

Review

Use of *N*-Heterocyclic Carbene Compounds (NHCs) Under Sustainable Conditions—An Update

Abdelkarim El Qami, Adrien Kibongui-Fila and Sabine Berteina-Raboin * 

Institut de Chimie Organique et Analytique (ICOA), Université d'Orléans, UMR-CNRS 7311, BP 6759, Rue de Chartres, CEDEX 2, 45067 Orléans, France; abdelkarim.el-qami@univ-orleans.fr (A.E.Q.); adrien.kibongui-fila@etu.univ-orleans.fr (A.K.-F.)

* Correspondence: sabine.berteina-raboin@univ-orleans.fr

Abstract

In this review, we focused on advances made over the last two decades in the field of catalysis using *N*-heterocyclic carbenes (NHCs), which can be used for metallic or non-metallic catalysis. We listed the advantages of these NHCs and their modes of action in various couplings. With regard to metal catalysis, we have focused here on palladium and nickel catalysis, and then we looked at their use without transition metals. The work mentioned, in this review, only concerns research carried out under sustainable conditions, both in terms of the types of reactions and reaction conditions used (solvents, quantities, accessibility, and easy purification).

Keywords: *N*-heterocyclic carbenes; sustainable conditions; catalysis; green solvents

1. Introduction

Interest in *N*-heterocyclic carbene (NHC) compounds began at the end of the last century due to their interesting properties in organometallic catalysis. They were first described as organometallic complexes in 1968, in parallel with the work of Wanzlick [1] and Öfele [2]. These *N*-heterocyclic carbenes were isolated in the early 1990s and are characterized by a 6-electron carbon in a nitrogenated heterocycle. This nucleophilic species is stabilized on the one hand by steric hindrance and on the other hand by the electron-donating effects of the nitrogen atoms adjacent to the carbene. These entities can advantageously replace phosphine-type ligands and form complexes with transition metals, with the added advantage of high thermal and air stability [3]. Catalytic applications have been described for palladium, platinum, nickel, ruthenium, rhodium, gold, and copper [3–9]. They have their own specific characteristics, which can be summarized as follows: They are electron-rich ligands that prove to be very powerful sigma donors, with possible retro-donation from the metal involved in stabilizing the entire structure [10,11]. Furthermore, the donation capacity of NHCs is more or less constant, which is not the case for phosphines, which they can advantageously replace. Indeed, the strong electronic induction of NHCs on the metal plays an important role in the various stages of the catalytic cycle, particularly in oxidative additions, which can thus be carried out directly on bonds that are not very reactive or not reactive at all, such as C-H or even C-C bonds [6]. Unlike phosphines, metal–NHC bonds are strong and stable, which avoids the need to add ligands and allows the catalytic system to withstand many external parameters such as humidity and oxygen in the air, as already mentioned. The steric properties of different carbene molecules play an important role in stressing the metal coordination sphere and



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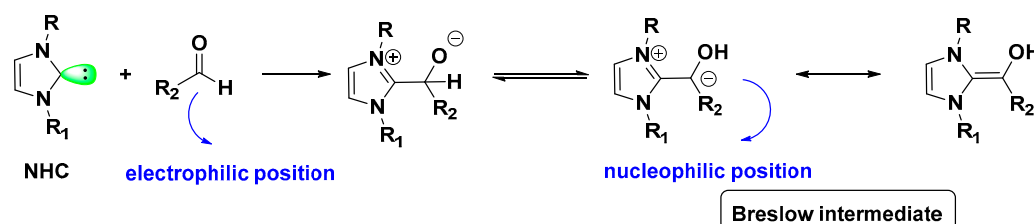
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thus in catalytic efficiency [11]. It should be noted, however, that although transition metal catalysis is very efficient, it has disadvantages inherent to metals, such as cost and toxicity, at least for some metals. The use of NHC in organocatalysis makes it possible to overcome these problems. In 2011, F. Glorius et al. [12] provided an excellent overview of the various possible uses of these NHCs, mainly involving Breslow's nucleophilic intermediate. They summarized the possibilities and optimal reaction conditions for producing interesting molecules with good selectivity. Indeed, their use allows for dual activation via the positively polarized proton in the Breslow intermediate on the one hand, and the attack of the nucleophilic fraction on the other, in a concerted manner (Scheme 1).



Scheme 1. Dual activation via the positively polarized proton in the Breslow intermediate.

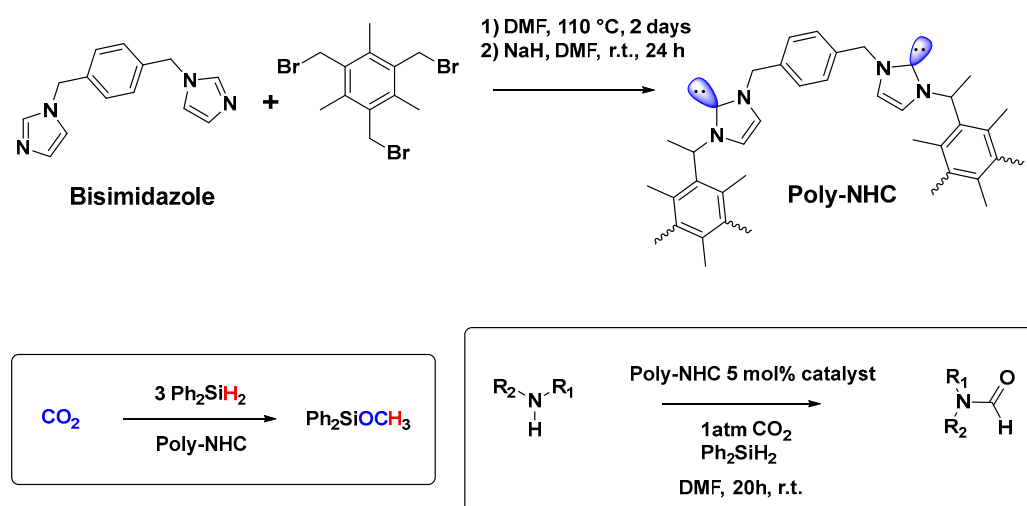
Another advantage of *N*-heterocyclic carbene catalysts is their ability to catalyze the formation of heteroatomic bonds with good regioselectivity and/or stereoselectivity, thereby limiting atomic losses due to purification methods. This is possible given the well-known umpolung and non-umpolung processes involved in the use of these catalysts. We have already mentioned Breslow intermediates among the species generally involved in these processes, but there are also homoenolates and enolates, as well as α , β -unsaturated acylazoliums, to name but a few. These synthons are important and highly reactive, giving rise to numerous reactions, including Stetter and Claisen rearrangements, as well as cycloadditions and various C-C and C-heteroatom functionalizations. The use of NHCs provides efficient access to many heterocyclic molecules of therapeutic interest [13].

Similarly, F. Verpoort and H.D. Velazquez [14] produced an excellent detailed review of NHC transition metal complexes in aqueous or aqueous/organic media, based on research conducted in this field during the first decade of the 2000s. They showed that most catalytic reactions could be carried out in water or at least in a water/organic solvent mixture, provided that the reactants involved were soluble and stable in these media. NHCs, which are advantageous substitutes for phosphine derivatives, are well suited to these media. Research on the recyclability of ligands and solvents then continued. As researchers remain very interested in the field of catalysis, we have decided, given the current challenges, to focus on the use of these NHCs in environmentally friendly conditions. To this end, we will study their use in reactions that they help to promote, such as CO₂ reduction [15] or CO₂ capture as described by Y. Zhang et al. [16], as well as their use in so-called green solvents and their potential effectiveness without metals. With regard to metal-catalyzed reactions, we have chosen to focus this review on the results of the last two decades in palladium and nickel catalysis. We focused on these two metals because they are the most commonly used catalysts, with a fairly wide range of reactions studied; they are readily available commercially; and they are generally less expensive than other catalysts such as ruthenium or gold, for example. According to our bibliographic research, which is probably not exhaustive, environmentally friendly conditions mainly concern catalysis in aqueous media [14] or in other green solvents, without solvents, or in ionic liquids not treated here. The use of complexes supported on polymeric supports or nanoparticles has also been reported.

2. Discussion

The impact of the solvents used is very important for the sustainability of the processes, as they account for a large part of the atomic loss. If we examine the solvents used in the field of NHCs, we find a large number of ionic liquids. In 2013, A. Inesi et al. [17] showed that a catalytic system derived from an ionic liquid could be used effectively. This is a mixture (RTIL–NHC) of a room-temperature ionic liquid (RTIL) and NHC that can be produced under mild conditions by cathodic reduction of imidazolium-based ionic liquids. The authors tested various reactions in this medium, which yielded the expected products with very good yields. These reactions include benzoin condensation, the Stetter reaction, the synthesis of α -butyrolactones, the synthesis of esters, the Henry reaction, and the Staudinger reaction. The concentration of NHC in the RTIL can be controlled during electrolysis. The ionic liquid was tested and reused over several cycles without significant change in yields. However, the NHCs electrogenerated by cathodic reaction originate from the judicious choice of RTIL precatalysts, and their reactivity may differ from that observed in a conventional medium. We will not discuss here reactions with NHC catalysts in various ionic liquids as solvents, as this has already been addressed in reviews [18,19].

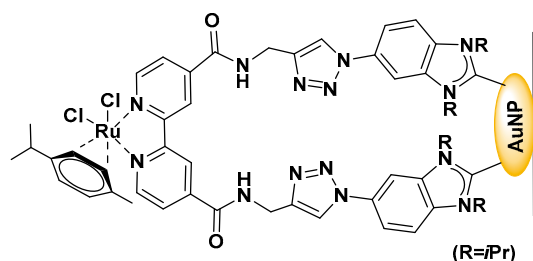
Poly-*N*-heterocyclic carbenes (poly-NHCs) has been used to reduce carbon dioxide. Solid poly-NHC particles can act as heterogeneous organic catalysts for the conversion of carbon dioxide to methanol. Furthermore, these solid catalysts are easily recyclable, and Y. Zhang et al. [16] have developed an imidazolium polymer that can be used effectively for the reduction of CO₂ to methanol. To do this, they use hydrosilanes as hydride donors in the presence of their NHC catalyst, which traps CO₂ and reduces it to methanol according to Scheme 2. They also used these poly-NHC particles to formylate primary or secondary amine bonds in the presence of CO₂ at atmospheric pressure, although the yields were lower than those obtained in homogeneous catalysis. However, it should be noted that the recyclability and ease of scaling up of these heterogeneous catalysis processes more than compensate for the lower yield.



Scheme 2. CO₂ reduction using poly-*N*-heterocyclic carbenes.

Photocatalysis is also increasingly used because of its potential, as it can be highly selective. It can be carried out using photoelectrodes and resistant ligands. NHCs are particularly well suited to this use in terms of stability and robustness. Y.S. Nam et al. [20] recently developed a RuCY complex (cis-dichloro-(4,4'-diphosphonato-Rubpy)(p-cymene) which they immobilized on a gallium nitride/gold nanoparticle support. The NHC was grafted onto gold nanoparticles (AuNPs) by isolated lone pair donation (Scheme 3). This assembly serves as a photocathode, which they placed in the presence of a hematite

photoanode, enabling them to create a photoelectrochemical cell capable of reducing CO_2 to formate in a quasi-quantitative manner and concomitantly with the oxidation of water under visible light at $243 \text{ mW} \cdot \text{cm}^{-2}$.

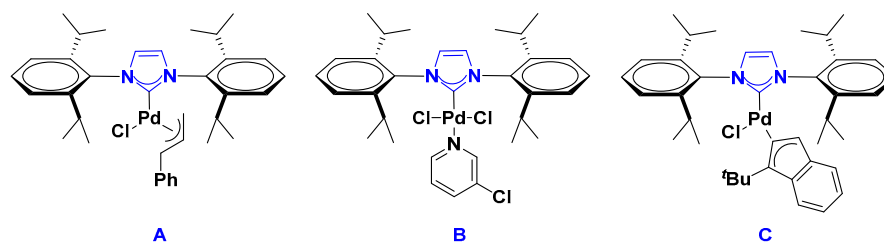


Scheme 3. RuCY complex (cis-dichloro-(4,4'-diphosphonato-Rubpy)(p-cymene) with NHC was grafted onto gold nanoparticles (AuNPs) by lone pair donation.

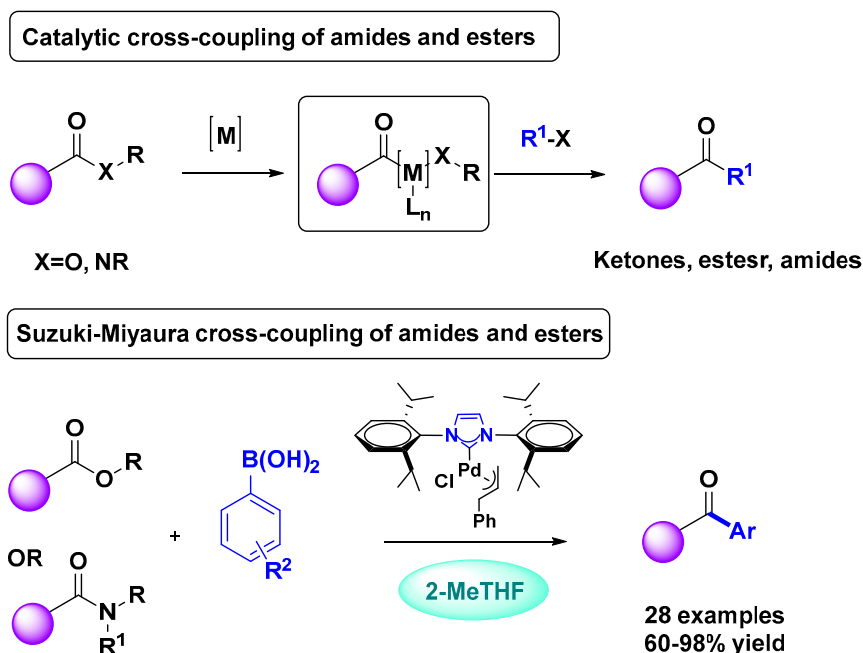
Various transformations in the energy field concerning CO_2 reduction, oxygen reduction, and urea electrosynthesis may involve NHC ligands to control different parameters such as redox interactions between the ligand and the metal, selectivity, and the possibility of activating the starting product as listed by A. Rapakousiou [21]. These NHCs can be bound to conductive supports that increase the surface area of action or make the system much more sustainable. Charge transfers and reactivity are thus improved. In this review, A. Rapakousiou emphasizes the essential nature of these NHCs, whether used in homogeneous or heterogeneous catalysis, for the development of sustainable and selective electrocatalytic technologies.

2.1. Palladium Catalysis

Since amide and ester functions are present in a large number of commercial compounds, natural compounds, and drug candidates, it is interesting to be able to use these compounds as starting materials for other transformations. Thus, in 2019, Szostak et al. [22], as part of their ongoing efforts to develop NHC ligands and catalysts using them, developed the first Suzuki–Miyaura-type cross-coupling reaction between amide and ester electrophiles and various boronic acids to develop ketone compounds. To increase the sustainability of the methodology, they developed it in 2-methyltetrahydrofuran (2-MeTHF) [23], an environmentally friendly and renewable solvent. Their protocol involves commercially available Pd(II)-NHC precatalysts [24–27] (Scheme 4) which, in the presence of only 3% mol of catalyst, allow the desired products to be obtained with near-quantitative yields relative to the amide starting materials. The cross-coupling reaction takes place at room temperature with only a very slight excess of boronic acid (1.2 equiv.) in environmentally friendly 2-methyltetrahydrofurane (Scheme 5). For ester starting materials, the conditions are similar but require 2 equiv. of boronic acid, and the yields are slightly lower (60% to 98%). Like most carbene catalysts currently in use, these catalysts are stable to air and moisture.

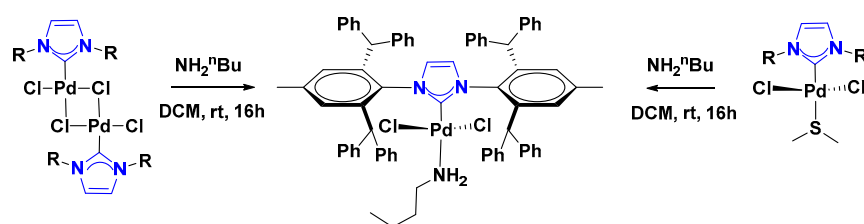


Scheme 4. Structures of precatalysts Pd(II)-NHC: (A): $[\text{Pd}(i\text{Pr})(\text{cinnamyl})\text{Cl}]$; (B): Pd-PEPPSI-*i*Pr or $[\text{Pd}(i\text{Pr})(3\text{-Cl-py})\text{Cl}_2]$; and (C): $[\text{Pd}(i\text{Pr})(\text{indenyl})\text{Cl}]$.



Scheme 5. Activation of amides and esters and their sustainable Suzuki–Miyaura cross-coupling in 2-MeTHF.

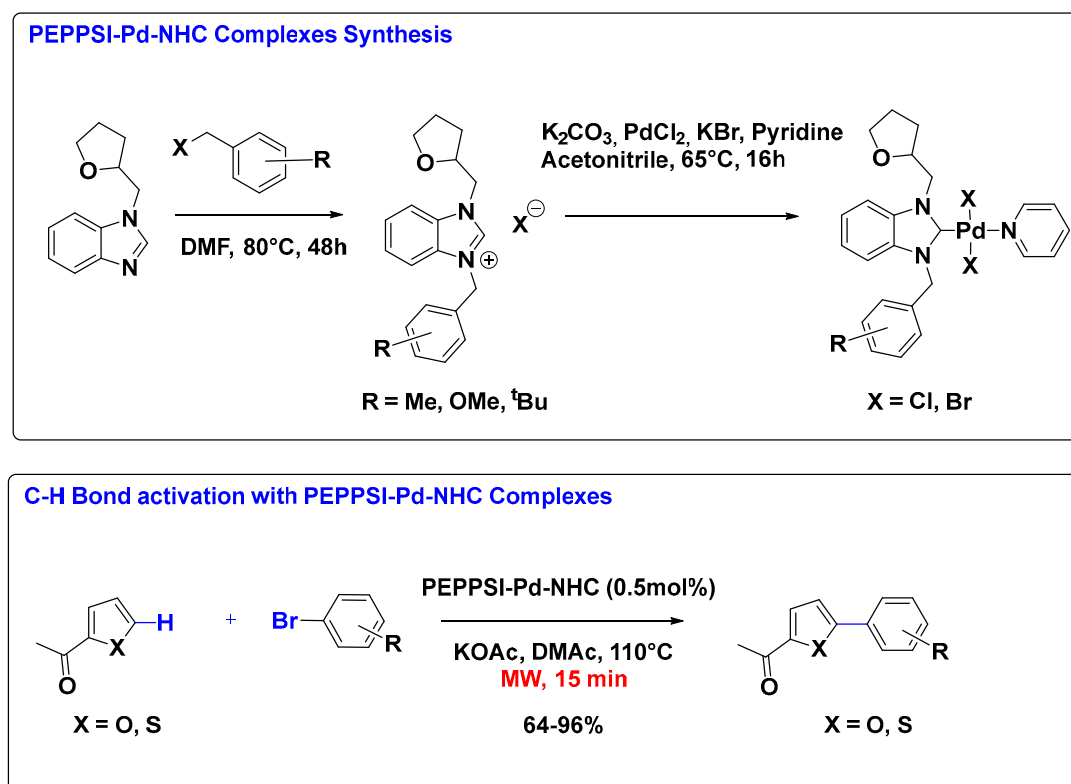
We cannot discuss palladium couplings in the presence of NHC ligands without mentioning the formation of C–N bonds present in most molecules of biological interest [28]. One of the most significant advances in this field concerns the work of Buchwald and Hartwig, who developed the palladium-mediated amination reaction [29,30]. They continued to improve this reaction in terms of reducing the catalytic load and using various ligands [31]. Other work carried out by our team on a new biomass-derived solvent, eucalyptol or 1,8-cineole, has also enabled the formation of C–N bonds in the presence of simple ligands and under sustainable conditions [32,33]. The efficiency of this reaction has been continuously improved, in particular through the use of Pd precatalysts that are stable in air and moisture, namely catalysts with NHC ligands. S. Nolan et al. [34] have very recently developed two precatalysts obtained by simple procedures and exhibiting activities superior to those already reported for homologous precatalysts used in these amination reactions. It should also be noted that the solvent used, 2-MeTHF, is a green solvent and that they were able to reduce the catalyst loading to 0.1 mol% while working at low temperatures (40 to 80 °C) [34]. These new trans-[Pd(NHC)(NH₂ⁿBu)Cl₂] precatalysts are obtained by adding n-butylamine to dimeric precursors [Pd(NHC)(μ-Cl)Cl]₂ or to trans-[Pd(NHC)(Dimethylsulfide)Cl₂] complexes, that are more sustainable than previous systems. Buchwald–Hartwig amination is more effective with [Pd(*i*Pr*)(NH₂ⁿBu)Cl₂] (Scheme 6), a catalyst that even allows selective monoarylation of primary amines. The selectivity is due to the spatial reactivity of the catalyst, which also explains the lack of reactivity of secondary amines, as these generate more bulky tertiary amines.



Scheme 6. New trans-[Pd(NHC)(NH₂ⁿBu)Cl₂] precatalyst synthesis from dimer precursors [Pd(NHC)(μ-Cl)Cl]₂ or trans-[Pd(NHC)(Dimethylsulfide)Cl₂] complexes.

With NHCs, there is therefore a whole range of selectivity possibilities that seems unlimited, depending on the steric hindrance of the ligands on the one hand and the coupling envisaged on the other. M. Szostak et al. [35] published a very interesting review this year in which they trace the entire literature on Buchwald–Hartwig amination from the beginning of the century to the present day. As already mentioned above, NHC–Palladium complexes significantly improve Buchwald–Hartwig amination, and the authors also investigate the use of numerous NHC–Nickel complexes for this amination reaction. Some examples of NHC–Cobalt and NHC–Rhodium complexes are also mentioned. The essential role of these metal–NHC complexes in the development of carbon–nitrogen bonds for the synthesis of molecules for therapeutic purposes is clearly highlighted.

Most recently, N. Ozdemir et al. [36] described the synthesis of new PEPPSI–Pd–NHC palladium complexes that can be used under mild conditions. These new catalysts were used for the efficient arylation of 2-acetylfuran as oxygen-containing heterocycles and 2-acetylthiophene as sulfur-containing heterocycles (Scheme 7). They were functionalized with various aryl bromides by microwave irradiation, reducing reaction times to 12 min to a maximum of 30 min, depending on solvent used. The efficiency of the synthesis of biaryl compounds also depends on the steric hindrance of the NHC ligands used. In addition, this type of catalyst makes it possible to reduce the catalyst loading to 0.5 mol% in 15 min of microwave irradiation.



Scheme 7. PEPPSI–Pd–NHC for C–H bond activation under microwave irradiation.

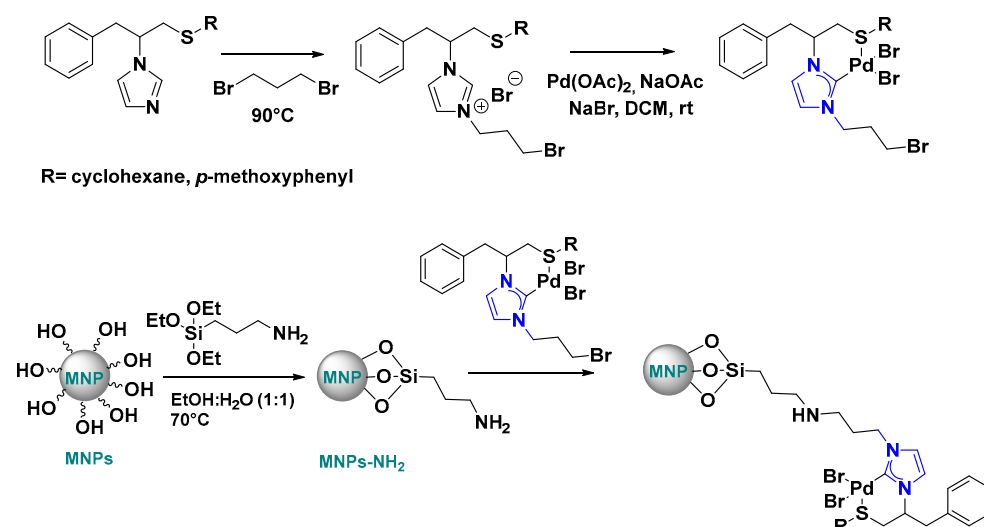
T.M. Aminabhavi et al. [37] also studied the advantages provided by NHC–Palladium complexes. They focused their study in particular on the use of palladium–pyridine–PEPPSI complexes in organometallic chemistry under sustainable conditions. They characterized highly effective precatalysts, given their significant electronic effects, which are often used for industrial catalytic transformations. The authors explore the synthesis routes for these different palladium–PEPPSI catalysts as well as their use in the various Suzuki–Miyaura, Sonogashira, Negishi, and, of course, Buchwald–Hartwig couplings. They also

present some recent developments on these complexes on solid supports, which will be discussed below.

B.H. Lipshutz et al. [38] based their literature review on palladium-catalyzed aminations in general, with NHC ligands or other ligands, focusing mainly on environmentally friendly methods. There are many more ecological protocols that are listed there with couplings performed in aqueous media, in ionic liquids or other unconventional solvents, or even without solvents. Similarly, various more sustainable synthesis processes are described for the formation of C-N bonds, such as continuous flow synthesis and mechanochemistry.

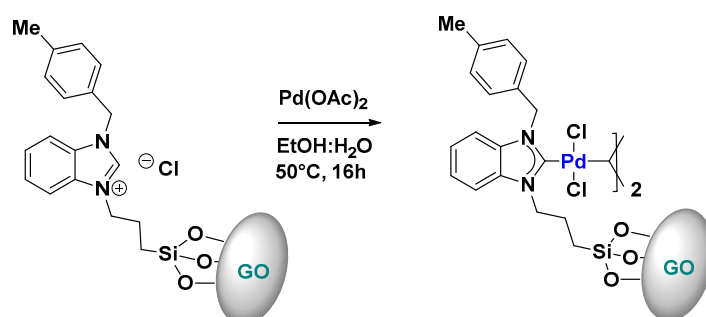
Supported Pd-NHC Catalysts

In 2024, P. Mao et al. [39] developed the synthesis of two new palladium-NHC complexes supported by magnetic nanoparticles (MNPs). These stable complexes have the added advantage of being recyclable. They have been shown to be usable for 10 cycles without significant loss of activity. These complexes have been fully characterized and have shown very interesting catalytic activity, both for conventional Suzuki–Miyaura cross-couplings and for the reduction of 4-nitrophenol. The latter has been studied because of its toxicity [40,41] and its widespread use in various industries. It contributes significantly to chemical pollution of industrial waste and has the disadvantage of not being easily biodegradable. Being able to reduce it easily and sustainably to the less toxic 4-aminophenol is obviously an interesting challenge, and studies have already been conducted in this direction with certain NHC–palladium complexes [42,43]. In addition, it could potentially be reused as a starting product in other synthetic transformations for the development of molecules of interest, thus creating a virtuous circle. Immobilized heterogeneous catalysts are easy to handle and can be removed by simple filtration [44–46], which is an important advantage in terms of sustainability, as purification methods have a very significant environmental impact. Among the various immobilization materials that can be used, P. Mao et al. [39] chose magnetic nanoparticles, which can be easily separated from the system using an external magnetic field [47]. Other teams have considered these same supports for immobilizing NHC catalysts synthesized with varying degrees of ease [48–50]. The work of P. Mao et al. [39] is interesting because, compared to others, they generate their complexes (MNP-NHC-Pd) more quickly (Scheme 8) from isolated and pure NHC–palladium complexes, thus contributing further to the efficiency of the catalytic steps and the sustainability of the process.



Scheme 8. Synthesis of NHC complex and immobilization on MNPs to lead to MNPs-NHC-Pd catalysts.

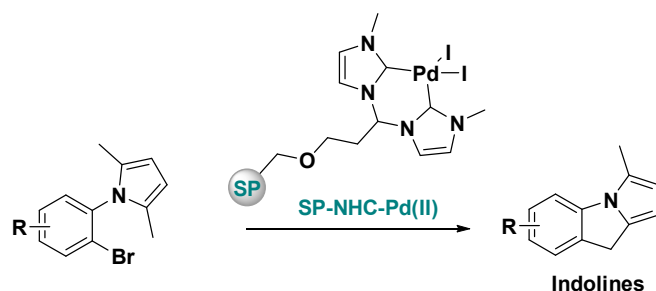
Given current issues and the popularity of NHC compounds often associated with noble metals, it is natural that researchers are now interested in immobilizing these catalysts in order to reduce their environmental impact. Indeed, metal complexes are often difficult to recover or recycle, resulting in significant atomic loss. Furthermore, given their scarcity, recycling these metals to avoid unnecessary extraction from the earth is important. G. Prabusankar et al. [51] have written an excellent review entitled “Graphene Oxide-supported Metal *N*-Heterocyclic Carbenes Catalysts” which presents a sustainable approach to relatively easy catalyst recovery and reuse. The graphene oxide (GO) or reduced graphene oxide (rGO) [52–54] used has a surface [54] that allows NHCs to anchor and then graft onto the metal. Compared to other supports, such as polystyrenes, and other solid phases, such as polyethylene glycols, this type of heterogeneous catalyst has the advantage of being relatively inert. Other polymeric supports have functions that can be disruptive and folds that can generate steric hindrance that is detrimental to catalytic reactions. It is therefore important to carefully choose the solid support, depending on the desired selectivity. Here we have chosen to focus our analysis on palladium and nickel as metals, but G. Prabusankar et al. [51] explored research in this field on many noble metals in 2023. With palladium, they reported on work carried out on various couplings, including Suzuki–Miyaura, Heck, Sonogashira, and Hiyama, with various Pd-NHC-GO or rGO catalysts in aqueous or alcoholic solvents, or even a mixture of both (Scheme 9). The NHC ligand is generally bound to noble metals after grafting onto graphene oxide, but the metal-bound catalyst can also be grafted relatively easily. Again, the proportions of catalysts are sometimes well below 1 mol%. They also explored various studies on rhodium, ruthenium, iridium, platinum, copper, and gold catalysis using graphene as a heterogeneous support. It should be noted that graphene oxide (GO) or reduced graphene oxide (rGO) supports have the advantage of being commercially available, easily anchored via aromatic π -conjugates, and inert. These aromatic π -conjugates can be covalent [55] or non-covalent [56]. Although the use of this type of heterogeneous catalyst has great potential, it is an area of research that needs to be developed, hence the interest in the recent review by G. Prabusankar et al. [51], which brings together the main works published in this field.



Scheme 9. Synthesis of Pd-NHC-GO: example of palladium *N*-heterocyclic carbene catalyst grafted on graphene oxide (GO).

In addition to the classic reactions catalyzed by palladium, less frequent intramolecular C(sp³)-H activation reactions were also studied using a supported recyclable catalyst (Scheme 10). L. Vaccaro et al. [57] had already synthesized indolines via C(sp³)-H arylation with a supported complex [44,58,59]. The solid-phase-supported palladium(II)-bis(NHC) catalyst is used here in cyclopentyl methyl ether (CPME), which significantly reduces waste, as this solvent is recyclable in the same way as the catalyst. This sustainable catalyst enabled the intramolecular C(sp³)-H activation of methylpyrrole derivatives, providing access to synthons present in more complex molecules of therapeutic interest, such as

Mitomycin C and Tylophorine. The authors studied this catalysis under different base and ligand conditions and demonstrated that the catalyst could be reused for five cycles without loss of activity. They proved the effectiveness of their method by determining the E factor in comparison with other methods [60]. In this study, other ecological indicators were evaluated, such as the stoichiometric factor, material recovery parameters, and others. All these elements contribute to confirming that the method described meets many criteria for making this catalytic process a sustainable method.



Scheme 10. Palladium-catalyzed intramolecular C(sp³)-H activation reactions using a supported and recyclable catalyst.

Despite all the advantages of supported catalysts, one of their disadvantages is the possible deactivation of the catalyst due to aggregation during the process. To overcome this problem, an NHC coordinated with palladium was homogeneously inserted into a hyper crosslinked microporous composite polymer. S. K. Ghosh et al. [61] were thus able to develop highly resistant heterogeneous palladium catalysts. These catalysts were used effectively for Suzuki–Miyaura reactions carried out on a large number of reagents with near-quantitative yields at room temperature with only 0.04 mol% equivalent of catalyst. The latter can be reused for at least 10 catalytic cycles. Among the possible porous materials, a biocompatible, natural, abundant, and inexpensive porous support, chitosan, has been developed in the form of an appropriately cross-linked aerogel onto which the catalyst has been covalently grafted [62–65]. This catalyst has thus been used for scale-up and has enabled gram-scale syntheses in the laboratory. It is not inconceivable that the possibilities of porous materials based on natural products could be further expanded.

In the same vein, S.A. Patil et al. [66] developed a new NHC–palladium (II) complex grafted onto cellulose derived from bagasse (Cellu@NHC-Pd). Bagasse, a residue from the sugarcane industry, undergoes basic treatment to produce cellulose [67,68] (Figure 1). The use of cellulose as a polymer support for supported catalysts contributes to waste recycling and is therefore a sustainable process. This heterogeneous catalyst, Cellu@NHC-Pd, is synthesized from cellulose by reaction with (3-chloropropyl)triethoxysilane in water [69], a chlorinated derivative to which 1-isopentyl-1*H*-benzo[*d*]imidazole is added.

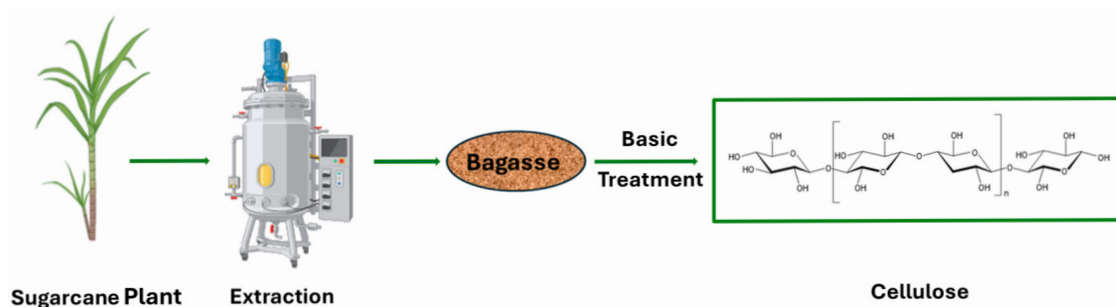
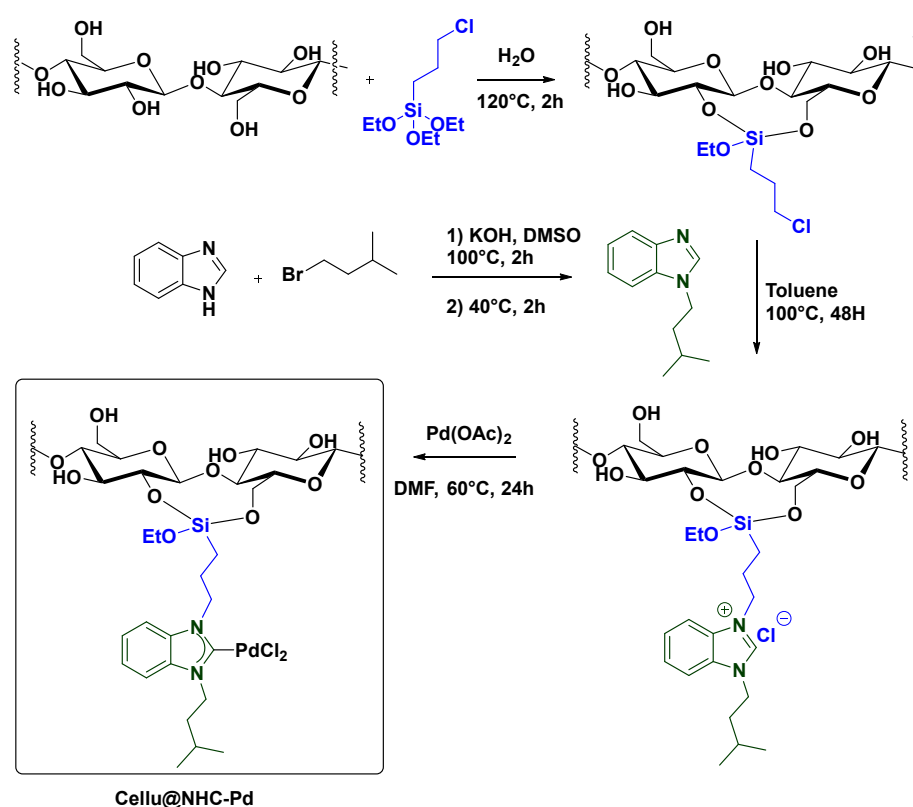


Figure 1. Production of cellulose by basic treatment of bagasse from agricultural sugarcane waste.

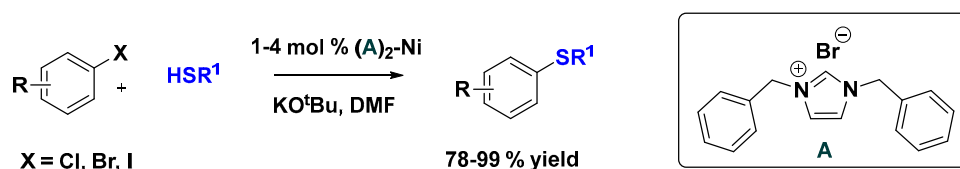
The grafted NHC is then treated with palladium acetate for 24 h to generate this heterogeneous catalyst on a solid support on natural product waste (Scheme 11). It has been thoroughly characterized by the authors using various analytical techniques available for this type of compound. It has been applied to Suzuki–Miyaura and Mizoroki–Heck cross-coupling reactions in an ethanol/water mixture [70]. The expected products are obtained with yields generally above 90% for Suzuki–Miyaura coupling in less than one hour at room temperature. However, yields are slightly lower for Mizoroki–Heck coupling, which requires a temperature of 60 °C to be effective. In addition, this catalyst loses its effectiveness on both couplings when recycled, with the yield halving after the third recycling. There is therefore room for improvement in this area, and further research is needed to find other natural materials that could be more easily recycled.



Scheme 11. Preparation of heterogeneous catalyst (Cellu@NHC-Pd).

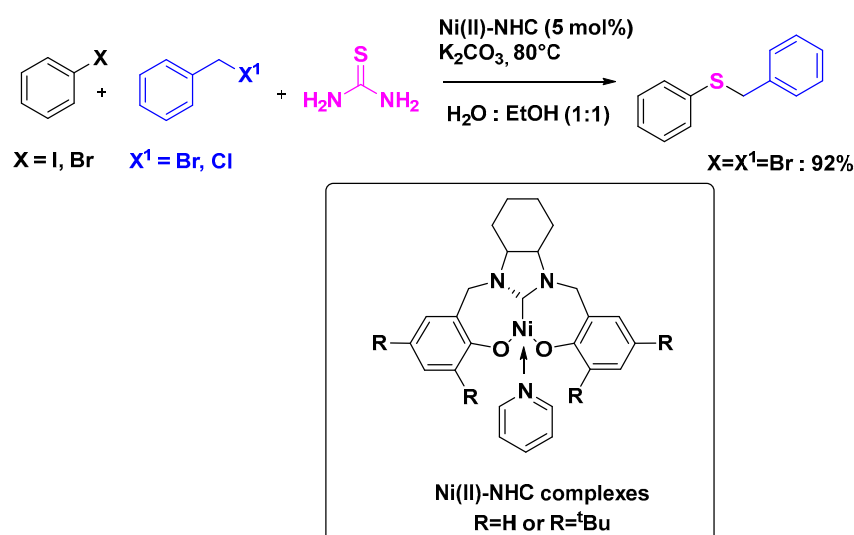
2.2. Nickel Catalysis

Since 2007, researchers have also been interested in more sustainable methods for using catalysts carrying NHC ligands, which led Y. Ying et al. [71] to develop the use of these catalysts to achieve C–S couplings (Scheme 12). Similar palladium-catalyzed couplings pose certain catalyst poisoning problems when coupling with sulfur-containing reagents due to the affinity of sulfur for palladium. These couplings require that the reactions be carried out in such a way that the sulfur-containing reactants do not come into prolonged contact with the palladium in order to avoid adsorption and catalyst poisoning. They developed the first catalysts of this type, which proved to be effective, even highly effective, with various aryl halides. However, the catalytic activities were highly dependent on the electronic and steric properties of these ligands. On the other hand, they were attractive because they were easy to synthesize and inexpensive. These Ni–NHC catalysts therefore represented an excellent alternative for the formation of C–S bonds by organocatalysis.



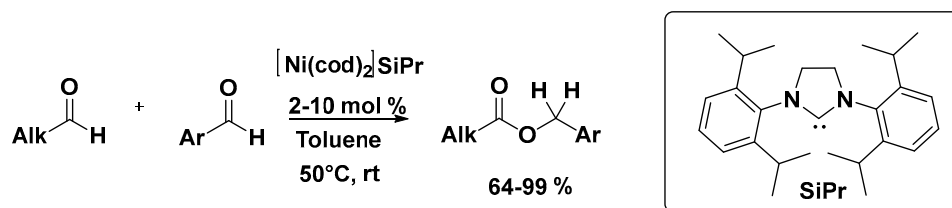
Scheme 12. Ni-NHC catalyst for C-S coupling with thiols.

More recently, in 2023, F. Varmaghani et al. [72] developed the synthesis of nickel (II) complexes containing NHC ligands with varying degrees of steric hindrance. These were used to efficiently carry out C-S coupling reactions in a mixture of water and ethanol as solvents. This type of catalyst has enabled the production of thioethers with high yields by coupling aryl and alkyl halides in the presence of thiourea. The authors demonstrated that the nickel complex with $R = H$ is much more effective than the complex with $R = tBu$, which has a more sterically hindered NHC ligand (Scheme 13). The reaction conditions used in this study, namely a mixture of water and alcohol, particularly ethanol, as solvents and a one-pot protocol, combine the characteristics that make this process a sustainable process for the formation of C-S bonds.



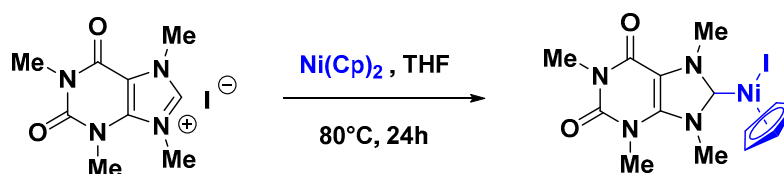
Scheme 13. Ni-NHC catalyst for efficient C-S coupling reaction with thiourea.

In 2011, L.J. Gooßen et al. [73] focused on sustainable esterification methods, particularly the Tishchenko reaction. More traditional esterification methods involving condensation between carboxylic acids and alcohols have the disadvantage of being reversible and requiring excess reagents or catalytic processes and other carboxylate alkylation methods, and these methods are often expensive and generate waste. Tishchenko developed the use of various aldehydes which, through homocoupling, lead to the corresponding esters. However, since all the atoms present in the starting products are found in the product, this method incorporates one of the principles of green chemistry: atom economy. In order to diversify the available molecules, mixed ester syntheses were attempted, and it was found that aldehydes with electron-donating groups were better hydride donors than those with electron-withdrawing groups [74]. At the same time, Ogoshi et al. [75,76] showed that Ni-NHC complexes were active catalysts for this reaction and that with sterically hindered SiPr-NHC ligands, the Tishchenko cross-reaction could be very effective under equimolar conditions (Scheme 14). Ogoshi's protocol thus allows the synthesis of symmetrical or asymmetrical esters while reducing the potential waste from this type of synthesis.



Scheme 14. Ni-NHC catalyst for cross-Tishchenko reaction.

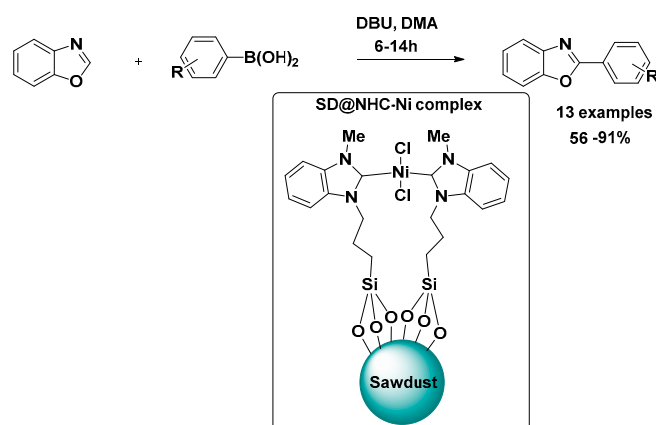
In sustainable chemistry, the use of natural and renewable resources for the development of ligands that can be used in catalysis is a highly sought-after goal. Among transition metals, nickel appears to be an interesting alternative to palladium. It is a relatively abundant metal and therefore inexpensive. Among abundant and non-toxic natural resources, Szostak et al. [77] have recently focused on xanthines, such as caffeine and theophylline, for use in catalysis. They claim to have developed the first Ni-NHC complexes derived from xanthine as a sustainable alternative to imidazol-2-ylidenes (Scheme 15). These xanthines, which have an imidazole ring, are well suited for the generation of NHC. They have also been previously studied as metal complexes with silver, gold, platinum, and palladium for their fairly effective antimicrobial and anticancer activities [78–81]. Szostak et al. [77] applied these Suzuki–Miyaura cross-coupling reactions to 3 mol% Ni-NHC with very satisfactory yields from aryl bromides. To ensure the same yields in the presence of aryl chlorides, it is necessary to add tri-aryl-phosphine (5 mol%) to the catalytic system (3 mol% Ni-NHC). The authors also report on the steric properties of their ligands and their electron donor and acceptor properties, demonstrating the potential applications of these natural carbene ligands as replacements for the better known imidazol-2-ylidenes.



Scheme 15. Ni-NHC carbene complexes derived from xanthine used for Suzuki-Miyaura Cross-coupling.

Supported Ni-NHC Catalysts

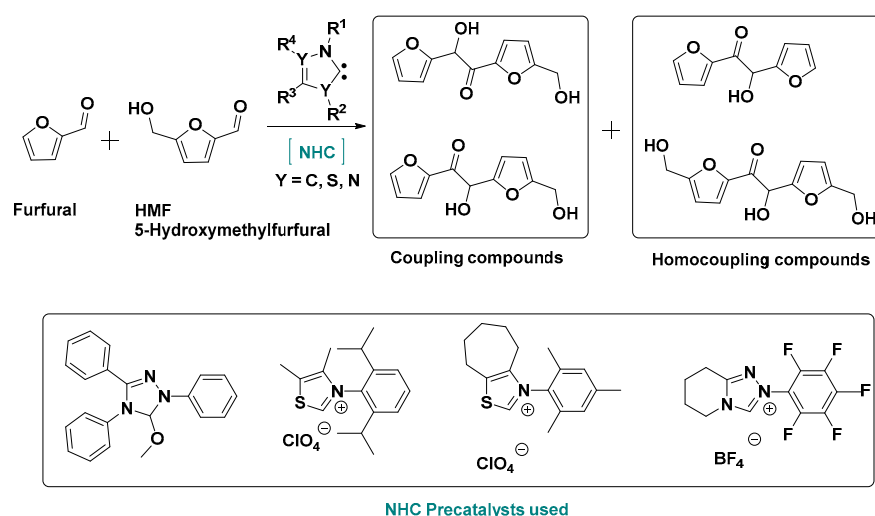
With regard to nickel catalysts, R. Salunkhe et al. [82] developed a nickel NHC complex covalently grafted to 1-methyl imidazole in a sawdust matrix. The SD@NHC-Ni complex is generated from wood sawdust previously modified with chloropropyl, which is then reacted with nickel acetate. This catalyst was used in this work for a C–H activation reaction of benzoxazoles in the presence of aryl boronic acids. Wood sawdust, a waste product from related industries, can therefore be used to synthesize heterogeneous catalysts. This method, like the one using cellulose seen above for palladium catalysts, is sustainable because it contributes to waste recycling. In addition, the catalyst can be reused over several cycles without significant loss of activity. Indeed, it is only after the sixth consecutive cycle that approximately 10% of yield is lost. The authors were thus able to obtain the desired 2-substituted benzoxazoles with good yields ranging from 56% to 91% (Scheme 16).



Scheme 16. 2-substituted benzoxazoles synthesized catalyzed by SD@NHC-Ni complex.

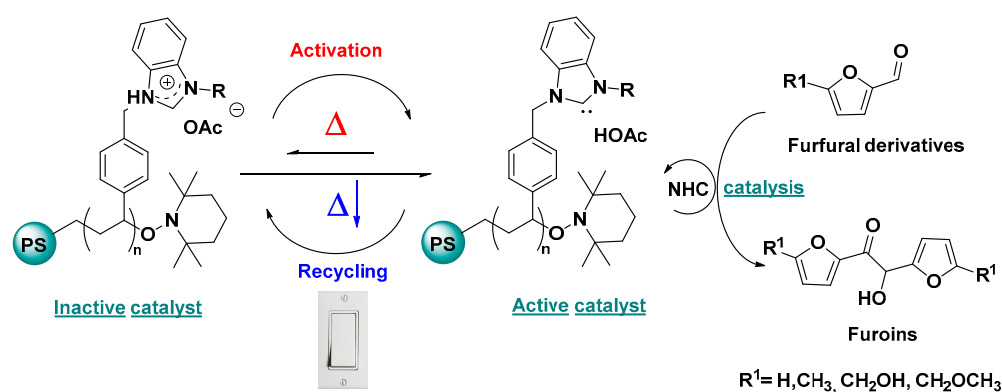
2.3. NHC Catalysis Without Metal

We will now review the recent use of NHCs as metal-free catalysts under environmentally friendly conditions, starting with the work of E.Y.-X. Chen and J. Wilson [83] on the use of cellulosic plant biomass as a source of furfural derivatives such as furfural and 5-hydroxymethylfurfural (HMF), which can be used in the recycling of waste from corn cultivation, for example. These compounds are relatively abundant, are produced by the dehydration of sugars, and can be used as a starting point for obtained biofuels through catalysis [84]. In order to modify their physical properties of volatility and, in particular, to transform them into biofuels of good energy quality [85,86], the chain must be lengthened by coupling two molecules through the formation of C-C bonds to obtain the desired furoins (C10 to C12) [87]. This elongation must be controlled in order to avoid the polymerization of furfural derivatives during caramelization processes, which are well known in the food industry. The cross-coupling of these two entities, furfural and 5-hydroxymethylfurfural, has been considered using NHC catalysts in solution. Various coupling products were obtained, and their proportion varied little depending on the NHC organic catalyst used (Scheme 17). However, the overall conversion can be influenced by the type of base or solvent. Homocoupled and coupled furoins were obtained with a slight excess of cross-coupling products. These products can be selectively oxidized to furanyl α -diketone in air and without metal. They were all isolated, purified, and fully characterized.



Scheme 17. Catalyzed NHC homocoupled and cross-coupled furoin synthesis.

E.Y.-X. Chen continued his research in this field, but this time using azolium salts grafted onto polystyrene [88]. Their efforts focused on the catalyst itself, which was coupled with an acetate counterion, allowing the catalyst to reach thermal equilibrium between its active and inactive forms [89]. By regulating the temperature, it is possible to generate sufficient quantities of the active form for catalysis to take place, while lowering the temperature deactivates it and allows it to be recovered and recycled. It acts as a kind of on/off switch, depending on requirements (Scheme 18). Several azoliums have been tested and the auto-coupling yields obtained are very interesting (>95%). The recyclability of the catalyst over five cycles is effective, as it only results in a 5% decrease in yield for furfural auto-coupling [90]. As for 5-hydroxymethylfurfural, the proton in the hydroxyl function poses certain stability problems in the reaction, particularly through reaction with the acetate ion, and contributes to reducing the yield or making recycling difficult. Protecting this function, although it constitutes an additional step, improves yields and, in addition, some protections allow for other industrial applications.

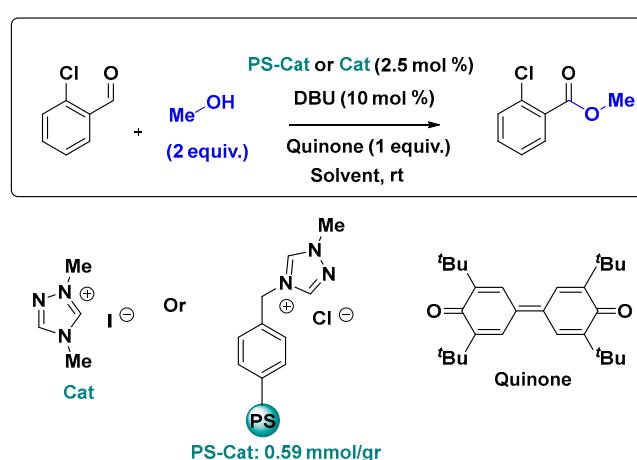


Scheme 18. Thermal equilibrium between active and inactive forms of catalysts that acts as an on/off switch.

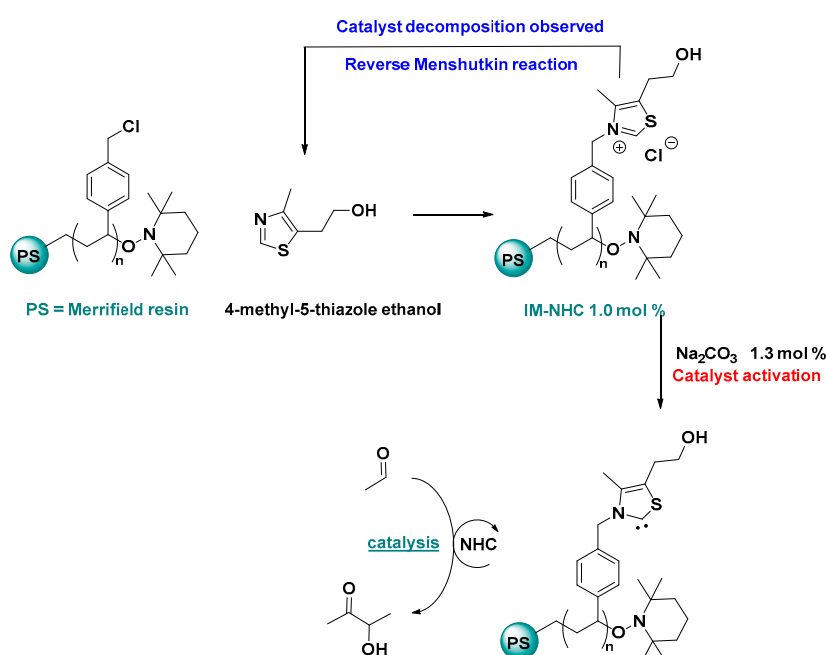
C. D'Agostino et al. [91] studied the formation of esters by coupling aldehydes and alcohols using NHCs supported on polystyrene in various solvents. Depending on the solvent, polystyrene has the ability to swell or deflate, facilitating or hindering access to functionalized sites. The authors studied the impact of this modification of the surface and the accessibility of the reactants depending on the solvent used, but also the impact on the transition states and certain reactions depending on the polarity of the medium. As indicated for metal catalytic systems, the use of a supported catalyst makes the process more sustainable due to easier purification. Catalysis takes place in the presence of an equimolar amount of a quinone-type oxidant at room temperature in the presence of 10 mol% of 1,5-diazabicyclo(5.4.0)undec-7-ene (DBU), which activates the triazolium salt immobilized on polystyrene [92] and used at 2.5 mol%. Several polar solvents (tetrahydrofuran (THF), dimethylformamide (DMF), and dichloromethane (DCM)) were tested, for which the heterogeneous catalyst does not appear to behave differently from the homogeneous catalyst (Scheme 19). However, as the polarity of the solvent decreases with toluene, which is slightly less polar, and, finally, non-polar cyclohexane, the results are no longer the same. This is therefore an important parameter to take into account, depending on the reactions and the type of polymer support used.

A.J. Vorholt et al. [93] reported in 2024 the auto-addition of acetaldehyde in ethanol to generate 3-hydroxy-2-butanone (acetoin), which does not appear to have been studied previously. The formation of the C-C bond in this synthesis is facilitated by the use of an NHC catalyst, which, until then, had mainly been used with aromatic aldehydes [94,95]. This reaction is involved in the industrial mechanism of bioethanol dehydration. In this

work, the use of NHC catalysts supported on Merrifield resin by a covalent bond allowed the authors to increase the sustainability of the process through easier purification and, in addition, to carry out the reaction in a continuous flow to further increase sustainability. Various thiazolium salts were considered in the liquid phase before being coupled to the Merrifield resin. One of the most effective and readily available NHC catalysts in solution was chosen to be coupled to the resin (Scheme 20). This supported complex was characterized and used for the transformation; however, unlike the solution catalyst, it generates other by-products and tends to partially decompose, depending on the duration of use, through a reverse Menshutkin reaction [96–99] to 4-methyl-5-thiazole ethanol. The authors are currently continuing their research on this metal-free heterogeneous catalyst in order to eliminate this Menshutkin degradation reaction, which has an impact on yields. Their continuous flow tests have enabled them to achieve better selectivity, but not better yields, and the catalytic activity also decreases over time.



Scheme 19. Oxidative coupling with carbenes supported on polystyrene or not in the presence of quinone derivative as an oxidant in various solvents.



Scheme 20. Preparation of supported complex IM-NHC on Merrifield resin for synthesis of acetoin from acetaldehyde.

Finally, in the context of metal-free catalysis, J.C-G. Zhao and T. Chanda have listed recent advances in organocatalyzed asymmetric domino reactions [100]. Domino, tandem, and even multicomponent reactions, which are not always easy to classify, are often used in the biosynthesis of natural compounds [101,102]. These reactions meet many criteria of green chemistry, including atom economy, and enable the development of complex structures from relatively simple synthons. J.C-G. Zhao and T. Chanda discuss the use of NHCs to activate certain substrates that are difficult to activate by other means, as these NHCs can be produced in an asymmetric version [100]. Various examples of the use of chiral NHCs for asymmetric domino transformations are listed [103,104]. Substrates that can be activated by such catalysts include esters, which can be activated by the Lewis basic nature of the NHC [105,106], and aldehydes or ketones, which are also excellent substrates [107,108].

3. Conclusions

The activation possibilities offered by these NHCs are considerable. Although they can be used in metal catalysis, they also make it possible to avoid the use of these metals, which are sometimes toxic, expensive, or often rare, thus contributing to the preservation of natural resources. Many asymmetric and non-asymmetric ligands can be synthesized or are commercially available. They can be grafted onto various polymeric supports relatively easily, allowing them to be used in a wide range of environments and for a very wide range of reactions. They can be adapted to syntheses with or without solvents. They have the advantage of being efficiently recyclable over several cycles in many cases. Their development is virtually infinite, making these NHCs an important part of the organic chemist's toolbox.

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Abbreviations

The following abbreviations are used in this manuscript:

NHCs	N-heterocyclic carbenes
RTIL	Room-temperature ionic liquid
NPs	Nanoparticles
MNPs	Magnetic nanoparticles
AuNPs	Gold nanoparticles
CPME	Cyclopentyl methyl ether
THF	Tetrahydrofuran

2-MeTHF	2-Methyltetrahydrofuran
DBU	1,5-Diazabicyclo(5.4.0)undec-7-ene
HMF	5-Hydroxymethylfurfural
DMF	Dimethylformamide
DMA	Dimethylacetamide
DCM	Dichloromethane
PS	Polystyrene

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