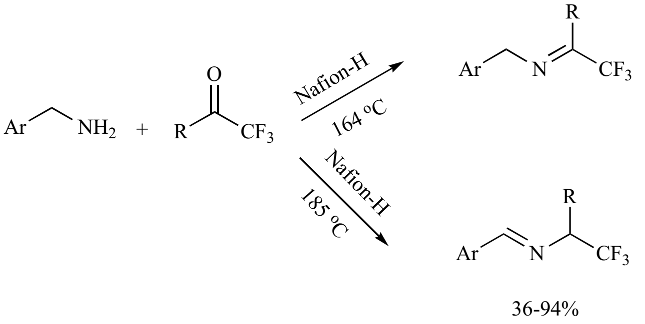


Scheme 22.

3.5. Rearrangements

Rearrangements are useful transformations to obtain compounds that are difficult or tedious to obtain in a direct route. Solid acids such as zeolites played an important role in early rearrangements in the chemical, particularly in the petrochemical industry, serving as catalysts for alkene isomerization or cracking reactions.

The superacidic Nafion-H and Nafion SAC-13 were found to be effective solid acid catalysts for the synthesis of trifluoromethyl ketimines from benzylamines and trifluoromethylated ketones (Scheme **23**) [98]. The reaction occurs *via* a condensation and a subsequent benzylimine-benzaldimine rearrangement *via* a facile 1,3-hydrogen shift. The reaction can be carried out under a wide range of reaction conditions such as microwave irradiation and flow system. It appeared that with the appropriate selection of the temperature one could direct the reaction to form the simple Schiff-base (164°C) or the rearranged benzaldimine (185°C) as major products. As the major goal of this work was to synthesize aldminines *via* the rearrangement, the initial step toward the formation of the benzylimine was not investigated separately and yields were not determined.



Scheme 23.

3.6. Ring Transformations

Ring transformations include cyclization as well as ring-opening reactions, both are important synthetic tools [99].

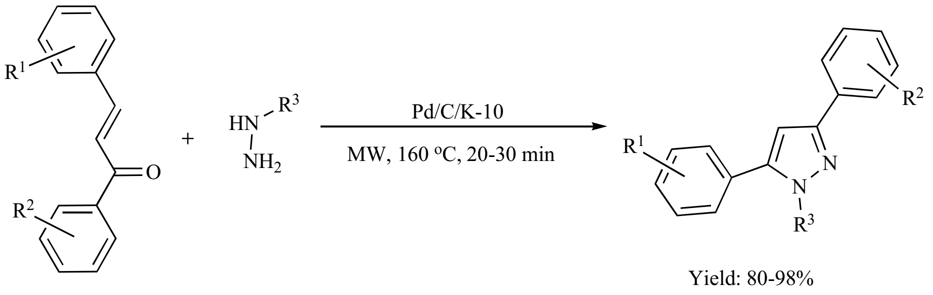
Cyclizations: The above described Pd/C/K-10 bifunctional catalyst was applied in the microwave-assisted synthesis of pyrazoles from chalcones and hydrazines. The concept was also similar to those mentioned above, K-10 catalyzed the condensation and subsequent cyclization, and the Pd promoted the last dehydrogenation/aromatization step. A broad variety of hydrazines and chalcones were applied to assess the scope of the method. The products were obtained in good to excellent yields (Scheme **24**) [100].

Phthalaldehydic acid (2-carboxybenzaldehyde) served as starting materials for the synthesis of valuable products. Its K-10 montmorillonite-catalyzed reaction with methylaryl and cyclic ketones yielded isobenzofuran-1(3*H*)-ones in excellent yields (90-98%) *via* condensation and successive lactonization reactions (Scheme **25**) [101]. A similar reaction using aryl-hydrazines led to the formation of phthalazinones by forming a hydrazone intermediate that immediately underwent cyclization (Scheme **25**) [102]. The application of microwave irradiation substantially increased the reaction rates in both reactions and the products formed in short reaction times (1-40 min).

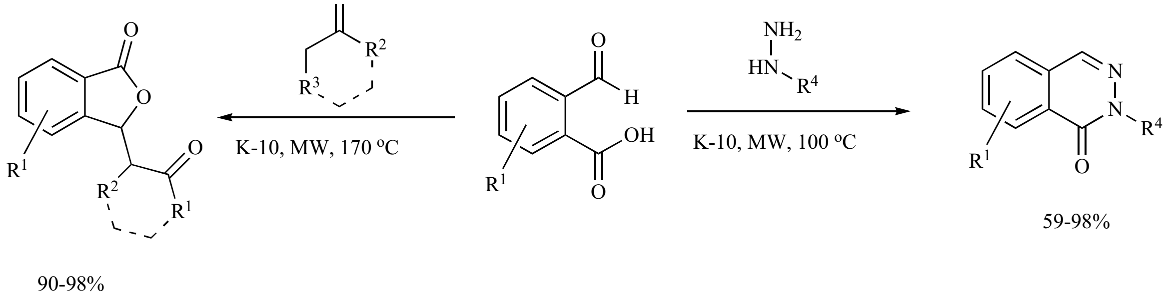
The synthesis of a broad variety of N-acyl-indoles and sulfonyl-pyrroles was completed by the cyclization of 2,5-dimethoxy-tetrahydrofuran with amides [103] or sulfonamides and amines [104] by microwave-assisted K-10 catalysis (Scheme **26**). The product N-sulfonyl-pyrroles were found to be effective (IC_{50}=32-135 nM) inhibitors of the FBPase enzyme, and thus could be considered as drug candidates for type 2 diabetes [105].

The synthesis of benzimidazoles, benzodiazepines, quinoxalinones was achieved by a solvent-free microwave-assisted K-10 montmorillonite-catalyzed method. A variety of substituted *o*-phenylenediamines readily reacted with ketones, aldehydes and bifunctional reagents to form the products (Scheme **27**) [106]. The bicyclic condensed heterocycles were obtained in moderate to excellent yields (53-99%) and excellent selectivities in short reaction times (mostly 1-10 min).

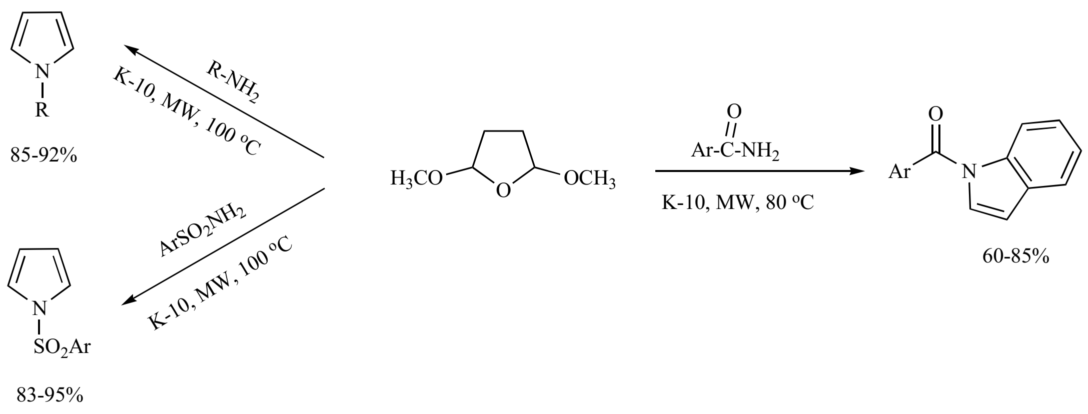
The synthesis of β-carboline-core based drug candidates was achieved by a Pd/K-10-catalyzed microwave-assisted Pictet-Spengler cyclization of substituted tryptamines with various aromatic aldehydes and glyoxals (Scheme **28**) [107]. The reaction proceeded by the acid (K-10)-catalyzed formation of an imine between the tryptamine and the carbonyl compounds and the subsequent cyclization to the tetrahydro intermediate. The additional Pd content of the catalyst completed the process by catalyzing the oxidative dehydrogenation/aromatization step. The compounds were found to be excellent inhibitors of amyloid-beta oligomer formation and butyrylcholinesterase activity, and also showed moderate anti-fibril properties [108].



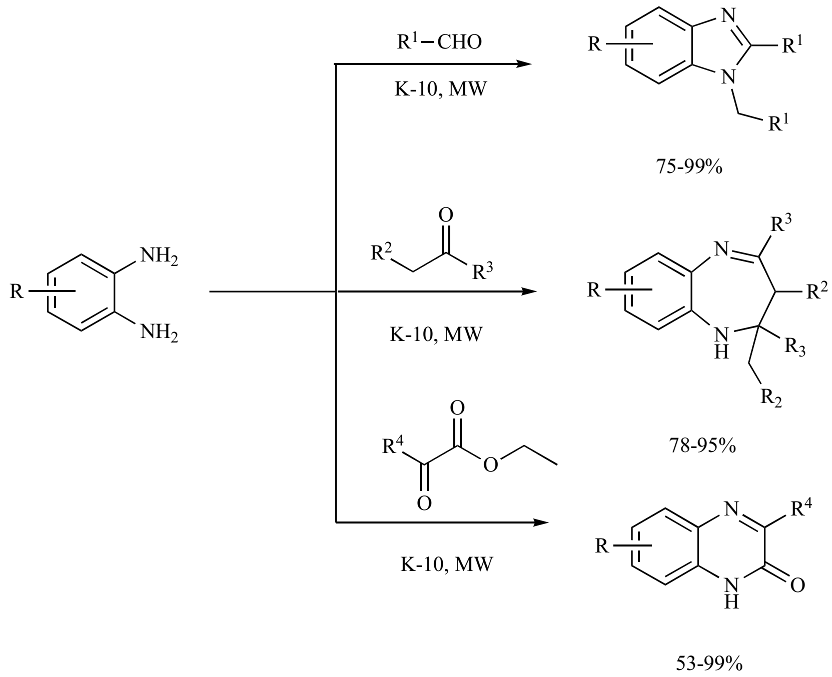
Scheme 24.



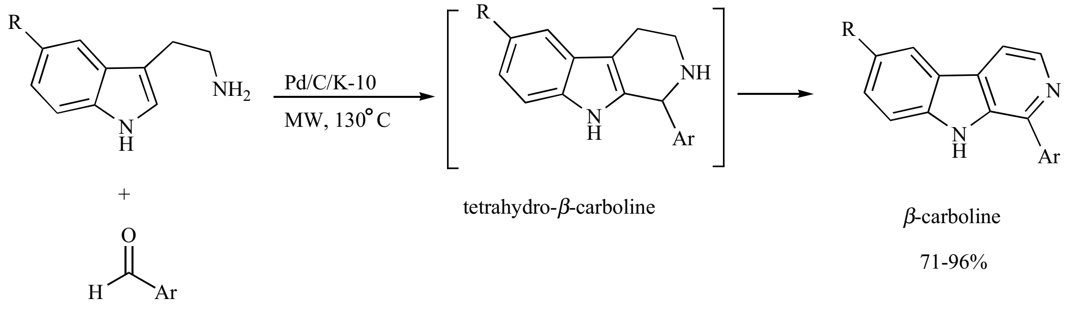
Scheme 25.



Scheme 26.



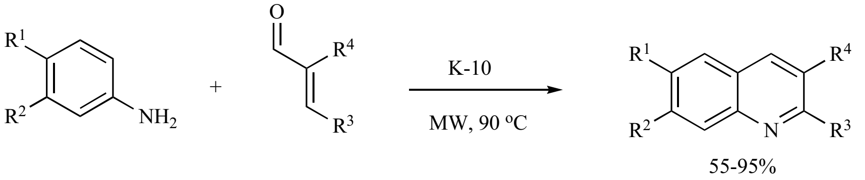
Scheme 27.



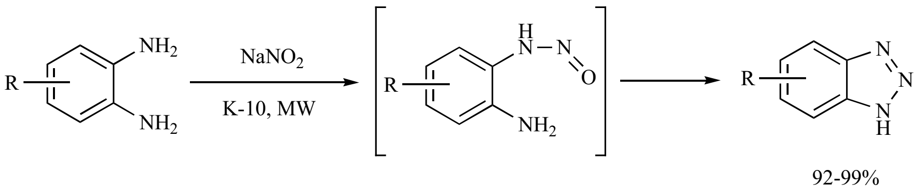
Scheme 28.

A similar approach was applied for the K-10-catalyzed microwave-assisted synthesis of quinolines from anilines and cinnamaldehydes (Scheme **29**) [109]. Reactions were completed in a matter of minutes and although mostly excellent yields were obtained, substrates with potential electron pair donor substituents, such as methoxy, only resulted in moderate yields, likely due to a complexation with the Lewis acid centers of the catalyst.

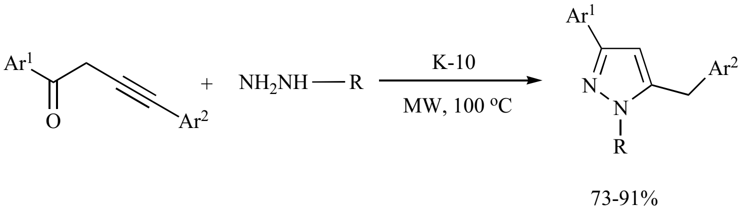
The microwave-assisted solid phase diazotization of *o*-phenylenediamines with K-10 montmorillonite appeared to be a novel method for the synthesis of 1,2,3-benzotriazoles (Scheme **30**) [110]. The method was based on a sequence of reactions that was initiated by the acid centers of K-10, namely the production of nitrous acid that reacted with the amino group of the phenylenediamine. Once the nitroso intermediate formed it underwent an immediate ring closure with the other NH_2 group due to their close proximity forming the benzotriazoles. The reaction showed broad applicability providing high yields for all substrates used.



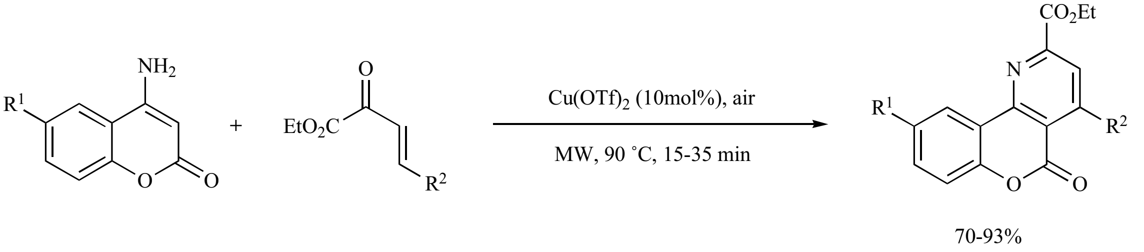
Scheme 29.



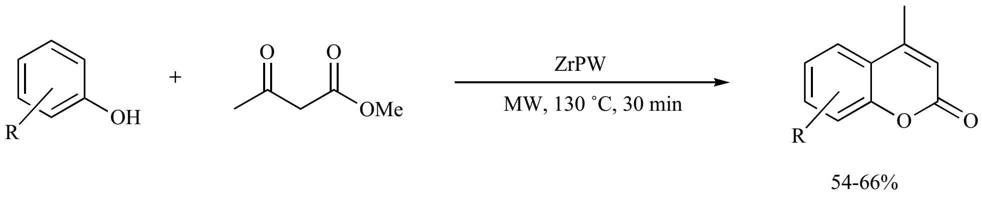
Scheme 30.



Scheme 31.



Scheme 32.



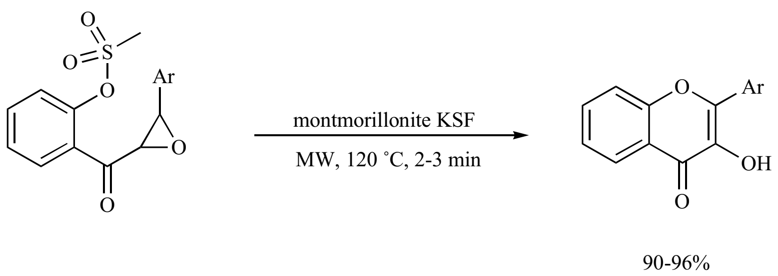
Scheme 33.

The K-10-catalyzed microwave-assisted 5-*exo-dig* cyclocondensation of alk-3-yn-1-ones with hydrazines led to the successful synthesis of diversely substituted pyrazoles (Scheme **31**) [111]. The combined application of the clay-based solid acid and microwave irradiation allowed the elimination of organic solvents during the heating and the products were obtained in excellent yields. Due to the different reactivity of the carbonyl group and the triple bond the reaction occurred with exclusive selectivity.

Several K-10-catalyzed cyclization reactions were assessed regarding their energy efficiency comparing microwave-assisted and conventionally heated examples. Six reactions were compared using the normalized energy consumption. It was found that the microwave activated ones were more energy efficient than the traditional counterparts in five of the six reactions. However, the one example when the traditional heating was more energy efficient indicates that every reaction should be individually assessed for energy efficiency, and the green label should not be automatically applied for microwave-assisted synthesis [112].

Cu triflate catalyst was successfully applied for the synthesis of fused chromenopyridines. The reaction has been performed under green conditions, using air as oxidant in a solvent-free system [113]. Due to the favorable redox properties of Cu, the Lewis acid catalyzed the Michael-addition as well as the final oxidation of the intermediate to the product (Scheme **32**). Although the intermediate underwent aromatization even in a catalyst free system, the yield and reaction rate improved significantly when the catalyst was present providing excellent yields.

The solvent-free Pechmann condensation was applied for the preparation of coumarins *via* an acylation-cyclization sequence of phenols with methyl acetoacetate using zirconium(IV) phosphotungstate (ZrPW) as a solid acid catalyst [114]. The expected products were obtained in short reaction times, albeit in moderate yields (Scheme **33**). The catalyst appeared to be recyclable, although it required an acid recovery treatment to restore its catalytic activity. A similar study applied Envirocat EPZ-10 as a catalyst for this reaction [115]. Although the conditions were about

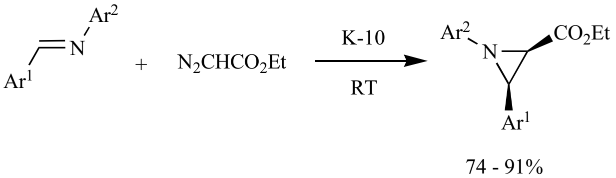


Scheme 34.

the same, the new catalyst appeared to make a significant difference and resulted in good yields.

The successive ring opening-cyclization of epoxychalcones in the presence of montmorillonite KSF under microwave-assisted solvent-free conditions resulted in the formation of flavonols (Scheme **34**) [116]. A broad scope of different aromatic substituents was tolerated and the formation of the products occurred in excellent yields in very short reaction times.

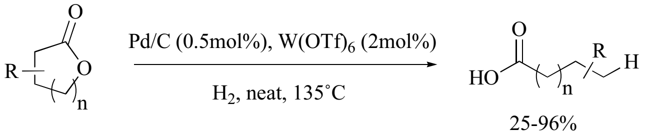
Aziridines are versatile synthetic building blocks that are used in highly regio- and stereoselective ring-opening reactions. K-10 montmorillonite has been applied as a catalyst for the synthesis of aziridines in a simple, ambient temperature approach using imines and ethyl diazoacetate as starting materials (Scheme **35**) [117]. The reaction resulted in the formation of *cis*-aziridines. The solid, easily recyclable catalyst, the short, room temperature reactions, the high atom economy, the excellent yields (90%) and exclusive selectivity all point toward an excellent example of sustainable synthesis.



Scheme 35.

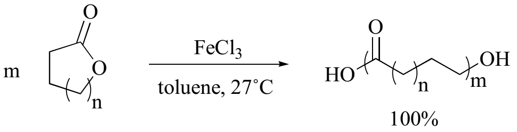
A microwave-assisted aminolysis of epoxides was catalyzed by $BiCl_3$ on SiO_2, an efficient heterogeneous catalyst. The reaction readily provided β-amino alcohols in high yields under solvent free conditions [118]. The catalyst could be recycled for five times without loss in activity. The microwave activation enhanced the yields even under shorter reaction times compared to conventional heating. A broad variety of epoxides could be successfully applied with negligible substituent effect (Scheme **36**).

Acids have been proven to serve as effective catalysts for the ring-opening reaction of lactones as well. As acidic conditions are also likely to catalyze the reverse reaction, i.e. lactone formation, the ring opening often is only successful if an immediate subsequent reaction is involved further transforming the primary product hydroxy-acids. In a recent study, Zhu *et al.* showed that metal triflates can be efficient in the ring-opening-hydrogenolysis of lactones to produce the corresponding carboxylic acids (Scheme **37**) [119]. While several different metal triflates were effective in the reaction, tungsten was found to be the most active. The metal cation acts as a Lewis-acid in both the ring-opening polymerization as well as the depolymerization forming an unsaturated acid that is then reduced by a conventional Pd/C catalyst. A broad range of different sized lactones could be transformed under relatively mild conditions and in mostly high yields.



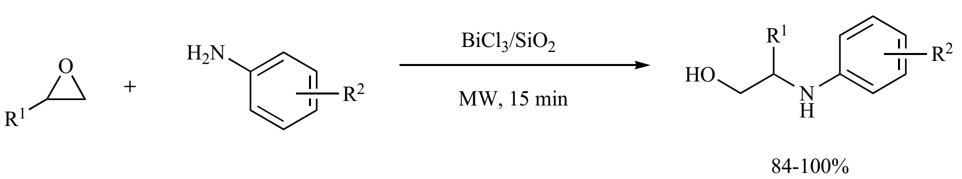
Scheme 37.

Gowda and Chakraborty used the environmentally benign Lewis acid $FeCl_3$ as catalyst for the ring-opening polymerization of lactones (Scheme **38**) [120]. The reactions gave full conversion to the polymer and good molecular weights of the polymers were obtained. The molecular weight distribution was shown to be superior to that obtained with other more complex iron catalysts.



Scheme 38.

Similar reactivity was obtained for the ring-opening polymerization of β-butyrolactone and lactide using a zinc-amine complex [121]. Miller *et al.* demonstrated that the Sb_2O_5 is effective in catalyzing the ring-opening polymerization/poly-condensation reaction between lactones and aromatic hydroxyacids [122]. The products were obtained in high yields and good molecular weights.

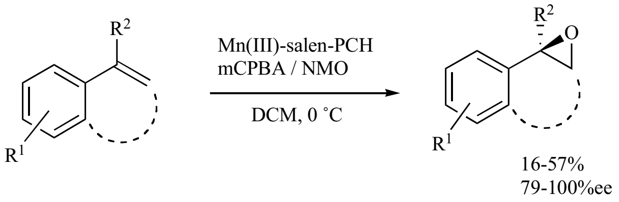


Scheme 36.

3.7. Asymmetric Synthetic Applications

The most common way to design heterogeneous catalytic applications is to immobilize either a chiral modifier on the surface of a solid catalyst or a chiral catalyst (*e.g.* metal complex) on the surface of a catalyst support.

The group of Freire and Pires showed that the asymmetric epoxidation of styrenes was possible under heterogeneous conditions using a manganese (III) salen complex immobilized on functionalized porous clay heterostructures (PCHs) [123]. The thus prepared catalyst enabled to obtain the desired epoxides in high enantiomeric excess but only in low yields (Scheme **39**). While the method is attractive due the use of a heterogeneous catalyst and the high enantioselectivities obtained, the use of dichloromethane as solvent and the non-recyclability of the catalyst limit the performance with regard to green chemistry metrics.

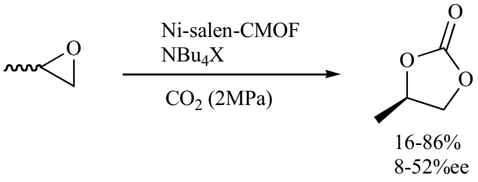


Scheme 39.

Lin *et al.* used a chiral metal-organic framework (CMOF) containing Mn-salen unit as linker for the asymmetric epoxidation of cyclic alkenes [124]. By generating isoreticular MOFs with different cavity size the authors observed that the epoxidation rate was clearly dependent on the channel dimension. While the catalyst could be recycled for up to 4 times without loss of activity and enantiomeric excess, the reaction suffered from the need of dichloromethane as solvent and 2-(*tert*-butyl-sulfonyl)iodosylbenzene as oxidant (Scheme **40**).

Similar results were obtained by Huang *et al.* using a Jacobsen's type catalyst bound to zirconium poly(styrene-phenylvinylphosphonate)-phosphate (ZPS-PVPA) and mCPBA/NMO as an oxidizer [125]. The reactions proceeded with high yields and enantioselectivities and the catalyst was reused for up to seven times without notable loss of activity and enantioselectivity. The authors showed that the reaction performed well on a large scale using the same procedure giving identical yields and enantioselectivities. Dichloromethane, used as the solvent for the reaction, however, led to an increase in the environmental impact of the reaction.

Using a CMOF containing a Ni-salen moiety as catalyst the insertion reaction of carbon dioxide into propylene oxide was possible [126]. The reaction used racemic propylene oxide as starting material and did not require the use of a solvent (Scheme **41**). Although the enantioselectivities obtained were moderate and the conversion was low, this method represents an interesting new procedure for a chiral resolution reaction.

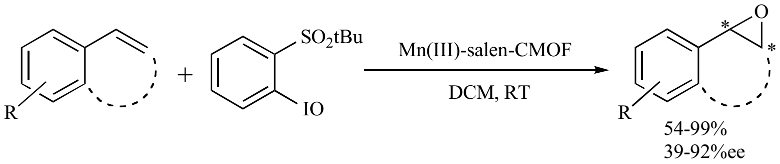


Scheme 41.

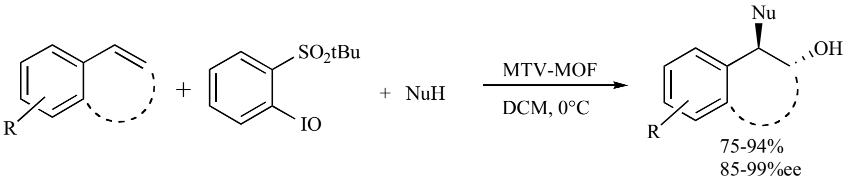
The sequential one-pot asymmetric epoxidation-ring-opening reaction of alkenes was shown to be effectively catalyzed by a multivariate MOF [127]. The MOFs used contained salen units with different metal ions as active centers. A variety of nucleophiles was used in the ring opening and the products were generally obtained in high yields and regio- as well as enantioselectivities (Scheme **42**). As described previously, 2-(*tert*-butyl- sulfonyl)iodosylbenzene was used as the oxidant and dichloromethane as solvent which significantly increases the environmental impact of the reaction.

Jiang and co-workers showed that a porphyrin-salen based MOF can be used as a catalyst in the asymmetric cyanosilylation of aldehydes (Scheme **43**) [128]. The reaction provided the desired products with moderate to high yields and enantioselectivities. The easy product separation and recyclability of the catalyst are negatively counterbalanced by the use of stochiometric amounts of PPh_3O as an activating agent and the use of dichloromethane as a solvent.

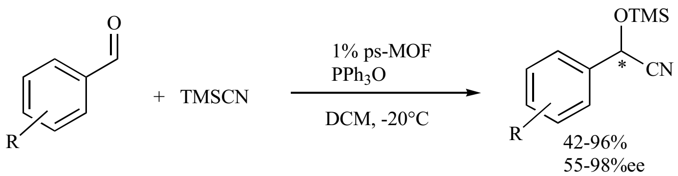
Cui *et al.* used a chiral porous organic framework (POF) functionalized with Rh as Lewis acid catalyst for the asymmetric conjugate addition of arylboronic acids to unsaturated ketones [129]. A variety of enones and arylboronic acids were coupled in mostly high yields and enantioselectivities (Scheme **44**). The catalyst was easily recovered by centrifugation and could be reused for five consecutive runs without significant loss in activity and enantioselectivity. The environmental impact of the reaction is increased by the fact that 50 mol% KOH have to be added and the reaction needs to be run in a dioxan-water mixture. The authors also demonstrated that the chiral POFs can be used as a separating agent in chromatography.



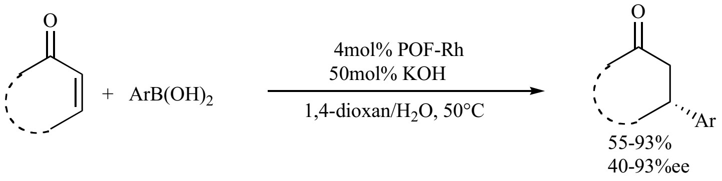
Scheme 40.



Scheme 42.



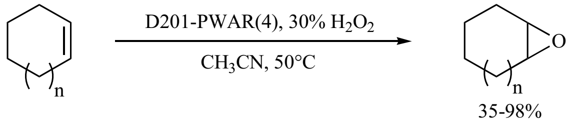
Scheme 43.



Scheme 44.

3.8. Oxidation of Alkenes

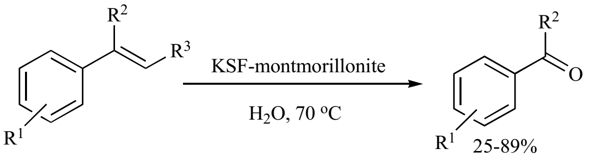
The oxidation of alkenes is traditionally performed by using organic peroxides or inorganic metal oxides in high oxidation states, both systems producing a large amount of low-value byproducts. To overcome this issue the use of solid acids in combination with environmentally friendly oxidizing agents such as hydrogen peroxide or oxygen has been explored. Xia *et al.* used 30% H_2O_2 and a solid phosphotungstic acid catalyst for the epoxidation of cyclohexene (Scheme **45**) [130]. The catalyst was prepared by simple exchange reaction with an anion-exchange resin and performed the desired reaction in high yields and selectivities. The catalyst could be recycled for up to five times without losing activity and selectivity. The authors also demonstrated that the scope could be extended for other substrates but with decreased yields and selectivities.



Scheme 45.

In a very similar approach the same group used a polystyrene-bound peroxophosphotungstic acid as a catalyst for the epoxidation of various dienes with H_2O_2 [131]. The best results were obtained with dicyclopentadiene where the monoepoxide was obtained in nearly quantitative yield. The catalyst could be recycled for up to eight times without losing activity.

The solid acid KSF montmorillonite successfully catalyzed the aqueous phase oxidative cleavage of styrenes to benzaldehyde with air, in a process that can be viewed as an environmentally benign alternative to ozonolysis (Scheme **46**) [132]. Although the reaction showed high selectivity and conversion in the oxidation of styrene, the cleavage of substituted derivatives occurred in lower yields and selectivities. The Fe-content of the catalysts was proposed as a major contributor to the mode of action, although the acid centers played a role in the cleavage of the intermediates.

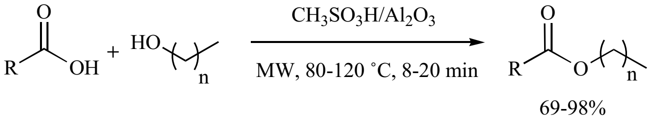


Scheme 46.

3.9. Miscellaneous Reactions

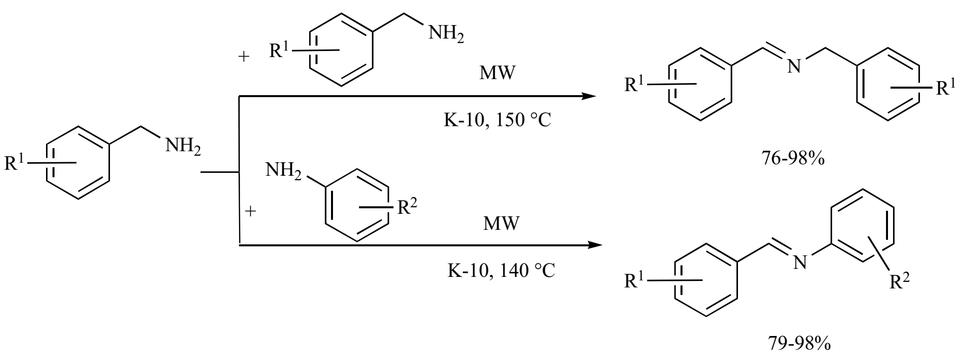
It appears that acidic montmorillonites possess properties that allow them to serve as mild oxidation catalysts as well. K-10 montmorillonite successfully catalyzed the partial oxidation of benzylamines to benzaldehydes and the immediate successive condensation of the product benzaldehydes with the excess amine to form benzylidene-benzylamines. Using a mixture of benzylamines and anilines mixed products, *e.g.* benzylidene-anilines were also obtained in excellent yields (Scheme **47**) [133, 134].

A tailored catalyst, methanesulfonic acid deposited on Al_2O_3, was applied in the esterification of carboxylic acids in a solvent-free, microwave-assisted process [135]. The scope of the reaction was broad; a variety of aromatic and aliphatic acids could be esterified with common alcohols. The process provided high yields in short reactions (Scheme **48**) and could be extended to the esterification of α-aminoacids.

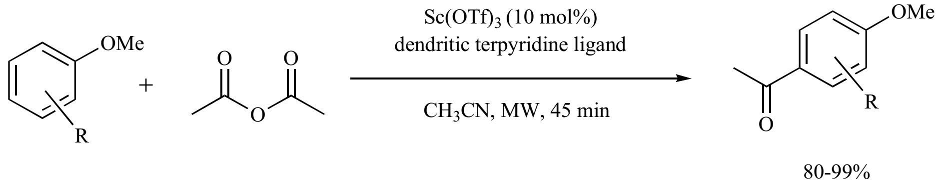


Scheme 48.

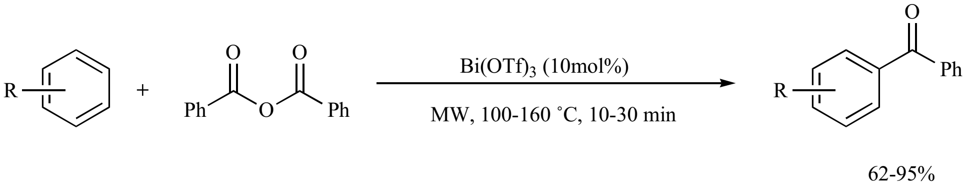
Solid acids have also been applied in the degradation and transformation of natural saccharides using a variety of these materials [136]. For example a patented method proposed a highly effective polymerization of building blocks derived from unlimited resources such as glycosides, employing solid superacid catalysts [137]. The method consists of reacting the starting materials with sulfonated metal oxides, such as sulfonated iron oxide or zirconia sulfate, by a melt polymerization or a solution polymerization process. For instance, D-glucose was polymerized without solvent in an electric furnace using an equivalent amount of sulfated zirconia at a temperature corresponding to the melting point of the saccharide for 24h. The method allowed the production of multiple polymers of saccharides in one simple step making the procedure relatively environmentally friendly compared to the wasteful multi-steps traditional methods.



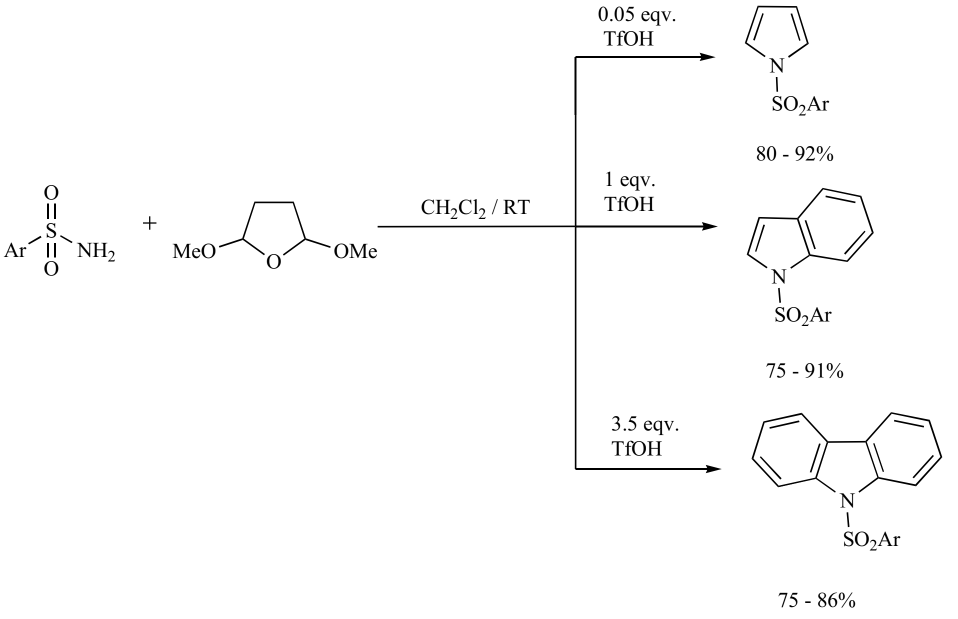
Scheme 47.



Scheme 49.



Scheme 50.



Scheme 51.

The above subchapter gives an overview of the many application possibilities of solid acids in synthetic processes. A wide variety of approaches are described. Essentially, solid acids can be applied and thus can replace harmful mineral acids in every process that has been attempted by traditional acid catalysis. It is widely believed that these materials are the future of acid catalysis and accordingly the development of the field is rapid and extensive. In addition to the common solid acids, such as clays, zeolites and acidic ion-exchange resins, several new classes of materials were introduced to the field and helped extending applications and will have a great impact on upcoming developments of new and potentially greener processes.

4. SYNTHETIC APPLICATIONS IN HOMOGENEOUS SYSTEMS

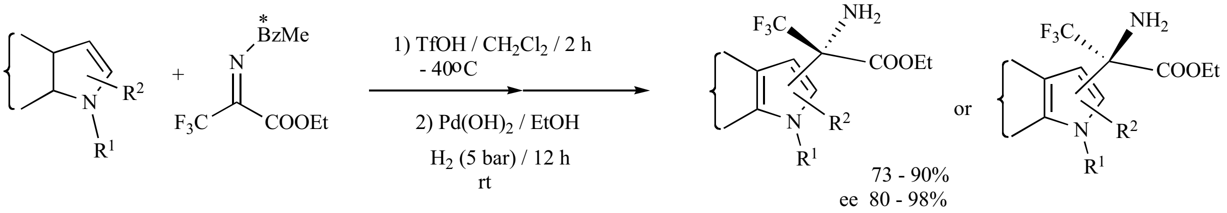
4.1. Friedel-Crafts and Related Reactions

The major goal in contemporary, sustainable homogeneous Friedel-Crafts chemistry is to replace the traditional catalysts, such as mineral acids and moisture sensitive Lewis acids with water stable recyclable acids.

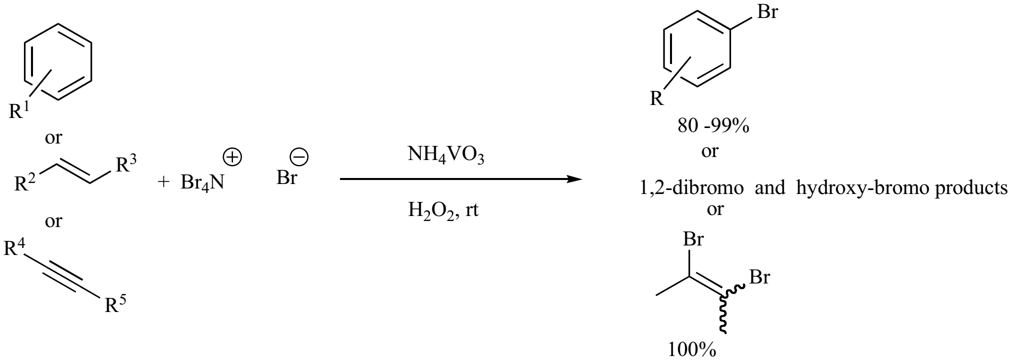
Acylation: Metal triflates are one of the most popular green acid catalysts in homogeneous catalytic applications. Anisole derivatives were acylated with acetic anhydride using Sc(OTf$_3$) and a dendritic terpyridine ligand as the catalyst (Scheme **49**) [138]. The application of microwave heating ensured short reaction time when derivatives with strong electron withdrawing groups were used. The catalyst, while soluble in the reaction medium, was also found recyclable, which is an important green feature and a significant step forward from traditional methods that use aluminum chloride.

Bi(OTf)$_3$ was described as an efficient catalyst for the microwave-assisted solvent-free Friedel-Crafts acylation of benzene derivatives with benzoic anhydride [139]. The benzoylation readily occurred with a wide variety of aromatics in short reaction times (Scheme **50**). The catalyst was found recyclable and only a negligible activity loss was observed after five consecutive reactions. It was noted that although conventional heating also produced the products it required significantly longer reaction times.

Alkylation: An efficient triflic acid catalyzed one-pot synthesis of N-substituted pyrroles, indoles, and carbazoles was achieved using a successive cyclization/annelation approach [140]. The reaction was carried out applying aryl sulfonamides and 2,5-dimethoxy-tetrahydrofuran as a starting materials (Scheme **51**). Although the first step to form pyrroles is a simple cyclization, the subsequent steps to form indoles and carbazoles occurred *via* the aromatic alkylation and aromatization. The reactant/triflic acid ratio



Scheme 52.



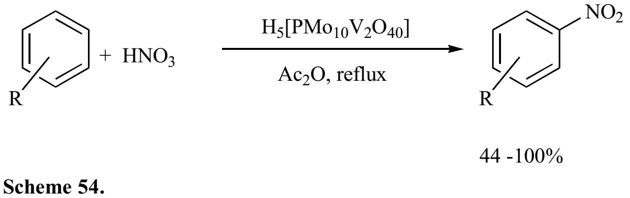
Scheme 53.

successfully controlled the formation of the desired product, thus indoles or carbazoles could be prepared without isolating any intermediate product. Despite the use of dichloromethane the rest of the system appears to be green involving a recyclable acid, the one pot-five step reaction (for carbazoles) and the room temperature reactions.

Triflic acid was also found to be an effective catalyst for the preparation of unnatural organofluorine amino acid esters [141]. The highly stereoselective aminoalkylation of indoles and pyrroles was carried out by using chiral 3,3,3-trifluoro-pyruvate-α-methylbenzyl imines. The reaction sequence was completed by a subsequent Pd-catalyzed hydrogenolysis to remove the methylbenzyl group provided the products in high yields and excellent enantioselectivities. The product α-trifluoromethyl-α-(heteroaryl)-glycine esters were isolated in high yields and excellent enantioselectivity (Scheme **52**).

Halogenation: The bromination of aromatic compounds, alkenes and alkynes was achieved using ammonium vanadate as a catalyst using tetrabutylammonium bromide as a bromine source (Scheme **53**) [142]. Hydrogen peroxide was applied as an auxiliary oxidant to produce Br$_2$ from the reagent. The process gave a broad variety of products in good yields under mild conditions, *e.g.* at room temperature. When alkenes and alkynes used the reaction resulted in mixtures. Using alkenes, 1,2-dibromo and hydroxy-bromo products formed, while in the case of alkynes, the reaction stopped at the dibromoalkene phase resulting in the formation of *E*/*Z* isomers with high selectivity for the *Z*-product.

Nitration: Heravi *et al.* described the nitration of aromatics with vanadium substituted phosphomolibdic acid in acetic anhydride as a solvent using nitric acid as the nitrating agent (Scheme **54**) [143]. Although the yields were mostly moderate the catalyst could be reused without significant loss in its activity.



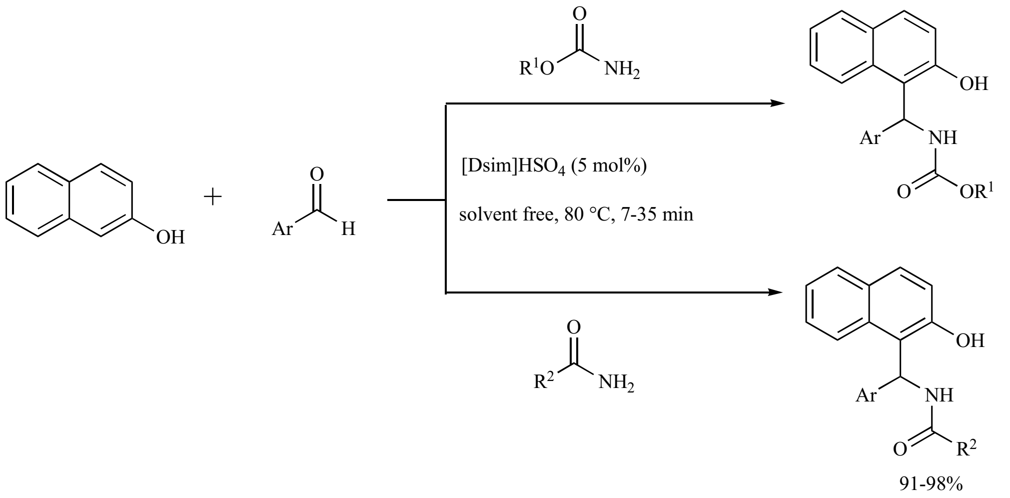
Scheme 54.

Bismuth (III) triflate was also found to be an excellent catalyst for the above reaction using toluene as a model substrate [144]. Using dichloroethane as solvent and HNO$_3$ as the nitrating agent the catalyst resulted in complete conversion of the starting material, essentially yielding 100% product. The catalyst was reused in the reaction five times and no activity loss was observed during the subsequent runs. The same reaction could be carried out using N$_2$O$_5$ as a nitrating agent [145].

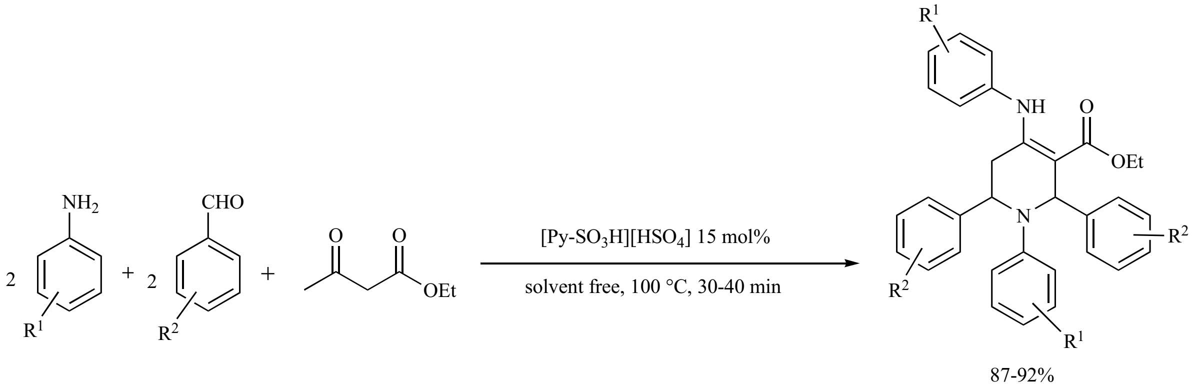
4.2. Multicomponent Reactions

Reported methods about multi-component sustainable syntheses catalyzed by homogeneous acid catalysts are scarce in the literature. A few acid driven-organic reactions in homogeneous systems are described in this part. Most methods use heteropolyacids, acidic organocatalysts and metal triflates; some other methods use unique homogeneous acid catalysts and constitute isolated examples. It must be noted that although they possess relatively good environmental-friendliness, their green potential is not always ideal. The limited number of existing methods, together with the yet-to-be improved sustainability of the presently selected works, illustrates the need for more research in this area.

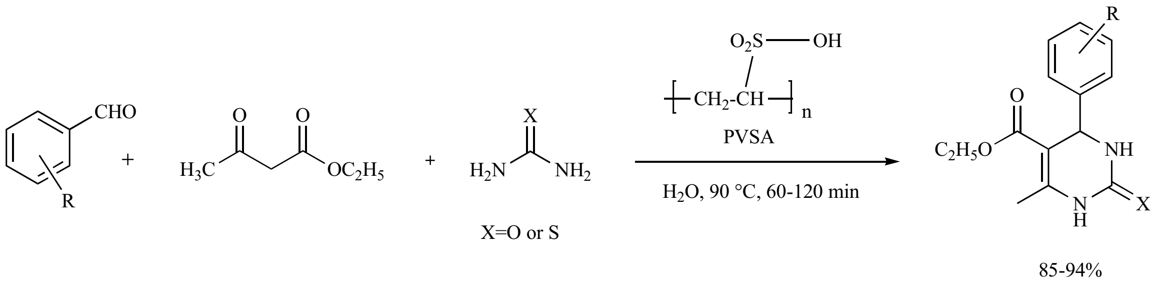
While ionic liquids are often used as reaction media, their specific properties also allow them to promote different reactions depending on their composition. As a result they have the ability to serve as catalysts as well. For instance, acidic functions can be introduced within the structure of the salt, providing acidic properties. A novel ionic liquid with Brønsted acidic properties was reported by Zare *et al.* and applied as a catalyst for the three-component synthesis of napthol derivatives [146]. The ionic liquid 1,3-disulfonic acid imidazolium hydrogen sulfate (DsimHSO$_4$) successfully promoted the condensation of β -naphthol with arylaldehydes and alkyl carbamates or amides with high yields in short reaction times (Scheme **55**). Despite the controversial eco-friendliness of ILs due mainly to their long and potentially wasteful synthesis, in this study, the IL was used in catalytic amount and was recyclable; consequently it limits the amount of waste generated. In addition, the proposed method has a significantly lower environmental impact than other methods often suffering from toxic catalysts in high loading, harsh conditions or long reaction times.



Scheme 55.



Scheme 56.

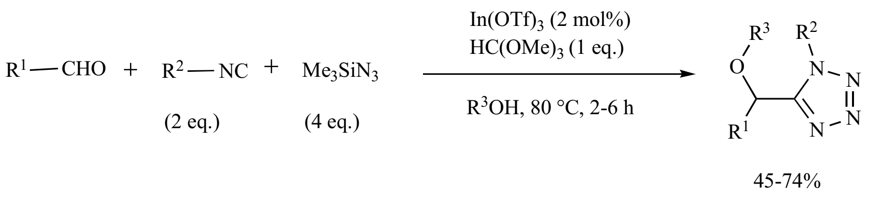


Scheme 57.

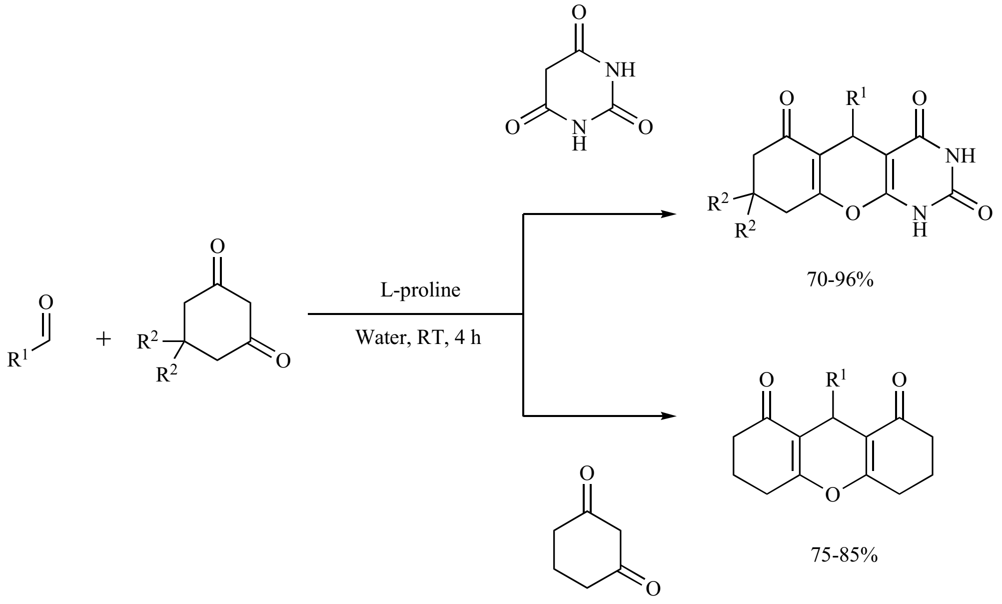
Biologically active tetrahydropyridine derivatives were synthesized in presence of a similar ionic liquid ([Py-SO_3H]HSO_4 - sulfonic acid pyridinium hydrogen sulfate) serving as an eco-friendly catalyst (Scheme **56**) [147]. The one-pot three-component condensation of various aromatic aldehydes, aromatic amines and ethyl acetoacetate was carried out without solvent at 100°C to reach yields above 80%. The IL played the role of both Brønsted and Lewis acid to assist the formation of the multiple intermediates. Not only did the reaction proceed better without solvent but the method also proved to be significantly more efficient that previously reported systems using organic solvents and/or toxic catalysts. After extracting the reaction mixture, the IL was used for five consecutive cycles with no noticeable loss of activity.

Polymers are tunable structures that can easily be functionalized. Attaching acidic functions to a polymeric chain forms an interesting material that can potentially be used as a catalyst. A simple and green protocol was reported for the three-component synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones (Scheme **57**) employing the water-soluble and reusable polyvinylsulfonic acid as a Brønsted acid catalyst [148]. This soluble solid-state analogue of sulfuric acid offers many advantages: it has a higher acid density than sulfuric acid, it can be used in aqueous media and has the potential to be recycled, it is cost-effective and easy to handle. As a result, the acid-catalyzed cyclocondensation of aldehydes, ethyl acetoacetate and urea or thiourea was conducted in water at 90°C affording excellent yields. The products were extracted from the mixture and the catalyst could be recycled after simple evaporation of water. The results obtained were comparable and even superior to most conventional metal-based procedures both in terms of yield and reaction rate.

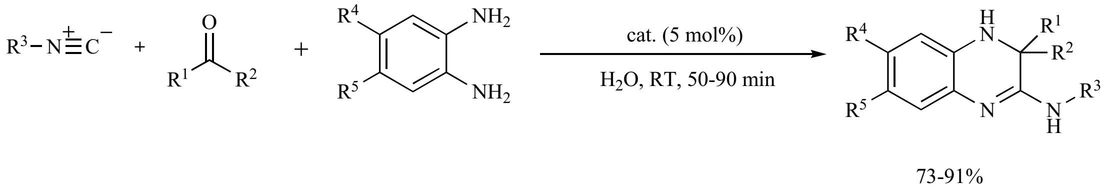
Indium triflate is another metal-triflate with catalytic activity [149]. The four component reaction of aldehydes, isocyanides, azidotrimethylsilane, and aliphatic alcohols was reported using indium triflate as a mild Lewis-acid catalyst (Scheme **58**). The



Scheme 58.



Scheme 59.



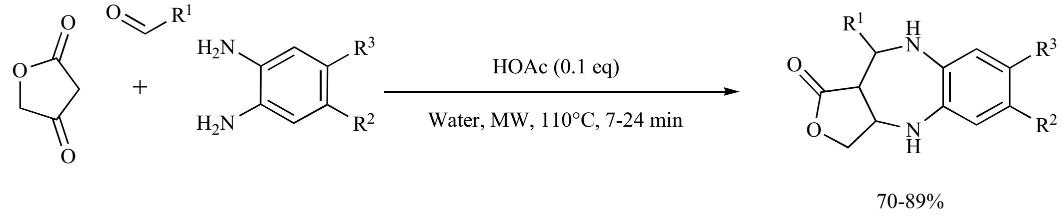
Scheme 60.

reaction starts with the Lewis-acid driven formation of carboxonium ion intermediate from the aldehyde and the aliphatic alcohol that also serves as a solvent. Interestingly, an optimum catalyst loading was reported for this reaction with yields ranging from moderate to good depending in part on the nucleophilicity of the isocyanide. The reaction shows some green features; it required low catalyst loading of a stable Lewis acid. However, the catalyst was not recyclable and afforded only moderate yields for some substrates. As another drawback of the method; excess amount of some of the reactants was necessary to observe conversion.

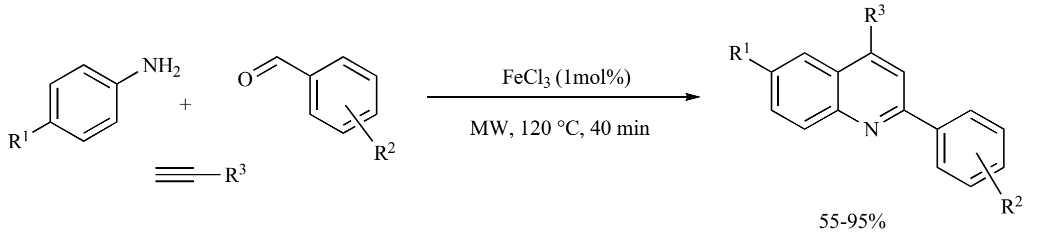
A few organocatalyst-driven multi component syntheses were reported under mild conditions in aqueous medium making them interesting methods from the green chemistry perspective. For instance, L-proline is a well-known organocatalyst that has successfully catalyzed multiple organic transformations. Myrboth *et al.* described the asymmetric multi-component synthesis of chromeno[2,3-d]pyrimidine-triones and xanthene dione derivatives using L-proline as a catalyst [150]. Aromatic aldehydes, dimethylcyclohexane-1,3-dione/cyclohexane-1,3-dione and barbituric acid were reacted at room temperature in water to afford chromeno[2,3-d]pyrimidine-triones in good to excellent yields and moderate to high enantioselectivities (Scheme **59**). The method was equally successful when using two equivalents of cyclohexane-1,3-dione in place of barbituric acid to form xanthene dione derivatives. The reaction was mostly assisted by the nucleophilic properties of the amino group of L-proline although its acidic properties contributed. The yields seemed not to be affected by the presence of electron withdrawing or donating substituents. The very mild reaction conditions and the non-toxic nature of the catalyst certainly contribute to reduce the environmental impact of the method despite the relatively high catalyst loading (15%).

The functionalization of organocatalysts with Brønsted acid groups creates acidic organocatalysts suitable to perform conventional Brønsted acid-catalyzed reactions. A guanidinium-based sulfonic acid functionalized organocatalyst was developed and proved its effectiveness to replace the traditional liquid mineral acids for the multi-component synthesis of a variety of quinoxaline-, pyrazine- and urazole-derivatives in aqueous media (Scheme **60**) [151]. The reactions proceeded smoothly in less than two hours at room temperature or reflux depending on the substrate type. The method also presented the benefits of heterogeneous systems because the product precipitated and was filtered out while the catalyst was extracted from water with ethyl acetate and reused for other cycles with consistent activity.

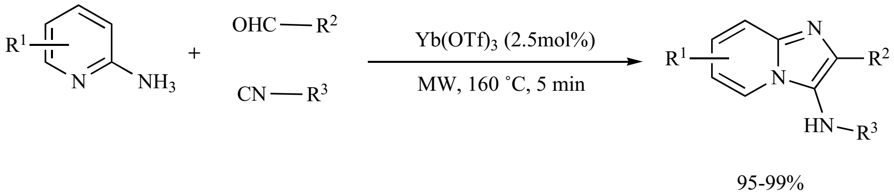
A similar method was developed by Wang *et al.* for the synthesis of the polycyclic benzoazulen-1-ones [152]. Although the authors called this procedure "catalyst-free" one should not



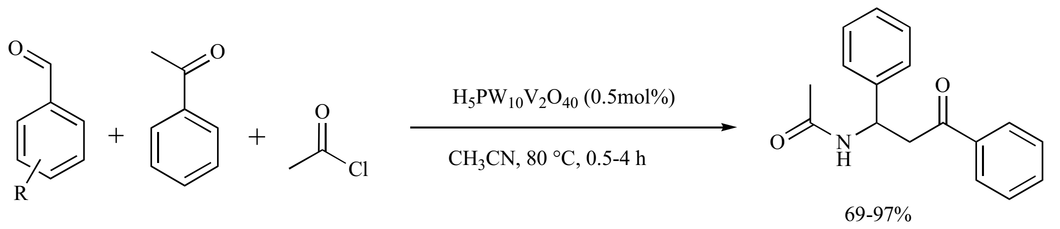
Scheme 61.



Scheme 62.



Scheme 63.



Scheme 64.

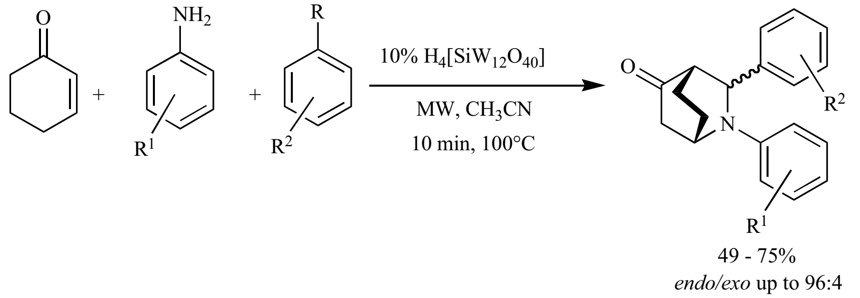
overlook the fact that the solvent acetic acid indeed acted as a mild strength acid catalyst. The microwave activation and the small amount of mild acid represented sufficient conditions to achieve high yields in short times. The substrate scope of the reaction was broad, showing little substituent effect (Scheme **61**).

A solvent free A^3-coupling was developed for the synthesis of quinolines (Scheme **62**) [153]. Microwave heating was used to activate the system and $FeCl_3$ was used as a catalyst. The reaction provided high yields for most substrates, although starting materials with strong electron-withdrawing substituents lowered activity and decreased yields. The environmentally benign catalyst, the high reaction rates and relatively short times are the main green advantages of the process.

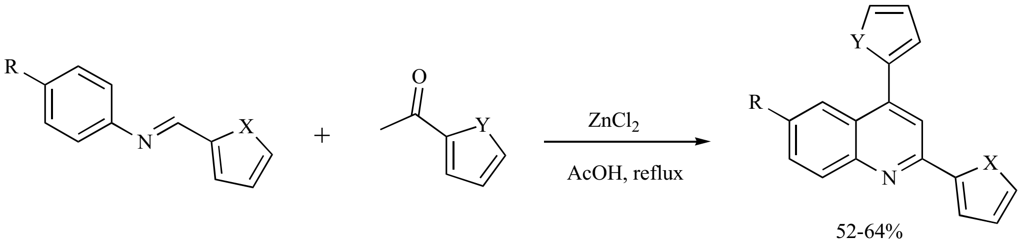
Imidazo[1,2-a]pyridines were synthesized by the multicomponent Groebke-Bienaymé-Blackburn reaction of 2-aminopyridines, aromatic aldehydes and isonitriles [154]. With the application of microwave activation, solvent-free conditions and $Yb(OTf)_3$ catalyst the products were obtained in excellent yields in short, only 5 min long, reactions (Scheme **63**). The sustainable conditions, the nearly quantitative yield ensured that the environmental impact of this method was significantly lower than that of available alternatives.

A heteropolyacid-catalyzed multicomponent condensation of an aryl aldehyde, acetyl chloride, acetonitrile, and enolizable ketone for the preparation of β -acetamido ketones (Scheme **64**) was described by Tayabee and Tizabi [155]. Several heteropolyacids were screened to compare their relative activity. The vanadium-substituted Keggin-type $H_5PW_{10}V_2O_{40}$ achieved the highest yields. Interestingly, despite its lower Brønsted acidity it showed better performance than the traditional Keggin-type heteropolyacid $H_3PW_{12}O_{40}$. In fact, the high catalytic activity is believed to be not only due to the acidity but also to the electron acceptor property of vanadium. Although, the high yields and short reaction times suggest an environmentally friendly protocol, there are a few disadvantages. The reflux conditions, the use of acetonitrile as solvent, as well as the required preparation of the metal-substituted heteropolyacid all increase the overall environmental impact of the protocol.

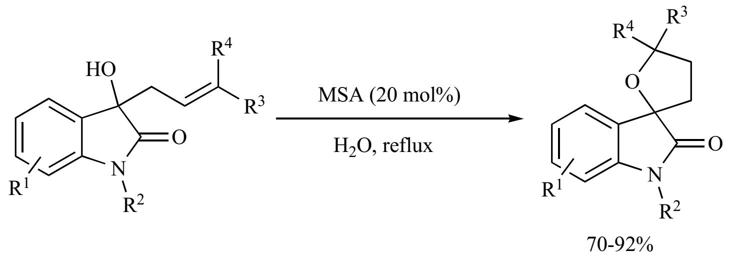
The heteropoly acid-catalyzed microwave assisted three component aza Diels-Alder cyclization of cyclohexenone, substituted anilines and benzaldehydes to prepare azabicyclo[2.2.2]octan-5-ones (Scheme **65**) was described by Borkin *et al.* [156]. The multistep reaction occurred in a one pot fashion. In the first step a Schiff base formed in situ, which underwent an intermolecular cyclization with the cyclohexenone. Despite the short reaction times the yields were moderate to good and the products formed with excellent diastereoselectivity. The compounds were also tested in preliminary cholinesterase and amyloid β fibrillogenesis inhibition assays to probe them as potential anti Alzheimer's disease agents.



Scheme 65.



Scheme 66.



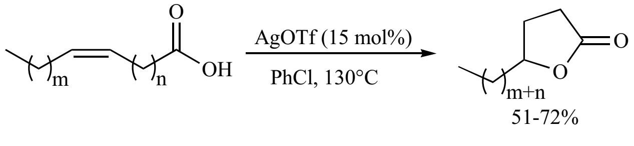
Scheme 67.

4.3. Ring Transformations

The formation of substituted quinolines was described using zinc chloride as the Lewis acid catalyst for the cyclization of ketones with imines (Scheme **66**) [157]. The reaction can also be performed as one-pot sequence without prior formation of the starting imines. The quinolines were obtained in moderate yields. Acetic acid was used as the solvent for the reaction allowing the formation of quinolines under environmentally friendly conditions.

Zhao *et al.* described a green way for the synthesis of substituted 3,2'-tetrahydrofuryl spiroxoindoles through cyclization of 3-allyl-3-hydroxy-2-oxoindoles (Scheme **67**) using methanesulfonic acid (MSA) as catalyst [158]. The reaction did not require any metal and water was used as the solvent. The authors showed that performing the reaction on a gram-scale was easily possible.

The group of Gooßen found that silver triflate was an effective Lewis-acid catalyst for the synthesis of γ-lactones from unsaturated fatty acids (Scheme **68**) [159]. The silver served as the catalyst for the migration of the double bond into proper position, as well as a catalyst for the lactone formation. Even though chlorobenzene was used as the solvent, the advantage of the reaction is in the remarkably high yield compared to previous known examples and given that several double bond migration steps have to be achieved before the cyclization can occur. Oligomerization was found to be the major side reaction, however, the formation of δ-lactones was not observed.



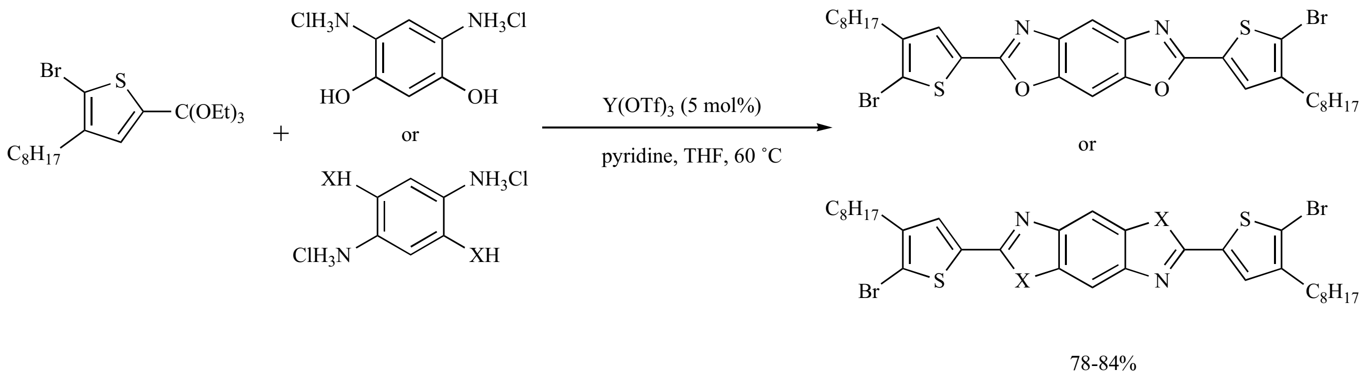
Scheme 68.

The synthesis of benzobis-azoles from an aromatic orthoester and diamino diols or dithiols using a Lewis acid catalyst (Scheme **69**) was described by Jeffries-EL *et al.* [160]. $Y(OTf)_3$ was used as environmentally benign catalyst and the desired products where obtained in high yields. The benzobisazoles formed served as monomers for the generation of conjugated polymers for use in organic LED. The drawback from the environmental point is that a pyridine/THF mixture had to be used as solvent for the reaction.

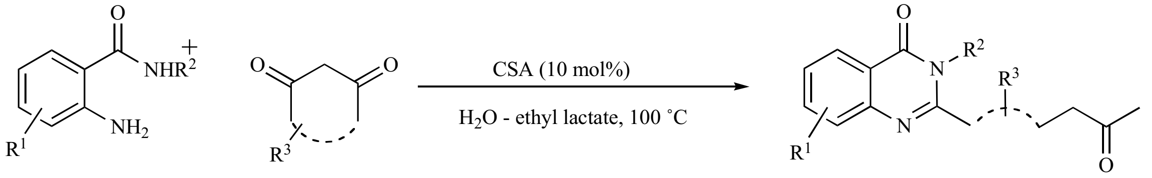
Uozumi and co-workers showed that camphorsulfonic acid (CSA) can be used as efficient catalyst for the synthesis of 4(*3H*)-quinazolinones [161]. The reaction used a water-ethyl lactate mixture as green solvent and was able to produce the desired compounds from a large variety of 2-aminobenzamides and 1,3-diketones (Scheme **70**). The diketones used can be both cyclic and acyclic and they undergo a C-C bond cleavage during the reaction.

The solvent- and metal-free synthesis of quinolines using a Brønsted acid was demonstrated by Bao *et al.* [162]. N-alkylamines were reacted with alkenes or alkynes and a catalytic amount of triflic acid to afford the formation of the quinolines in high yields (Scheme **71**). The reaction did not require any solvent and used oxygen as a green oxidant.

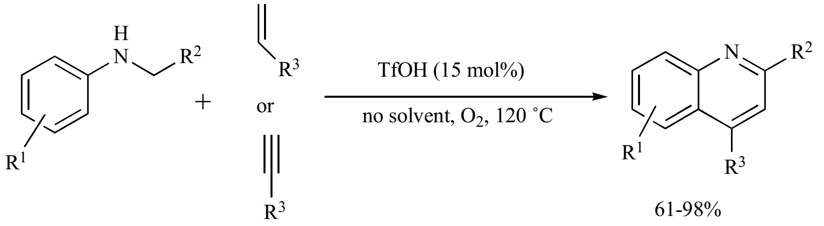
The group of Jirgenson developed a Lewis acid-catalyzed protocol for the formation of vinyloxazolines and vinyloxazines [163, 164]. Using bis(imidates) as starting materials the formation of the desired products was possible using a catalytic amount of $FeCl_3$ or $AlCl_3$ (Scheme **72**). The products were obtained in high yields and short reaction times. While the use of iron chloride is still acceptable within green chemistry, the use of aluminium chloride and dichloromethane should be avoided. The same group could also show that bis(trichloroacetimidate) can serve as starting material for the reaction [165].



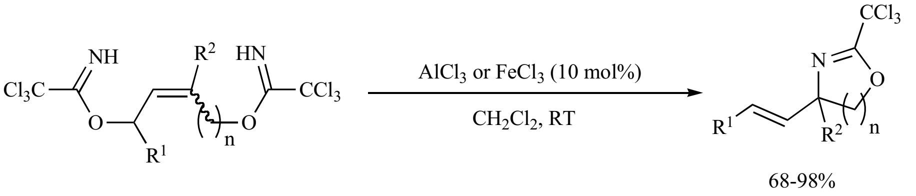
Scheme 69.



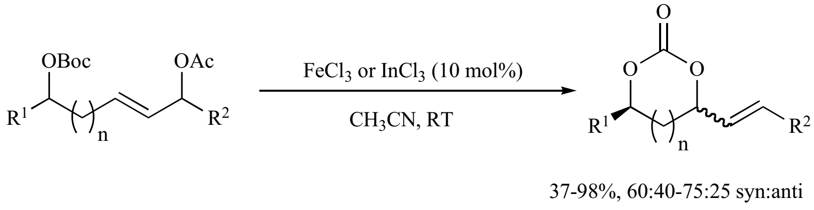
Scheme 70.



Scheme 71.



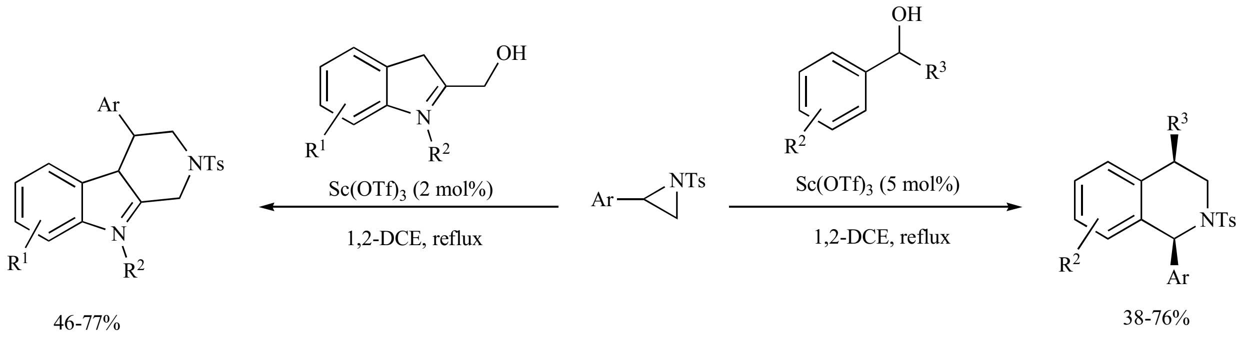
Scheme 72.



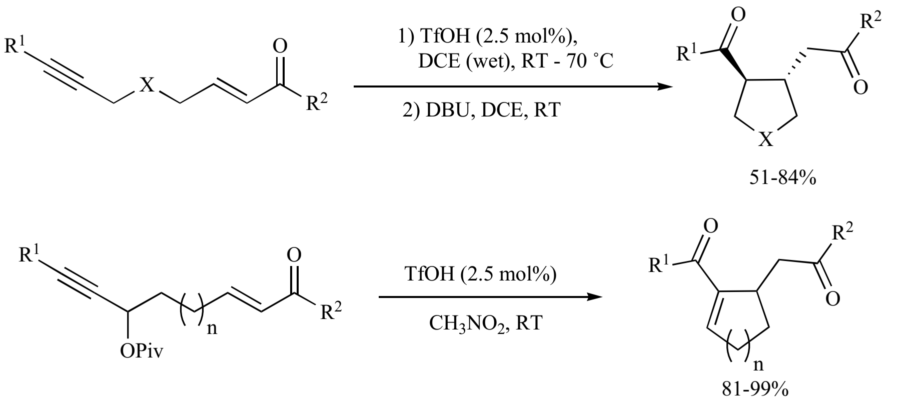
Scheme 73.

Cossy *et al.* demonstrated that iron and indium salts can serve as effective Lewis acid catalysts for the cyclization of *tert*-butyl carbonates to form cyclic carbonates [166]. Both five- and six-membered cyclic carbonates can be formed using this method. While iron proved to be effective for substrates containing only carbon and hydrogen, indium was shown to be superior when heteroatoms are present in the starting material (Scheme **73**). The *syn* diastereomer was always the major product obtained, albeit the selectivity was moderate in certain cases. Another drawback of the method was the use of the not-green solvent acetonitrile.

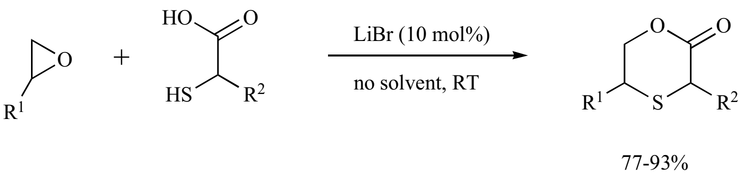
A scandium triflate catalyzed [3+3] annulation to form tetrahydro-β-carbolines and tetrahydroisoquinolines was developed by Wang *et al.* [167]. The transformation used benzylic alcohols and aziridines as substrates to give the desired products in moderate yields (Scheme **74**). The [3+3] process applied allows for greater product diversity than previously established methods. While scandium triflate can be considered a green Lewis acid, the use of 1,2-dichloroethane as solvent counterbalances the overall environmental friendliness of the procedure.



Scheme 74.



Scheme 75.

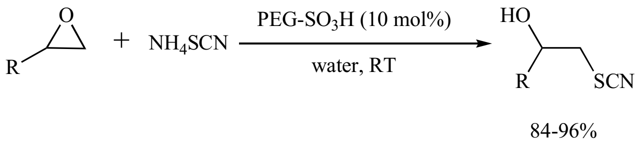


Scheme 76.

A new strategy for the en-yne-cyclizations was developed by Zhang and co-workers [168]. Instead of the traditional π-activation they chose to use a Brønsted acid to perform σ-activation of alkyne enones to trigger the cyclization and yield the desired 5-membered ring products (Scheme **75**). Depending on the starting material used, both saturated and unsaturated ring systems were obtained in moderate to high yields. While the initial cyclization yielded a mixture of *syn* and *anti*-isomers; a base-catalyzed isomerization led to the selective formation of the *anti*-isomer. Depending on the substrate, 1,2-dichloroethane or nitromethane had to be used as the solvent which increased the environmental impact of the reaction.

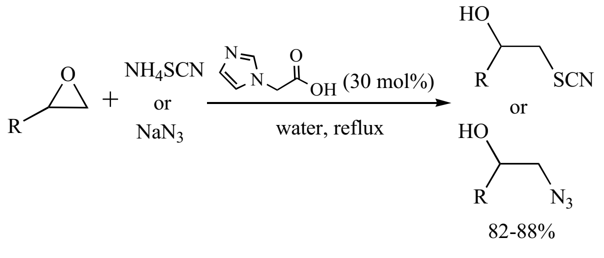
Lithium bromide was applied as Lewis acid catalyst for the ring expansion of epoxides with α-mercaptocarboxylic acids to form 1,4-oxathian-2-ones (Scheme **76**) [169]. The reaction proceeded under solvent-free conditions at room temperature resulting in the products in high yields. The epoxide opening was achieved with high regioselectivity and the catalyst was recovered after the reaction and reused without any loss of efficiency.

The ring-opening reaction of epoxides with ammonium thiocyanate was efficiently catalyzed by a PEG-supported sulfonic acid [170]. The water soluble polymer combines the best features of homogeneous catalysis with the easy separation of a heterogeneous catalyst. The reaction was carried out under mild conditions in water as the solvent and formed the β-hydroxy thiocyanates in excellent yields (Scheme **77**). High regioselectivities were obtained during the opening of the epoxide.

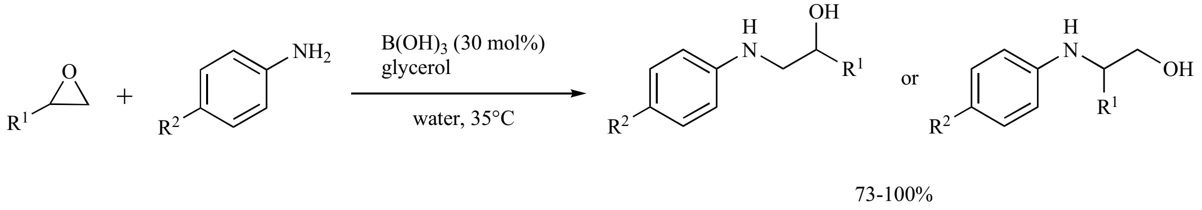


Scheme 77.

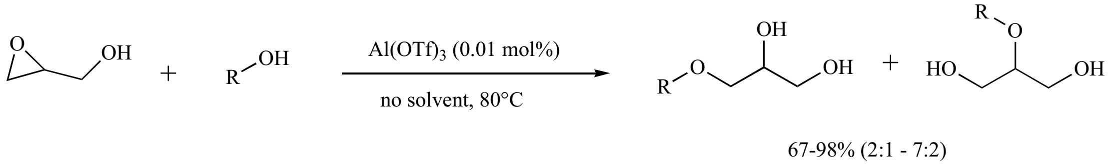
Nazari *et al.* described that a similar reaction of epoxides can also be catalyzed by imidazole-1-yl-acetic acid [171]. Ammonium thiocyanate and sodium azide was used as reagents for the ring opening reaction (Scheme **78**). The catalyst used was recycled after the reaction and reused for consecutive reactions without significant loss of activity. The products were obtained with high regioselectivity in most cases.



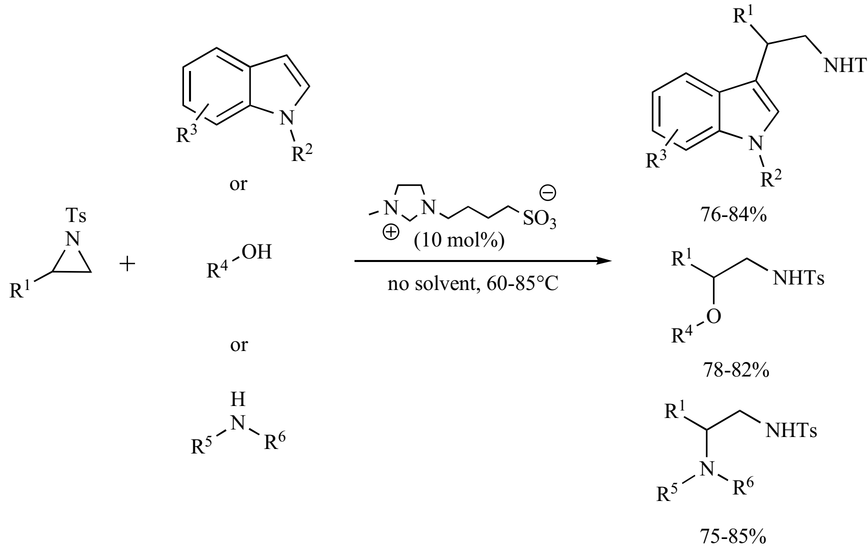
Scheme 78.



Scheme 79.



Scheme 80.



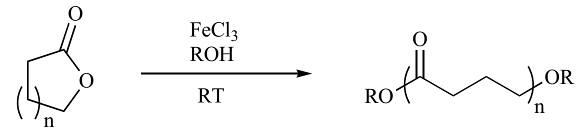
Scheme 81.

The ring opening of epoxides with aromatic amines (Scheme **79**) was described by Halimehjani *et al.* using boric acid and glycerol as a green catalytic system in water as the solvent [172]. The reactions proceeded with high yields and high regioselectivities under mild conditions. Glycerol acts as chelating agent for the boric acid thus increasing its acidity.

The catalytic etherification of glycidol with different alcohols (Scheme **80**) was described by Capacchione *et al.* [173]. Using a very low loading of $Al(OTf)_3$ as the catalyst the monoalkyl glycerol ethers were obtained in mostly high yields. The etherification happens preferentially at the terminal position, although the ratio between terminal and internal alkylation was not very high in many cases. The alcohol used for alkylation additionally served as the solvent, no other solvent was needed for the reaction.

Majee and co-workers developed a method for the ring-opening of aziridines with various nucleophiles (Scheme **81**) using an imidazole-based zwitterionic organocatalyst [174]. The catalyst acts as hydrogen donor to activate the aziridine towards the attack of the nucleophile. No solvent was needed for the reaction of carbon-, oxygen- and nitrogen-nucleophiles and the products were obtained in high yields and high regioselectivities with concern to the position of ring opening.

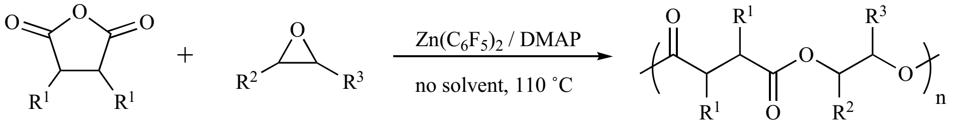
Iron chloride was used as the Lewis acid catalyst in the ring-opening polymerization of cyclic lactones by Chakraborty and Gowda [175]. The authors showed that ε-caprolactone, δ-valerolactone and β-butyrolactone can be polymerized effectively (Scheme **82**) to form polymers with a narrow molecular weight distribution. Through the addition of alcohols and the variation of the monomer-catalyst ratio the polymer properties can easily be tuned.



Scheme 82.

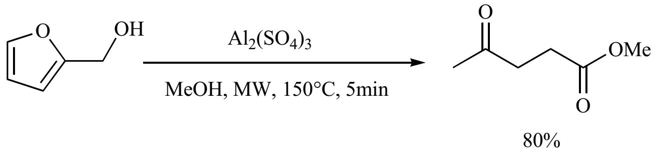
The ring-opening alternating co-polymerization of cyclic anhydrides and epoxides (Scheme **83**) was described using a Lewis acid-base pair as catalytic system under solvent-free conditions [176]. The combination of an organozinc compound with a N-heterocyclic organobase catalyzed the polymerization in most cases with high conversions, extremely high degree of alternation and a narrow molecular weight distribution.

The transformation of furfuryl alcohol to alkyl levulinates also readily occurred in methanol with microwave activation [177]. Several metal salts, including $CrCl_3$, $ZnSO_4$, $AlCl_3$, or $Al_2(SO_4)_3$ were tested as catalysts. $Al_2(SO_4)_3$ showed the best performance, likely due to its somewhat elevated Brønsted acidity. The high dielectric constant of the solvent, probably contributed to the



Scheme 83.

efficiency of the alcoholysis of furfuryl alcohol *via* its strong microwave absorption ability that ensured that in a 5 min reaction at 150°C, the reaction occurred (Scheme **84**) in 80% yield and nearly exclusive selectivity. During mechanistic investigations of the reaction mechanism key intermediates (methoxymethylfuran (MMF) and 4,5,5-trimethoxypentan-2-one (TMP)) were isolated. The catalyst was reused for six consecutive cycles with negligible loss in activity. Thus despite using DCM as solvent in the work up the method is rapid, efficient and partially environmentally benign.



Scheme 84.

4.4. Asymmetric Synthetic Applications

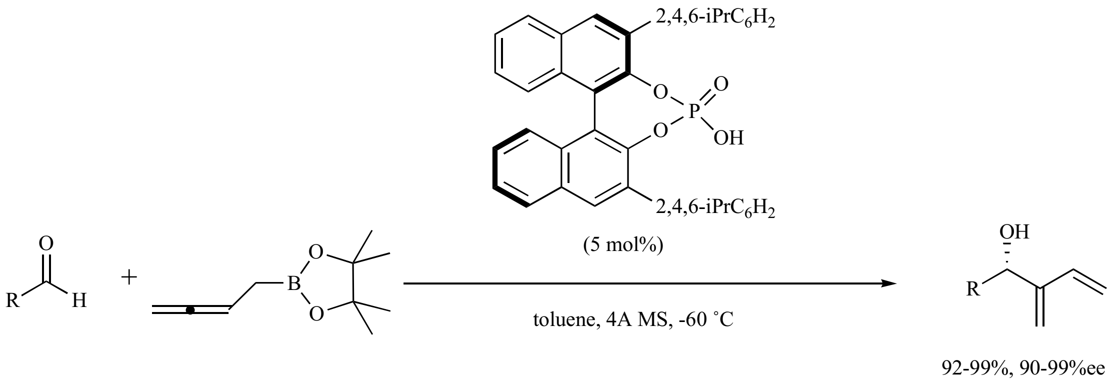
Catalysis by chiral phosphoric acids: Huang *et al.* showed that the catalytic asymmetric synthesis of chiral 1,3-butadienyl-2-carbinols was possible by using a chiral phosphoric acid as a catalyst [178]. The reaction between aldehydes and homoallenylboronates (Scheme **85**) did not require the use of a metal catalyst and furnished the products in excellent yields and enantioselectivities. The reaction was performed on a gram scale and the products were of interest due to their synthetic utility as shown by the authors through the synthesis of a NCSi-gb analogue using their methodology.

The generation of chiral quaternary centers was achieved by List *et al.* Chiral phosphoric acids enantioselectively catalyzed the α-amination of α-branched ketones (Scheme **86**), a transformation that cannot easily be achieved by traditional amine-catalysis [179]. High yields and good enantioselectivities were obtained for the amination in the α-position of several different cyclic α-branched ketones with diazocarboxylates.

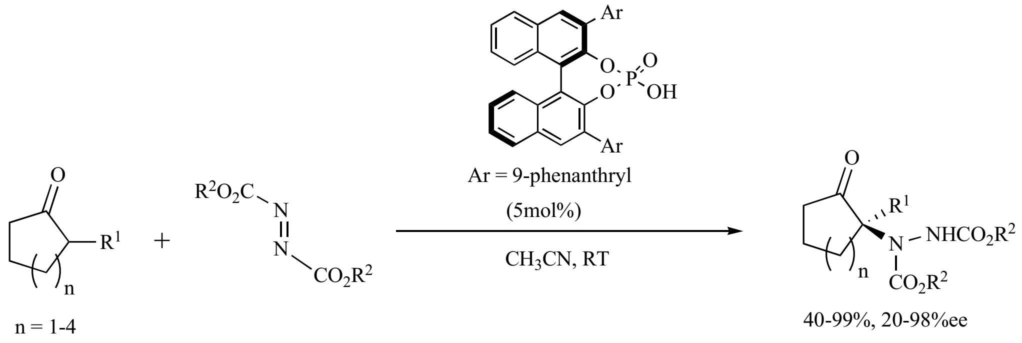
A solvent free variation of the above reaction was published by Toste *et al.* using a different chiral phosphoric acid [180]. Proper mixing was achieved by dissolving the starting materials in CH_2Cl_2. After evaporating the solvent, the residue was heated at 45°C for 40-60 h to obtain the α-aminated products in high yield and high enantioselectivities.

Chiral phosphoric acids were also applied for the Friedel-Crafts addition of benzoxazinones with substituted pyrroles (Scheme **87**) [181]. The products were formed in high yields and enantioselectivities generating a quaternary stereocenter. The presence of the CF_3-group seems to be essential as it contributes to hydrogen binding in the activation mode of the reaction.

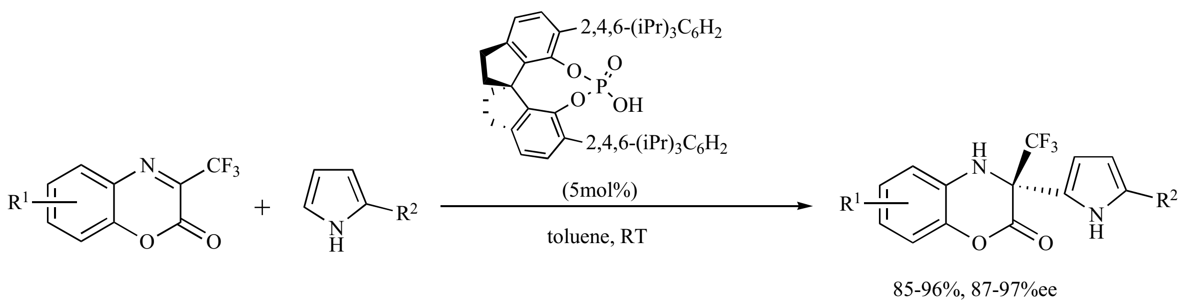
The asymmetric Friedel-Crafts addition of acetals to naphthols (Scheme **88**) was described by Da *et al.* [182]. Using a chiral phosphoric acid as catalyst and acetic acid as a co-catalyst the addition products were obtained in moderate yields and enantioselectivities. Even though the reaction was performed in dichloroethane as a solvent, the major benefit of the applied system was that the reaction could be performed under mild conditions.



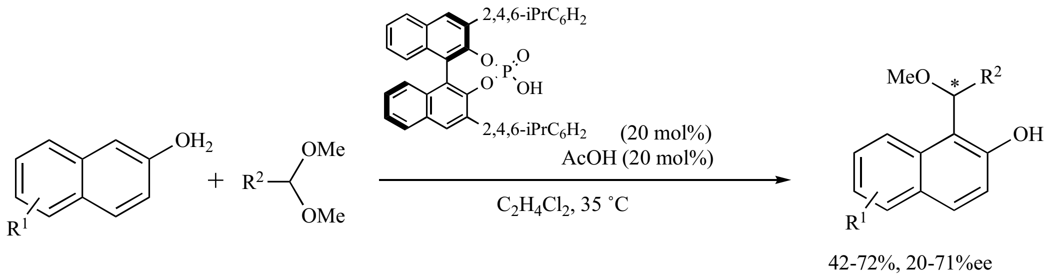
Scheme 85.



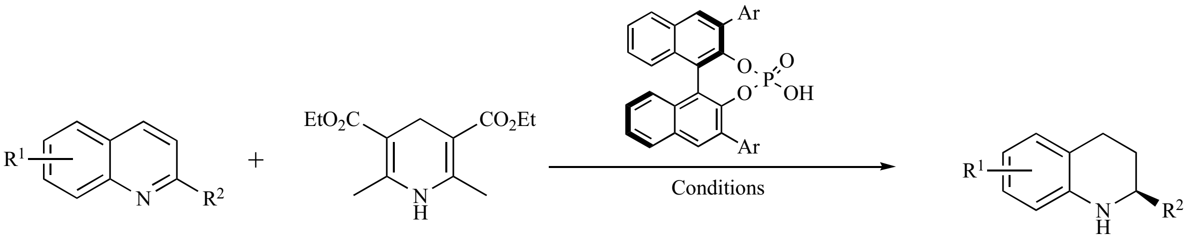
Scheme 86.



Scheme 87.



Scheme 88.



Conditions:	Yield:
Catalyst (0.5 mol%): Ar = 9-phenantryl $CHCl_3$, 60 °C, microreactor	91-97%, 94-99%ee
Catalyst (2 mol%): Ar = 2,4,6-$iPr_3C_6H_2$ diethylcarbonate, -10 °C	91-99%, 87-99%ee

Scheme 89.

The asymmetric transfer hydrogenation of a range of imines could also be catalyzed by chiral phosphoric acids. The enantioselective hydrogenation of different substituted quinolines (Scheme **89**) was shown by Rueping and his coworkers using only 0.5mol% of a chiral phosphoric acid as a catalyst [183]. Both a traditional batch reactor and a continuous-flow system were able to perform the reaction with the latter significantly improving the reaction yield (67 *vs*. 97%). More and Bhanage showed that the sustainable solvent diethyl carbonate could be used for the same reaction [184]. Similar high yields and enantiomeric excesses were obtained using a Hantzsch ester as the hydrogen donor.

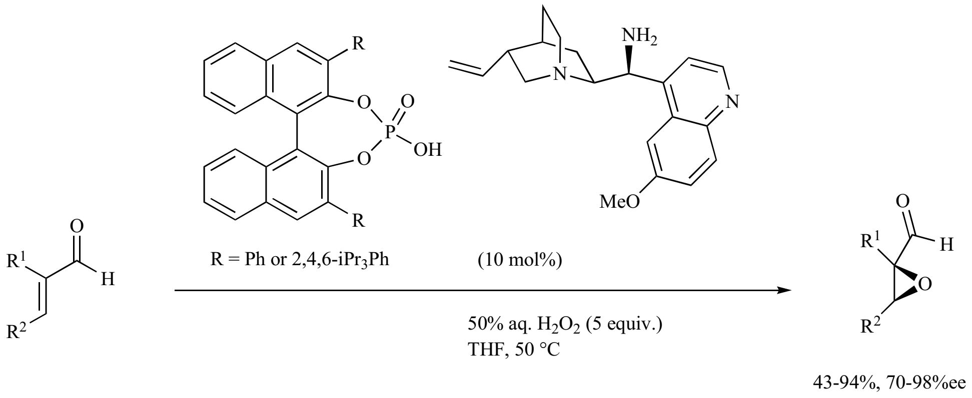
A binaphthol-derived phosphoric acid in combination with a cinchona alkaloid derived amine was an effective catalytic system for the enantioselective epoxidation of α,β-unsaturated aldehydes (Scheme **90**) yielding the products in moderate to high yield and high enantioselectivities [185]. Although the reaction was performed in THF, a not-green solvent, the system benefits from the use of hydrogen peroxide as an oxidant and the fact that the aldehyde could be used as a substrate, which is often not possible using other protocols due to the oxidation of the carbonyl group.

The enantioselective epoxidation of enynes was performed by using scandium triflate as the Lewis acid in presence of a chiral N,N'-dioxide as ligand [186]. The selective epoxidation of the alkene (Scheme **91**) was achieved in excellent yields and enantioselectivities using hydrogen peroxide as the oxidant. A low catalyst loading of 0.5% was applied and the reaction could also easily be performed on a gram scale. The high selectivity towards the alkene epoxidation overcomes the drawbacks associated with the synthesis of the ligand and the use of THF as a solvent.

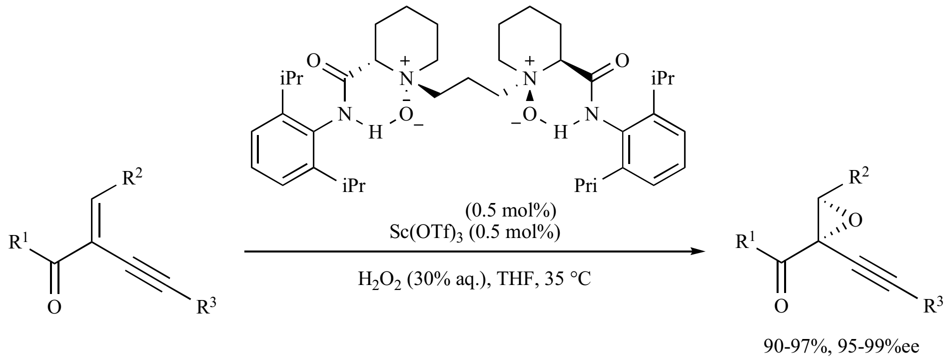
Using $ZnCl_2$ as a Lewis acid in combination with a prolineamide as chiral catalyst the asymmetric aldol reactions of aromatic aldehydes with ketones (Scheme **92**) was described in high yields, *syn:anti* ratios and enantiomeric excess [187]. In addition to the use of an environmentally benign catalyst the system also benefited from the use of a 1:1 water-ethanol mixture as a solvent system.

Penhoat *et al.* showed that this reaction can also be performed using unmodified proline and $ZnCl_2$ as Lewis acid [188]. The study had a smaller substrate scope and DMSO had to be used as a co-solvent making this approach less appealing from a sustainability point of view than the before mentioned $ZnCl_2$-prolineamide system.

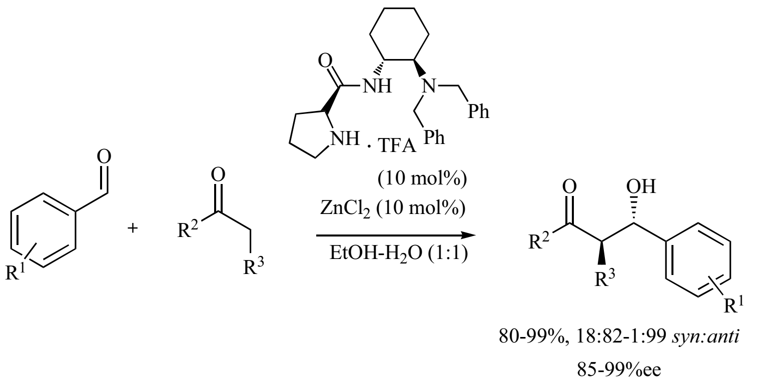
An environmentally friendly variation of the Mukaiyama aldol reaction was developed by Kobayashi and his co-workers [189]. It was shown that a large variety of Lewis acids can be used for the reaction of aldehydes with silyl enol ethers (Scheme **93**) in combi-



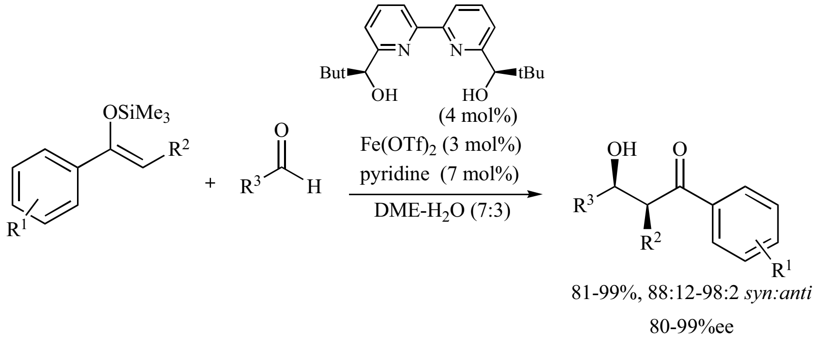
Scheme 90.



Scheme 91.



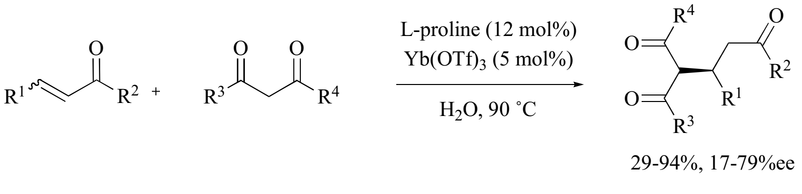
Scheme 92.



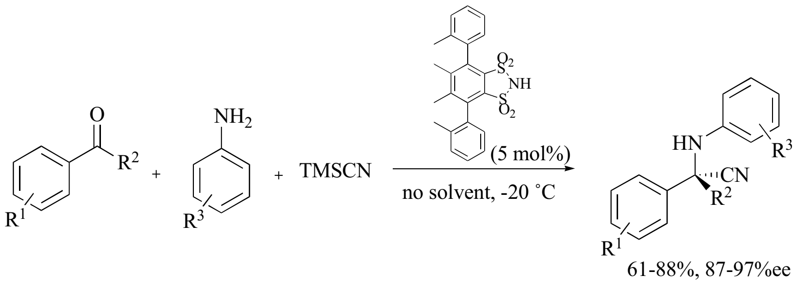
Scheme 93.

nation with a chiral bipyridine ligand. The environmentally friendly metal ions iron and bismuth showed especially good results using an aqueous solvent system. The desired aldol products were obtained in high yields and excellent *syn:anti* selectivities as well as enantiomeric excess.

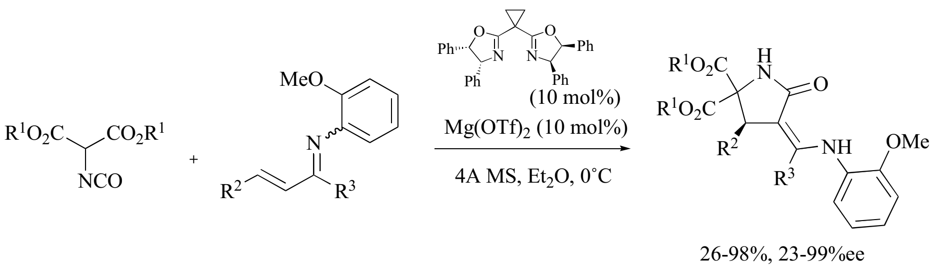
The asymmetric Michael addition using a catalyst made of $Yb(OTf)_3$ as Lewis acid and L-proline as a chiral ligand (Scheme **94**) afforded the corresponding addition products with yields up to 94% and high enantioselectivities under environmentally friendly conditions [190]. The reaction was performed in water as a solvent



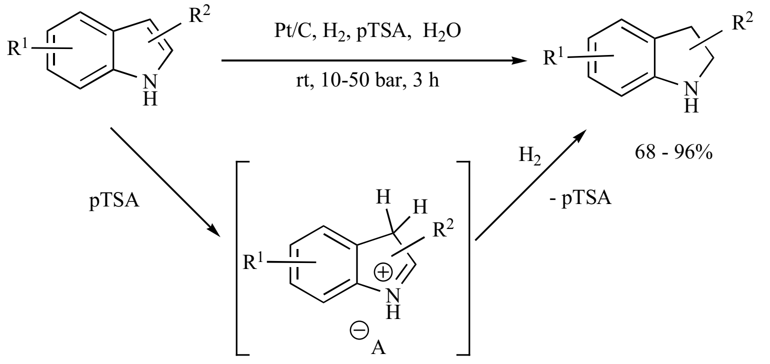
Scheme 94.



Scheme 95.



Scheme 96.



Scheme 97.

and the aqueous phase, containing the catalyst, was recycled several times without appreciable loss of catalytic activity.

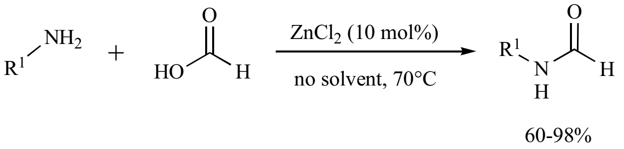
An asymmetric version of the Strecker reaction using a chiral Brønsted acid was described by Barbero *et al.* [191]. The use of substituted *o*-benzenedisulfonimides as a chiral catalyst allowed the formation of the α-aminonitrile from acetophenones, anilines and TMSCN in high yields and enantiomeric excess (Scheme **95**). The reaction was performed under solvent-free conditions and the catalyst was recycled three times without decrease in yield or enantioselectivity.

Using a chiral $Mg(OTf)_2$-BOX complex as a Lewis acid catalyst the formal [3+2] cycloaddition to form chiral γ-lactams (Scheme **96**) was possible in mostly high yields and enantioselectivities [192]. While the use of the imine was necessary for the success of the reaction, both stereoisomers of the imine could be used as starting material in the reaction, a separation was not necessary. A drawback from the green point of view is the need for diethylether as solvent in the reaction.

4.5. Miscellaneous Reactions

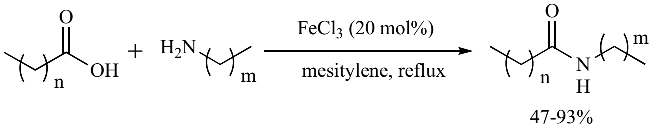
The combined application of acidic organocatalysis and heterogeneous catalytic hydrogenations allowed to solve a long standing problem the hydrogenation of indoles under aqueous conditions [193]. The typical conditions for indole hydrogenation are somewhat harsh and often result in indole over-hydrogenation. The reaction was carried out at ambient temperature in water as a solvent by using pTSA as an acidic organocatalyst that protonated indole and made it soluble in the aqueous phase. The protonation also destabilized the aromatic system helping the subsequent hydrogenation step (Scheme **97**) to produce the products in high yield.

The N-formylation of amines (Scheme **98**) was achieved in a $ZnCl_2$ initiated Lewis acid-catalyzed process [194]. The reactions proceeded without any solvent and the products were obtained in moderate to high yields. Both aromatic and aliphatic amines were successfully used as substrates for the reaction.



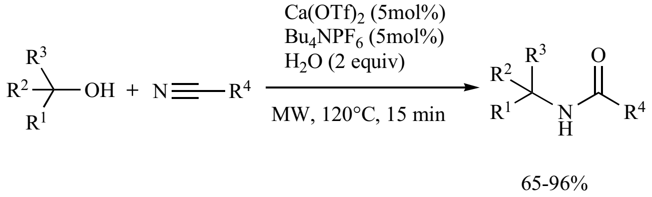
Scheme 98.

While $ZnCl_2$ was also used as the catalyst for the amide formation between fatty acids and long-chain amines (Scheme **99**), Sugi and co-workers showed that $FeCl_3$ performed slightly better in this transformation [195]. Using 20 mol% of the catalyst, the desired amides were obtained in mainly high yields. The use of the not-green solvent mesitylene was needed to remove water during the reaction to ensure complete conversion of the starting materials.



Scheme 99.

Another amidation reaction, using alcohols and nitriles (Scheme **64**) was described in a Ca(II) triflate-catalyzed Ritter reaction (Scheme **100**) [196]. The solvent-free microwave-assisted reaction resulted in high yields in short reaction times for a variety of alkyl and aryl substituted alcohols and nitriles. The reaction required the presence of a phase transfer agent (Bu_4NPF_6) which was thought to be necessary to activate the hydroxyl group.



Scheme 100.

Gu *et al.* showed that aqueous solutions of gluconic acid acted as a promoting medium for various reactions [197]. Amongst others, the Michael addition of indoles with various α,β-unsaturated compounds (Scheme **101**) was performed under milder conditions than previously reported. The reaction medium not only allowed to obtain the products in moderate to excellent yields, but also eased the separation of the product to a simple extraction. The reaction medium could then be reused for several runs without decrease in reaction yield.

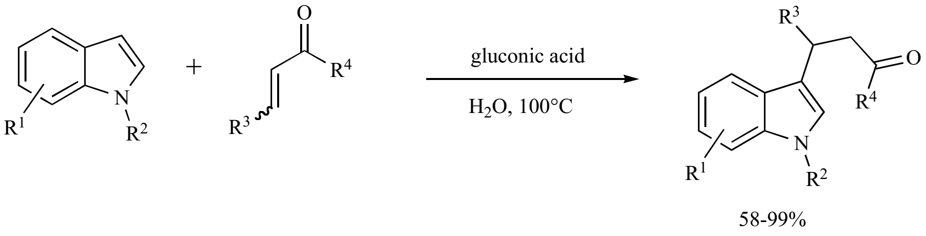
Simple amine hydrochlorides were demonstrated to be efficient, mild acid catalysts. Pyridium hydrochloride was found to be the catalyst of choice for the syntheses of tungsten *tert*-butylimido and adamantylimido alkylidene complexes, which are potential alkene methathesis catalysts [198].

The conversion of biomass to produce chemicals is becoming more-and-more attractive due to the need of identifying new non-petroleum based feedstock. While the advantages of using such biodegradable and abundant starting materials are obvious, the methods to transform them often used corrosive mineral acids. Research to develop new protocols offering lower environmental impact is in the forefront of biomass related research.

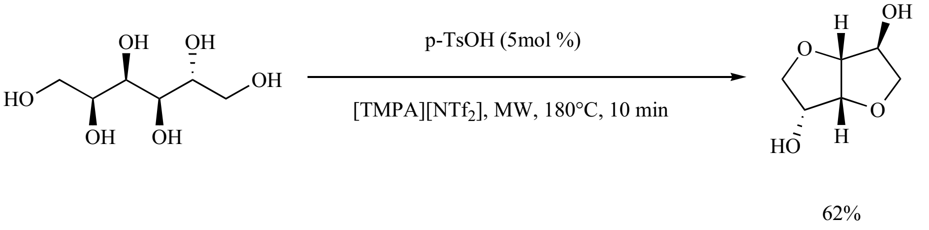
The cyclization of sorbitol to isosorbide (Scheme **102**) was successfully developed in a microwave-assisted transformation in ionic liquids [199]. The best performing IL was N,N,N-trimethyl-N-propylammonium-bis(trifluoromethylsulfonyl)amide ([TMPA][NTf_2]). Under optimized conditions the product yield was above 60% when the reaction was performed at 180°C for 10 min with a catalytic amount of *p*-toluenesulfonic acid. The IL likely improved the nucleophilicity of the substrate. The IL could be recycled for up to five times with only a negligible drop in yields. Although the reaction conditions are mostly green, the recovery process required the use of dichloromethane and thus contributed to the waste generation.

In similar processes the microwave-assisted dehydration of sugars by niobium and zirconium phosphates [200] and mesoporous SBA-15 catalysts [201] resulted in the formation of 5-hydroxy-methyl-furfural.

Based on the above surveyed results, the applications of water stable solid acids, although substantial in the reviewed period, probably are less extensive than those with solid acids. The well-known examples, such as heteropoly acids and metal triflates still dominate this field. Most of the new developments occurred in the area of organocatalysis especially in asymmetric organocatalysis. The introduction of the BINOL-based chiral phosphoric acids significantly extended the application possibilities and aided the expansion of this field that was led by chirally modified Lewis acids for an extended period. The future developments must address, however, the significant challenges these new catalysts face, in order to extend their applications, potentially, to the industrial level.



Scheme 101.



Scheme 102.

CONCLUSIONS

Recent advances in the application of environmentally benign acid catalysts have been reviewed. Due to the importance and magnitude of the contribution of the acid-catalyzed reactions to the development of sustainable synthetic methods, the topic remains at the forefront of synthesis research. The focus of new developments is finding novel applications for traditional reactions that occur under obsolete and unsustainable conditions. While the directions during the nearly 150 years of acid catalysis substantially changed over the past decades, the applications of acid catalysts will remain an important tool in organic synthesis development. Hence, the continuous development of green acid catalytic processes will likely be one of the major driving forces in the growth of sustainable synthesis development for the preparation of pharmaceuticals, fine chemicals and materials.

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