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Metal-NHC heterocycle complexes in catalysis and biological applications: Systematic review

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\textbf{A B S T R A C T}

N-heterocyclic carbenes are of central importance in many domains of chemistry such as organometallic, catalysis and bioinorganic. Their great importance is due to their ability to act as ligands with a large number of transition metals. These Metal-NHCs are used as catalysts in various organic transformations with good biological properties. A wide range of Metals - NHC has been found to be useful as a catalyst in various reactions using Ru, Pd, Ir, Au and Ag. This review examines the different classes of Metal - NHCs and their applications as effective catalysts in several types of organic processes, for example the formation of amide linkage, hydrogenation, isomerization, cycloisomerization, cyclopropanation, hydrosilylation, allylation and desilylation, enol-ester synthesis, heterocycle synthesis, C - C alkyne coupling.

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1. Introduction

N-heterocyclic carbenes (NHC) present a new category of electron donor ligands, which form dative metal–ligand bonds, which gives us a universal class of materials in organometallic and coordination chemistry [1]. N-heterocyclic carbenes are ligands whose synthesis is inexpensive and which are easily prepared. Their association with transition metals leads to complexes which are generally more stable than their analogs with phosphines, and their use in catalysis has shown over the last 50 years that their performances can equal and exceed those of phosphines. The NHCs offer the option of varying the N or C functionalization in the corresponding NHC precursors [2–5] (Fig. 1). They bind not only to many transition metals, whether in low or high oxidation states [6–9], but also to the main elements of group [10]. Over the past three decades, Metal-NHC complexes have experienced increased production in many areas of chemistry such as inorganic chemistry and catalyze chemistry [11–20]. NHCs can be divided into four main families according to the heteroatoms and the unsaturation’s they contain. These compounds are heterocycles having two or three heteroatoms. In general, imidazolinylidenes and imidazolylidenes are most often used as ligands in organometallic catalysis, while triazolinylidenes and thiazolinylidenes are mainly used in organic catalysis.

2. Introduction

2.1. N-heterocyclic carbene

At the beginning of the 20th century, carbenes were considered to be transient and very reactive species. At the end of the 1960 s, the work of Wanzlick [21] and Öfele [22] made it possible to isolate the first stable metal complexes with NHC as ligands, by adding the imidazolium salt to the mercury acetate, Wanzlick et al. [21] thus obtained another complex in which the NHC is coordinated to mercury. At the same time, Lappert became interested in the platinum complexes with these ligands. In 1971, he reported the synthesis of
the first platinum complex with an NHC obtained from enetetramine [23]. Subsequently, many complexes with large variety of metals have been synthesized [24–26]. The godfather of the NHCs, Mr. Arduengo, who gave the real start to carbene chemistry by isolating the first free, stable and crystalline NHC [27], followed by its analogs in 1992 [28] and then in 1995 [29]. In 1995, the Enders [30] scientific team proposed the synthesis of triazolylidene in two stages from salt by another method. Removal of methanol from the intermediate quantitatively led to the formation of NHC, which was also the first commercial carbene.

2.2. N-Heterocyclic carbene in catalysis

NHCs have been widely used in organic catalysis [31–32], especially in condensation reactions, because of their nucleophilic nature which allows these NHCs to react with different types of electrophiles. The most studied condensation reactions with NHCs are benzoin condensation, the Stetter reaction, as well as reactions using homo-enolates (Fig. 2).

It was in 1943 that Ugaï & Tanaka [33] discovered the capacities of NHCs to catalyze the benzoin condensation reaction. Indeed, thiamine (or vitamin B1, which includes a thiazolium nucleus) catalyzes the condensation of benzaldehyde on itself. The first asymmetric benzoin condensation reaction catalyzed by a chiral salt was reported by Sheedan et al. [34]. However, a very low enantioselectivity of 2% was obtained. Since then, different types of chiral NHC have been synthesized. In general, triazolium salts are better catalysts than thiazolium salts. In 1980, the Tagaki [35] team described the synthesis of the chiral thiazolium salt, which catalyzes benzoin condensation. Unfortunately, the observed yield and asymmetric induction are rather low. In 2002, Enders & Kallfass [36] reported the synthesis of the bicyclic triazolium salt which led to a large increase in asymmetric induction.

3. Catalysis by Ru-NHC complexes

3.1. Amide bond

The amide bond is one of the most important functional groups in contemporary chemistry. It is essential to sustain life, making up the peptide bonds in proteins such as enzymes. It is found in numerous natural products and it is also one of the most prolific moieties in modern pharmaceutical molecules. Despite their obvious importance, the majority of amide bond syntheses involve the use of stoichiometric amounts of coupling reagents, making them generally expensive and wasteful procedures. In the search for an alternative to coupling reagents and enzymes in amide bond synthesis, non-metal catalysts such as organocatalysts and boron reagents have been reported, although these still often suffer from low atom efficiency and difficult isolations. A possible solution to these drawbacks lies with Ru-complex catalyst. Increasing attention is now being devoted to developing such amide bond syntheses which are not only atom-economical but also low cost and more environmentally friendly. Employing Ru-complex catalyst in amide syntheses also creates the possibility to opening up previously unavailable synthetic routes to target molecules.

In 2011 an extra work [37] of a young team Jonathan MJ Williams & C. Liana Allen who put the action on the importance of Ru-NHC in the catalysis of the formation of the amide bond the most important in this work is the amide formation from different functions, for example carboxylic acids, aldehydes or alcohols (Fig. 3), nitriles.

A recent work [38] by S. N. R. Donthireddy & al. on the catalysis of the C-N bond by Ru-NHC. In this work they developed the imidazol-2-ylidene and the 1,2,3-triazol-5-ylidene for the used as ligands in order to complex them with Ru (II) for a catalysis of the CN bond via a hydrogen borrowing methodology (Fig. 4).
The synthesized ruthenium (II) complexes have been shown to be very effective in the formation of CN bonds across a wide range of primary amine and alcohol substrates under solvent-free conditions.

3.2. Carboxylic acids

New work published in 2019 by Wan-Qiang Wang et al. [39] on the dehydrogenation of alcohol to carboxylic acids this reaction was catalyzed by five Ru-NHC complexes carrying NHC helper ligands (Fig. 5).

3.3. Alkene hydrogenation

The big and fantastic work done by Nolan and al. [40] using Nucleophilic NHC / Iridium for the alkene hydrogenation and Ruthenium too for the same purpose [41] (Fig. 6)

3.4. C–H activation

The developments in the area of nucleophilic carbenes have indicated that these compounds could act as good catalyst for C–H Activation too by using Rhodium catalysts [42] (Fig. 7). Meanwhile, a series of novel palladium (II)–NHC complexes (NHC = N-heterocyclic carbene) were synthesized and were tested as efficient catalysts in the direct C–H bond activation of benzoxazole and benzothiazole with aryl bromides [43] (Fig. 8).

3.5. Suzuki – Miyaura coupling

The possessing of NHCs a strong σ-donating ability, which enabled chemists to structurally characterize several low-valent and low-coordinate metal complexes and studied the catalysts properties in coupling reaction [44]. In this reported work, the air-stable palladium – NHC complex (Fig. 9) was found to be catalytically active in Suzuki – Miyaura coupling reactions of aryl bromides.

Fig. 4. General scheme for the N-alkylation reaction via a hydrogen-borrowing pathway [38].

Fig. 5. The five NHC / Ru complexes prepared [39].

Fig. 6. Structure of Nolan catalysts based on Iridium [40].
3.6. Sonogashira coupling

A series of well-defined N-heterocyclic carbene palladium (II) complexes with general formula (NHC)Pd(N^O)(OAc) were prepared and exhibited moderate to high catalytic activities for the Sonogashira coupling [45] (Fig. 10). In the same topic a variety of NHC-Pd-PPh3 complexes with the bulky benzyladamantyl substituted N-heterocyclic carbene (NHC) were synthesized and proceeded to Sonogashira-Hagihara coupling reaction between aryl bromides and phenylacetylene in DMF. All palladium compounds are stable and have high catalytic activity on Sonogashira-Hagihara reaction by low catalyst loading [46] (Fig. 11).

3.7. Alkylation of amines with alcohols

A series of new ruthenium (II) complexes bearing N-heterocyclic carbene ligands with benzylic groups were prepared by transmetallation reactions between silver(I) N-heterocyclic carbene complexes and [RuCl2(p-cymene)]2 [47]. All of the obtained complexes were tested for the alkylation of aromatic amines with...
a wide range of primary alcohols under solvent-free conditions using the hydrogen borrowing strategy (Fig. 12).

3.8. Oxidation of alcohols

Among NHCs, the functionalized-NHC with reversible donor groups show great advantages in homogeneous reactions and in obtaining coordination complexes because they would allow a further fine-tuning of the metal environment in obtaining sophisticated complexes (Fig. 13). In addition, both ruthenium-NHC complexes were demonstrated to be efficient catalysts for the oxidation of various alcohols. Exploiting them as catalysts, a variety of carbonyl products were obtained in excellent yields [48].

3.9. Alkyne, aldehyde and amine coupling

Catalytic tests show that all these silver NHC complexes exhibit highly effective catalytic activity in the three-component coupling reaction of alkyne, aldehyde and amine forming propargylamines (Fig. 14) [49].

3.10. N-Alkylation of amine

Six ruthenium(II) complexes with the general molecular formula $[\text{RuCl}_2(\text{NHC})(\eta_6-p$-cymene)] were reported and fully tested as efficient catalysts for N-alkylation of aniline with arylmethyl alcohols using the hydrogen borrowing strategy, which is a cost-effective and environmentally attractive reaction for the preparation of N-alkylated amines (Fig. 15) [50].

3.11. Direct arylation of 2-Phenylypyridine

A series of new benzimidazolium halides were synthesized and were readily converted into ruthenium (II)–NHC complexes with the general formula $[\text{RuCl}_2(\eta_6, \eta_1-\text{arene–CH}_2-\text{NHC})]$, which they were used as efficient catalysts for direct arylation of 2-Phenylypyridine with (Hetero)Aryl chlorides in water (Fig. 16) [51].

3.12. Direct arylation of 2-Phenylypyridine

The pyridazine-bridged NHC/pyrazole ligand $L (HL = 3-[3-(2,4,6-trimethylphenyl)-3H-imidazolium-1-yl]-6-(3,5-dimethylpyrazol-1-yl)-pyridazine)$ that provides an organometallic and a classical N-donor compartment is shown to serve as a versatile scaffold for a
Fig. 14. Structure of NHC silver complexes based on pyrazole [49].

Fig. 15. Ruthenium NHC complexes used for N-alkylation amines in mild conditions [50].

Fig. 16. Structure of Ruthenium NHC catalyst for direct arylation [51].

Fig. 17. Proposed structure for gold NHC silver and copper for etherification reaction [52].
4. Biological activity of Ag-NHC

4.1. Antibacterial activity

Aqsa Habib et al. [53] have synthesized a new series of N-heterocyclic carbene ligands and their silver complexes (I). The ligands and their complexes have been tested in vitro on three bacterial strains (Bacillus subtilis, Bacillus cereus and Macrococcus brunensis) to assess their antibacterial potential. The in vitro antibacterial study of ligands and complexes has revealed that complexes are relatively more antibiotically active than ligands. Hemolytic and thrombolytic tests have shown that the compounds are safe for the blood of mice for preclinical testing (Fig. 18).

4.2. Anticancer activity

The team of Mr. Muhammad Atif [54] synthesized three Ag-NHC complexes with variation of the group attached to the ligand. The three complexes are in crystal form and analyzed by X-ray diffraction (Fig. 19). The three synthesized complexes were tested biologically for their anti-cancer activity in vitro against three cancer cell lines, including human colorectal cancer (HCT 116), the breast cancer (MCF-7) and erythromyeloblastoid leukemia cell lines (K-562).

In vitro anticancer activity has shown IC50 values between 0.31 and 17.9 µM in the case of K-562 and HCT-116 cancer cell lines and 15.1–35.2 µM in the event of MCF-7 taking commercially known anticancer agents, 5-fluorouracil, tamoxifen and betulinic acid which have IC50 values of 5.2, 5.5 and 17.0 µM, respectively.

In the same topic Chen et al. [55] have synthesized and characterized a series of promising multi-nuclear silver complexes bearing NHC ligands. The in vitro cell-based studies disclosed their potent anticancer activity across distinct cell types, including cisplatin-resistant cancer cells (Fig. 20).

In this study, silver-NHC buildings were set up by responding 1-(2,2-dimethoxyethyl)-3-(propyl-3-sulfonate)benzimidazolium and 1-(2,2-dioethoxyethyl)-3-(propyl-3-sulfonate)benzimidazolium with

![Fig. 18. Ag(I)–NHC complexes [53].](image1)

![Fig. 19. Ag(I)–NHC complexes [54].](image2)

![Fig. 20. Structure of multi-nuclear silver-NHC based on pyrazole [55].](image3)

![Fig. 21. Structure of Ag and Au-NHC complexes [56].](image4)
silver oxide on average state. Gold-NHC edifices were acquired by means of transmetalation of their silver precursors with [AuCl(S(CH3)2)] [Fig. 21]. IC50 values and cytotoxic impacts of these four complexes were controlled by the MTS put together examine with respect to three human cancer cell lines neuroblastoma (SHSY5Y), adenocarcinoma (HEP3B), and human fibroblasts (HF) [56].

In other study, we synthesized four novel unsymmetrically NHC Ag(I) complexes (Fig. 22). The Ag(I)–NHC complexes (2a-d) showed a dose and time-dependent cytotoxic activity against all cell lines. MDA-MB-231 human breast carcinoma cells were the most sensitive to the Ag(I)–NHC complex displaying IC50 lower than 1 μM all time points. Further, the IC50s for Ag(I)–NHC were higher in non-cancer cells, suggesting that complexes possessed noteworthy selectivity for human cancer cells [57].

5. Conclusion

In this review we tried to show the great importance of the Metal-NHC complexes in the field of catalysis also the great biological activity. It’s opened many future projects specially with using these species may be for fighting against Corona virus.

CRediT authorship contribution statement

Mohammed Jalal: Conceptualization, Methodology. Belkheir Hammouti: Supervision, Validation. Rachid Touzani: Data curation. Abdouhala Aouiniti: Formal analysis. Ismail Özdemir: .

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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