**Synthetic Routes to Late Transition Metal-NHC Complexes**

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**Transition metal complexes bearing *N*-heterocyclic carbene ligands (NHCs) have gained a place of crucial importance in numerous areas of research such as medicinal chemistry, material sciences and homogeneous/heterogeneous catalysis. In the present review, an updated overview of the main synthetic routes employed for the preparation of this broad class of compounds along with their main applications are reported. Particular attention will be paid to the synthesis of Late Transition metal-NHC complexes using weak bases, eco-friendly solvents and mild operating conditions. This simple synthetic approach, also known as the "weak base route", represents a recent development with yet unrealised potential.**

**A brief overview of *N*-heterocyclic carbenes**

Carbenes, in the broadest sense, are molecules containing a two-coordinate carbon with two unpaired electrons and, by virtue of their electronic deficiency, are traditionally considered highly reactive transient species involved in many organic transformations such as cyclopropanation of alkenes. After the first pioneering studies published independently by Wanzlick [1] and Öfele [2] in 1968, in which they described the first metal-NHC (NHC = *N*-heterocyclic carbene) complexes, Arduengo and co-workers obtained the first stable *N*-heterocyclic carbene ligand known as IAd (1,3-bis(adamantyl) imidazol-2-ylidene) [3]. This peculiar class of carbenes, in which the carbenic carbon is incorporated in a nitrogen heterocycle, has had a profound impact in several fields [4-9]. Currently, they play a role of paramount importance as ligands for a wide range of main group, transition metal and f-block species [5-6] with applications mainly in homogeneous and heterogeneous catalysis [8-10]. Such compounds can also act as efficient organocatalysts [11] and their azolium salts are extensively used as cations in ionic liquids [12].

The surprising stability of a number of *N*-heterocyclic carbenes is ascribable to both steric and electronic factors [13-14]. The presence of bulky substituents near the carbene carbon stabilizes these molecules from the kinetic point of view, disfavouring the well-known dimerization process (Wanzlick equilibrium) to the corresponding olefin [15]. However, the electronic stabilization imparted by the nitrogen atoms is predominant. The π-donor character of the adjacent nitrogens allows to partially saturate the electronic deficiency on the empty p-orbital present in the carbene carbon (Figure 1A). In this context, carbenes stabilized by one nitrogen atom (e.g. cyclic alkyl amino carbenes, CAACs) or by sulfur and oxygen atoms, are also worthy of mention. Moreover, NHCs that derive from heteroaromatic or fused heteroaromatic compounds are further stabilized due to their partial aromaticity. The majority of NHCs present a five-membered ring and, among these, the most commonly employed are imidazolylidenes, imidazolidinylidenes, pyrrolylidenes, oxazolylidenes, thiazolylidenes and triazolylidenes (Figure 1B).

Many cases have been reported where the imidazolylidenes or imidazolinylidenes bind the metal center of interest *via* C4 or C5 (the backbone), rather than *via* the carbonic carbon residing between the two nitrogens, and for this reason the term 'abnormal NHCs' is used [16]. The latter are generally strongly electron-donors and usually less stable than the classical NHCs.



**Figure 1. N-heterocyclic carbenes: an overview.**

(A) Classical NHCs and their applications. (B) Structure of most common NHCs.

*N*-heterocyclic carbenes have proven to be extremely versatile ligands as they are capable of forming strong bonds with different metal centers and, unlike phosphines, lead to the formation of very stable complexes toward oxygen, moisture and heat. The strength of the metal-carbene bond was initially ascribed to the excellent σ-electron donating character of the NHCs; however, recent evidence suggests that the contribution of both π-back-bonding into the carbene p-orbital and π-donation from the carbene p-orbital may not be negligible [13]. The high stability of transition metal complexes bearing NHC ligands is one of the main reasons for their growing use in the field of medicinal chemistry, especially for the development of new promising anticancer and antibacterial drugs [7].

The importance of NHC derivatives in the various areas listed above has resulted in numerous synthetic routes and protocols leading to their isolation on small and large scale. In this contribution, we provide a comprehensive overview of the most used synthetic strategies for the preparation of NHC metal complexes, with particular attention to the use of weak bases and mild conditions.

**Classical synthetic approach: free-carbene and transmetallation routes.**

The two most widely used methods for the synthesis of Transition-metal NHC complexes involve the use of free carbenes (isolated or generated *in situ*) or by carbene transfer reactions (transmetallation).

***The free carbene and oxidative addition routes***

The discovery of the first stable NHC (Figure 2A) has allowed the subsequent study of the coordination of these species on nearly all metal centers in the Periodic Table. In the early 1990s Hermann [17] reported the synthesis of carbonyl complexes of Cr, Mo, W, Fe and Ni, by direct reaction between a free NHC ligand and the M(CO)6 (M = Cr, Mo and W), Fe(CO)5 or Ni(CO)4 precursors (Figure 2B). Tolman had shown that Ni(CO)4 was an excellent model compound for the determination of the electronic properties of a given ligand (Tolman electronic parameter, TEP) [14]. The substitution of one carbonyl ligand by an NHC leads to the formation of the [(NHC)Ni(CO)3]complexes, whose infrared stretching frequency (A1 C-O vibrational mode) is heavily influenced by the donor or acceptor character of the substituting carbene employed.

Ligand displacement is one method to affix a NHC onto a metal. A more atom economical manner is to use precursors that adopt a bridged dimeric structure (e.g. [RuCl(μ-Cl)(η6-p-cymene)]2, [Rh(μ-Cl)(cod)]2, [Ir(μ-Cl)(cod)]2 and [Pd(μ-Cl)(η3-allyl)]2). In these cases, the addition of two equivalents of free NHC to the dimeric metal precursor leads to scission of the dimer and formation of the desired monomer species [18] (Figure 2C). NHCs are sometimes able to replace one or more phosphine ligand. Probably the most striking case for this possibility is found for the synthesis of the second-generation olefin metathesis catalysts reported by Herrmann [19], Nolan [20] and Grubbs [21] in the late 1990s (Figure 2D).

In all cases described above, the use of free NHC ligands is involved. In this regard, the most common source of free NHCs is the azolium salts. These salts, a number of which are commercially available, can be reacted with strong bases (e.g. NaH, NaOtBu, KHMDS and *n*-BuLi) in aprotic solvents (e.g. benzene, diethylether, tetrahydrofuran and dimethyl sulfoxide) and lead to the formation of the free carbene [18]. Since the azolium deprotonation with a strong base often leads to unstable carbene species, the *in situ* formation of free NHCs in the presence of the metal precursor of interest is often the preferred synthetic route and presumably disfavours carbene dimerization under these conditions (Figure 2E).

The use of an external base is not necessary if an azolium salt and a suitable metal precursor already containing a base such as Pd(OAc)2, Pd(acac)2, [Rh(acac)(CO)2] and [Ni(Cp)2] is employed.

Using this approach, Lin [22] and Cazin [23] reported the use of Ag2O and Cu2O as basic metal precursors, which lead to the corresponding carbene complexes (NHC)MX and water as a sole by-product.

Another method for the preparation of metal-NHC complexes, although less used than the other routes reported in this contribution, concerns the direct oxidative addition of the C2-H of azolium salts to electron-rich late transition metals.

In this respect, Peris [24] and Cavell [25] published in the early 2000s the synthesis of NHC complexes with group 9 and 10 metals exploiting the insertion of these metals into the azolium-X (X = H or halogens) bond (Figure 2F).

Finally, if we remain in the field of metals in low-oxidation state, it is worth mentioning that it is possible to synthesize some NHC complexes by the reaction of electron-rich olefins, which are originated from the dimerization of free carbenes (see Wanzlick equilibrium), with a great variety of metal precursors as reported by Lappert in the late 1970s [26] (Figure 2G).



**Figure 2. Synthesis of transition metal complexes by free NHC route.**

(A) Preparation of a stable free NHC. (B) Synthesis of carbonyl complexes of Cr, Mo, W, Fe and Ni. (C) Reaction of a free NHC with [Rh(μ-Cl)(cod)]2 dimer. (D) Synthesis of the second-generation olefin metathesis catalysts. (E) Example of carbene dimerization (Wanzlick equilibrium). (F) Synthesis of Ni- and Pd-NHC complexes with the oxidative addition route. (H) Synthesis of Ni(0)-NHC complexes starting from electron-rich olefins.

***Transmetallation route***

The free carbene route, although still employed for the preparation of numerous carbene complexes, requires the use of strong bases and rigorous inert conditions, with the associated considerable expenditure of time and money. An alternative strategy is represented by the transfer of the carbene fragment from a suitable metal center (generally Ag(I) or Cu(I)) to a precursor of the metal center of interest [22-23]. This synthetic strategy is commonly known as the *transmetallation route*.

The silver carbene complexes are nowadays widely used as transmetalating agents and, as previously mentioned, are generally prepared by reacting azolium salts and silver oxide(I) in a wide range of solvents [18]. This was the earlier method described in the literature for this purpose and surely accounts for the popularity of its use. The silver complex reported by Lin in 1998 [22] allowed to successfully obtain the corresponding Au(I) and Pd(II) benzimidazolylidene complexes with consequent precipitation of AgBr (Figure 3A).

The high cost and light-sensitivity of silver compounds have prompted the study of alternative transmetalating agents. In this respect, Albrecht and Cazin reported ten years ago [23] the possibility of using Cu(I) carbene derivatives as less expensive and almost equally effective agents for the preparation of a wide range of complexes with different transition metals (e.g. Au, Ru, Ir, Rh and Pd). Particularly efficient were the complexes of formula [Cu(NHC)Cl] (Figure 3B), which can be easily synthesized starting from azolium salts and Cu2O or through the weak base route, which is the main topic of the present review. Despite its convenience of execution, the transmetalation route suffers from poor atom economy and should be considered for larger scale application only if the silver or copper by-products are recycled.



**Figure 3. Synthesis of NHC transition metal complexes by transmetalation.**

(A) Synthesis of [Ag(NHC)X] and transmetallation on different metal centers. (B) Preparation of the less common [Cu(NHC)X] complexes and their use as transmetallating agents.

**Use of weak bases as eco-friendly route**

An alternative approach to the free carbene and transmetalation routes has been extensively investigated and involves the use of a weak base (e.g. K2CO3, NEt3 or NaOAc) in reactions with the azolium salt and a metallic precursor of interest. Operating in air, under generally mild conditions and in green solvents, a wide range of carbene compounds with various transition metals are obtained in high yields and purity using this method. What follows is an overview of the use of the *weak base approach* for the synthesis of complexes with different transition metals. Particular emphasis will be given to mechanistic studies used to explain the role of these weak bases in the formation of the final complexes.

***Gold-NHC complexes***

Gold carbene complexes were the first to be explored in detail through the use of the weak base route. Between 2009 and 2012 a limited number of papers described the preparation of [Au(NHC)Cl] complexes by direct reaction between gold precursors (e.g. [Au(DMS)Cl] or [Au(THT)Cl]) and azolium salts, in the presence of a weak inorganic base such as K2CO3 or NaOAc [27-29]. In these contributions, however, the most common NHCs were not taken into consideration and above all they involve the use of environmentally-unfriendly solvents such as xylenes, 3-chloropyridine or dimethylformamide and operated at high temperatures (80-120 °C) and required long reaction times (9-48h). With the aim of improving these processes, in 2013 we [30] and Gimeno [31] reported the synthesis of [Au(NHC)Cl] complexes with a large number of the most common saturated and unsaturated imidazolium salts, in the presence of one equivalent of K2CO3 (Figure 4A). These reactions, which are carried out in technical grade acetone (or dichloromethane) and under air, have good/excellent yields depending on the azolium salt used. It is worth mentioning that some of these compounds cannot be prepared with acceptable yields and purity by means of transmetallation processes. Moreover, compared to the free carbene route, this simpler approach permits to obtain products in higher yields in addition to the advantages of operating under mild conditions and in air. The remarkable potential of this approach has stimulated studies focusing on understanding the exact role of each component in this simple method.

The first and fastest step of the process appears to be the formation of the *aurate* intermediate [NHC-H][AuCl2]. As evidence of this, the treatment of the imidazolium salt with the gold precursor in the absence of base, yields the fully characterized *aurate* product in short reaction times and in high yield [30-31] (Figure 4B). In support of the hypothesis that such compounds may be intermediates along the process, the addition of one equivalent of potassium carbonate to an acetone solution of the *aurate* species afforded the final carbene complexes (Figure 4B). As a side-note, some of these *aurate* derivatives exhibit good antitumor, antileishmanial and anti-inflammatory activity [32-33].

At this point, how these intermediates interact with a weak base leading to the final [Au(NHC)Cl] complex remained a key question. The free carbene does not appear to be formed under these conditions [34]. Nuclear magnetic resonance (NMR) data support this lack of free carbene formation. The imidazolium and aurate salts have similar pKa for the azolium proton. This is unequivocally reflected in the ineffectiveness of a weak base itself (K2CO3 or NEt3) to enable the azolium deprotonation and formation of free NHC. Using as model base as NMe3, DFT calculations show a transition of the *aurate* intermediate to the final complex involves a concerted process in which the base contributes to the formation of the transition state [34] as is there to facilitate removal of the HCl generated. DFT calculations also highlight how the activation barrier strongly depends on the nature of the carbene ligand, so as to make a base like NMe3 (or NEt3) ineffective for certain NHCs such as 1,2,3-triazolylidenes. Conversely, potassium carbonate, whose exact role is still the object of mechanistic investigations, is in general much more efficient as a base compared to NEt3 and allows the formation of the 1,2,3-triazolylidene complexes in high yields and purity. In summary, the transformation of the *aurate* species into the desired product is the rate determining step of the overall process. The correct outcome of this type of reactions is therefore heavily influenced both by the nature of the base used and by the type of carbene ligand precursor employed.

In 2016, Gimeno and co-workers reported a method that allows to obtain [Au(NHC)Cl] complexes, widely studied as bioactive molecules [35] and homogeneous catalysts [36], also with poorly encumbered carbene ligands [37]. For these ligands, the reaction between the corresponding azolium salts and the gold(I) precursor in the presence of K2CO3 in acetone showed a consistent decomposition to metallic gold. To overcome this problem, the authors have highlighted that, by using the tetrabutylammonium acetylacetonate (NBu4(acac)) as a reagent, it is possible to obtain under mild conditions (CH2Cl2, RT, 1h) the products of interest in good yields and purity, both with bulkier (e.g. IPr, IMes and IAd) and smaller (e.g. IMe) carbenes (Figure 4A). The same group reported, in 2019, the use of very similar conditions for the synthesis of thiolate gold(I) complexes by reaction between [Au(NHC)Cl] and pentafluorothiophenol [38] (Figure 4C). Such compounds in the presence of AgOTf lead to bridging thiolate digold(I) complexes which have proven to be efficient catalysts in hydroalkoxylation of alkynes.

Starting from the complexes [Au(NHC)Cl] described above it is possible to have access to a large number of Au(I) carbene derivatives which have attracted a great deal of interest especially as homogeneous catalysts. A first example of such derivatives are the homo- and heteroleptic Au(I)-bis(NHC) complexes which have been successfully synthesized by Roesky [39] and our group [40] by simple addition of one equivalent of several imidazolium salts to an acetone (or dichloromethane) solution of the [Au(NHC)Cl] precursors in the presence of potassium carbonate (Figure 4D). With a similar approach, Baron and Biffis reported the synthesis of digold(I) complexes with bridging bisNHCs and their catalytic performance in alkyne hydroamination and cross-coupling reactions [41] (Figure 4E). Gold(I) biscarbene complexes, have been extensively studied as possible anticancer agents [42]. Until recently these were obtained through the free carbene or transmetallation routes or by using stronger bases such as NaOH as reported in 2015 by Cazin and co-workers [43].



**Fig. 4 Straightforward routes to [Au(NHC)Cl] and their derivatives.**

(A) Synthesis of [Au(NHC)Cl] complexes in the presence of K2CO3 or NBu4(acac). (B) Mechanism of formation of [Au(NHC)Cl] species. (C) Synthesis of thiolate gold(I) complexes. (D) Preparation of Au-bis(NHC) complexes. (E) Synthesis of Au(I) compounds bearing bridging bis(NHC) ligands.

In the same year, our group reported the synthesis of the first Au(I)-NHC acetonyl complex [44], which was initially observed as a by-product of the reaction between the imidazolium salt IPr·HCl and [Au(DMS)Cl] in acetone and in the presence of potassium carbonate, using longer times than those employed for the synthesis of [Au(IPr)Cl]. By carrying out the reactions at 60 °C for 48-72 h, depending on the carbene ligand, it was possible to isolate and fully characterize this novel category of complexes [Au(NHC)(CH2COCH3)] (Figure 5C). These species have proven to be powerful precursors for several organogold compounds as reported in Figure 5C, as well as an attractive alternative to the known [Au(NHC)Cl] and [Au(NHC)(OH)] synthons [45].

Au(I)-NHC hydroxide complexes have been extensively studied as silver-free catalysts for various processes such as alkyne and nitrile hydration, hydroamination, alkoxycyclization and Beckmann type rearrangement [46] (Figure 5B) and above all, by virtue of their high basicity (pka ≈ 30 in DMSO), they are important precursors of a wide variety of Au(I) species, with the advantage of not requiring inert atmosphere and additives [47-50] (Figure 5B). The most recent procedure for the preparation of [Au(NHC)(OH)] complexes is carried out in air using technical-grade tetrahydrofuran, a catalytic amount of tert-amyl alcohol (0.1 equiv.) and sodium hydroxide as a base [51-52] (Figure 5A). Furthermore, these compounds can be easily activated by addition of strong acids such as HBF4. From these studies, diaurate species of the formula [Au(NHC)2(μ-OH)][BF4] were (re-)discovered [46] (Figure 5A). The latter have received great attention as they have also proven to be efficient silver-free catalysts for many transformations [53-57]. The catalysis has exploited their dissociation in solution into [Au(NHC)][BF4] and [Au(NHC)(OH)] which can act as Lewis acid and base, respectively. Recent studies have highlighted the possibility of obtaining these dinuclear species by chloride abstraction from [Au(NHC)Cl] by a silver salt such as AgBF4 in acetonitrile [53]. The solvent stabilised cationic Au(I) complex [Au(NHC)(NCCH3)][BF4], can be used as a synthon to the dinuclear complexes by reaction withwater leading to the desired species [Au(NHC)2(μ-OH)][BF4]. In 2020, we have reported a sustainable and scalable synthetic protocol for the synthesis of Au(I)-NHC aryl complexes, which can be effectively used as starting material to access a wide range of Au(I) complexes [58] (Figure 5D). In particular, exploiting the knowledge acquired on the use of a weak inorganic base to form M-C bonds, a large number of Au(I)-aryl complexes stabilized by NHC ligands were synthesized in high yields, by reaction between [Au(NHC)Cl] and aryl boronic acids (1.1 equiv.) in the presence of K2CO3 (3 equiv.). These reactions take place in air, at room temperature and using ethanol as a more sustainable and low boiling solvent (Figure 5D). Previously, these complexes were obtained by using aryl-magnesium and aryl-lithium reagents [59], which are well-known for requiring inert conditions, and often low temperatures. Gray and Stockland [60] have obtained these same Au-aryl complexes by action of Cs2CO3 at 70 °C under inert atmosphere.

As far as the use of sodium acetate and triethylamine, these weak bases have recently been used for the preparation of digold(I) complexes bearing bridged bisNHCs [61] and NHC-Au(I) thiolate complexes [62], respectively (Figure 5E-F). Furthermore, Tunik and co-workers have isolated bis alkynyl complexes by reacting the starting digold(I) bisNHCs species with phenylacetylene in the presence of K2CO3 (Figure 5E). Finally, in 2020, Toste and co-authors reported on the use of K2CO3 for the synthesis of Au(III) complexes presented in Figure 5G [63].



**Figure 5. Synthesis and applications of Gold NHC complexes.**

(A) Preparation of [Au(NHC)(OH)] complexes and their use as gold synthons. (B) [Au(IPr)(OH)] as silver-free catalyst for nitrile hydration and alkoxycyclization reactions. (C-D) Synthesis and reactivity of Au(I)-NHC acetonyl and aryl complexes. (E-F) Use of sodium acetate and triethylamine, for the preparation of Au(I)-NHC complexes. (G) *Weak base approach* for the synthesis of Au(III)-NHC complexes.

***Copper- and Silver-NHC complexes***

After the initial work on gold(I) complexes, Cazin and co-workers reported the synthesis of [Cu(NHC)Cl] complexes under conditions very similar to those used for the analogous gold compounds [64]. The reaction between the starting azolium salts and CuCl in the presence of potassium carbonate under mild conditions (acetone at 60 °C for 24h) afforded the desired complexes in high yields and purity (Figure 6A). Previously, these compounds were obtained by the free carbene route or by reaction between the azolium salts and Cu2O as copper source in different solvents [23]. This latter route is still very attractive. The use of weak bases (Na2CO3, K2CO3 or Cs2CO3) in the presence of a copper source has already been explored by Jiang in 2012 [65]. However, this protocol required environmental unfriendly solvents such as 3-chloropyridine and high temperatures.

As previously stated, [Cu(NHC)Cl] complexes have been successfully used, over the past decade, as NHC transfer agents for a wide range of transitions metals, including Au(I), Ag(I), Ni(II), Pd(II), Rh(I), Ir(I), Ru(II) and Cr(III) [23, 66]. Moreover, this category of NHC-copper(I) complexes has been widely employed in numerous homogeneous catalytic processes such as in the hydrosilylation of carbonyl containing compounds, the [3+2] cycloaddition of azides and alkynes, in carbonylation and carboxylation reactions, in allene synthesis, C(sp3)-C(sp3) cleavage, in olefination of aldehydes and for ketones and allylic substitutions [67] (Figure 6B).

Silver(I)-NHC complexes are generally prepared by reaction between silver oxide and the azolium salt of interest in a wide range of solvents (see Figure 3A, *Transmetallation route*) [22]. The silver oxide acts as both metal center and makes use of the oxide ligand to deprotonate the azolium salt. However, some alternative synthetic strategies leading to Ag-NHC complexes have been recently developed by Gimeno [31] and Hii [68]. In particular, Gimeno and co-workers reported the synthesis of [Ag(NHC)Cl] complexes by reacting different imidazolium salts and AgNO3 in the presence of K2CO3 under mild conditions (Figure 6C). Silver nitrate is less expensive and significantly more stable than silver oxide. Moreover, this approach is conducted in shorter reaction times and provides high yields and purity of the final products [31].The [Ag(NHC)Cl] complexes already discussed in the previous sections remain commonly used transmetalating agents for the preparation of metal-NHC compounds.

Hii and co-workers reported the synthesis of Ag(I)-carboxylate complexes bearing different saturated and unsaturated NHCs with the weak base approach [68] (Figure 6D). Treating the starting azolium salts with the precursor [Ag(RCO2)] in the presence of K2CO3, it was possible to obtain in high yield the final [(NHC)Ag(RCO2)] species. The authors also reported a comprehensive and systematic study of ligand steric and electronic properties and the remarkable catalytic activity of the silver complexes in the cyclisation of propargylic amides to produce oxazolines.



**Figure 6. Synthesis and application of Copper and Silver NHC complexes.**

(A) Direct synthesis of [Cu(NHC)Cl] complexes. (B) Hydrosilylation and oxidative carbonylation reactions catalyzed by Cu(I)-NHC complexes. (C-D) Alternative synthetic routes to Ag(I)-NHC complexes.

***Palladium-, Nickel- and Platinum-NHC complexes***

Palladium-NHC complexes currently play a key role as homogeneous catalysts in cross-coupling reactions [69]. In the last decade, they have also gained increasing interest as promising anticancer agents by virtue of their good stability in the physiological environment and their marked antiproliferative activity also in tumor lines resistant to cisplatin and its second and third generation analogues (e.g. carboplatin and oxaliplatin) [70-75]. For this reason, any improvement achieved in their synthesis, both in terms of yield and purity and in terms of milder and eco-friendlier operating conditions, would be well-received in both academia and industry. In this regard, we recently reported the straightforward and eco-friendly route to neutral Pd(II)-allyl and cinnamyl complexes stabilized by different NHC ligands [76]. The reactivity of this class of palladium compounds towards several organic substrates has been widely explored in the past [77-78]. Besides their use in cross-coupling reactions, a most striking example of their importance can be found in the Tsuji-Trost reaction, in which the formation of an η3-allyl intermediate allows functionalization at the terminal position of the starting allyl substrate [79].

The synthetic approach we proposed to obtain this important class of complexes was similar to that reported in 2013 for [Au(NHC)Cl] complexes. Indeed, by reacting the imidazolium salt of interest with one key precursor ([Pd(μ-Cl)(η3-allyl)]2 or [Pd(η3-cin)(μ-Cl)]2) in the presence of K2CO3 (1 equiv.) and using technical grade acetone as a solvent (at 60 °C for 5-24h), the neutral [Pd(NHC)(η3-allyl)Cl]or [Pd(NHC)(η3-cin)Cl] complexes can be easily obtained in high yields and purity [76] (Figure 7A).

As already reported for the gold(I) and copper(I) complexes, by carrying out the same reaction in the absence of base it was possible to observe and isolate the corresponding palladates species, which constitute the key intermediates in the formation of the neutral allyl complexes [34, 76] (Figure 7A). The structures of these intermediates, which are stable both in air and in solution, shown H-bonding interactions between the acidic proton of the imidazolium salt and both chloride ligands of the palladate counter-ion. To confirm that these species are reaction intermediates, it was sufficient to treat them with K2CO3 and observe the formation of the final neutral allyl complexes. Both palladate intermediates [80-82] and final allyl complexes [83-87] have proven to be excellent and versatile pre-catalysts in numerous C-C, C-N and C-S formation reactions (Figure 7B). In particular, the effectiveness of these Pd(II) species is demonstrated by their ability to activate important organic molecules such as amides and therefore to use them as precursors of compounds of broad interest [88].

In the last two years, Visentin and Scattolin have also demonstrated the high anticancer activity potential of Pd(II)-allyl complexes [71, 89-91] and hypothesized how this can be explained. By analogy to the Tsuji-Trost catalytic cycle, a nucleophilic attack on terminal allyl carbon by thiol groups present in the biotarget (e.g. mitochondrial proteins) may be the answer [89]. Interestingly, some of these complexes have shown excellent selectivity towards cancer cells and have also been confirmed on more complex biological systems such as organoids and tumoroids extracted from real patients [89] (Figure 7C). The synthesis of Pd(II)-NHC complexes other than those listed above is still carried out mainly through the transmetallation route, in the hope of testing and validating eco-friendlier strategies as soon as possible.

Finally, as already mentioned in the free-carbene route section, precursors such as Pd(OAc)2 or Pd(acac)2 (acac = acetylacetonate), by virtue of the presence of a built-in basic ligand do not generally require the use of external bases [92-94] (Figure 7D). Their related NHC-bearing derivatives are active in important homogeneous catalytic processes [92-94].

Concerning nickel and platinum, in addition to the classic synthetic strategies, some rare examples of the use of weak bases for the formation of the final complexes have been reported. In particular, Bouwman [95] and Meyer [96] published on the synthesis of Ni(II) complexes bearing polydentate NHCs functionalized with anionic N-donor moieties, by reacting the starting imidazolium salts with NiCl2 in the presence of K2CO3 in DMF (130 °C for 16h) or MeOH (50 °C for 5h) (Figure 7E). Ni(II)-NHC complexes bearing the cyclopentadienyl fragment are generally synthesized with a base-free approach by direct reaction between NiCp2 and the imidazolium salt of interest [97] (Figure 7F). The corresponding allyl complexes are normally obtained with the free-carbene route [98-100].

Finally, four papers only on the weak base approach are particularly worthy of mention as regards the Pt(II) carbene complexes. In particular, Hor [101] and Chi [102] have reported on the synthesis of *cis*-dibromo or *cis*-dichloro Pt(II) complexes bearing different monodentate NHCs and a DMSO molecule (Figure 7G). The reactions were carried out by treating the starting azolium salts with the Pt(II) precursor (PtBr2 or *cis*-[PtCl2(DMSO)2]) in the presence of NaOAc or Na2CO3 in DMSO at 80-120 °C for 4h. Moreover, in 2015, Wendt and co-workers published details of the synthesis of *trans*-[Pt(IPr)(3-ClPy)Cl2] by reacting the PtCl2 precursor with IPr·HCl in the presence of K2CO3 using 3-chloropyridine as solvent (80 °C for 48h) [103] (Figure 7H).

In this respect, an interesting example of the use of K2CO3 was reported in 2019 by Kühn and Reich, in which they synthesized Ni(II), Pd(II) and Pt(II) complexes bearing a tetradentate NHC ligand [104]. In this specific case, the potassium carbonate acts as an additional base for the coordination of four NHC moieties starting from the acetate precursors M(OAc)2 (M = Ni, Pd, Pt).



**Figure 7. Synthesis and application of Palladium, Nickel and Platinum NHC complexes.**

(A-B) Straightforward route to Pd(II)-allyl and cinnamyl complexes stabilized by different NHCs and their catalytic activity. (C) Pd(II)-NHC η3-allyl complexes as promising anticancer agents. (D) Use of Pd(OAc)2 and Pd(acac)2 as precursors for Pd(II)-NHC compounds. (E) Use of potassium carbonate as a base for the synthesis of Ni(II)-NHC complexes. (F) Classical approach to [Ni(NHC)CpCl] complexes. (G-I) Use of weak bases for the preparation of Pt(II)-NHC complexes.

***Rhodium, Iridium and Cobalt complexes***

Very few papers have been published on the use of the weak base approach to obtain NHC complexes with metals of Group 9. In this regard, Straub and co-authors, in addition to having obtained interesting Pt(II), Pd(II) and Ni(II) bis(NHC-thiolate) complexes, also reported on the synthesis of a Co(III) octahedral complex bearing this class of bidentate NHCs [105] (Figure 8A). This species was obtained by reaction of CoCl2 with the corresponding imidazolium salt in the presence of K2CO3 in acetonitrile (80 °C for 18h).

Moreover, Straub described the preparation of an η3-allyldicarbonyl molybdenum(II) complex bearing NHC-thiolate ligands using the same approach (Figure 8A) [105]. NMR and IR spectra suggest the presence of the isomer with the NHC ligand positioned trans to the η3-allyl group.

In 2015, Plenio and Savka reported a straightforward procedure for the synthesis of [M(NHC)X(cod)] complexes (M = Rh, Ir, X = Cl, I) [106]. The reaction between the [RhCl(cod)]2 or [IrCl(cod)]2 precursors and various azolium salts in acetone at 60 °C and in the presence of K2CO3 afforded the final complexes in good yield and purity (Figure 8B). This is the exact protocol used for the gold-NHC complexes [30]. For the synthesis of the corresponding dicarbonyl complexes, CO is bubbled through the crude reaction mixture (Figure 8B). It is worthy to remind the Reader that complexes [M(NHC)Cl(cod)] (M = Rh, Ir), by reaction with CsOH, can easily lead to the [M(NHC)(cod)OH] species, which have proven to be powerful synthons for the synthesis of a large variety of Ir(I) and Rh(I) derivatives. These have also been used as well-defined alkene hydrosilylation and dehydrogenative silylation catalysts [107-108] (Figure 8C).



**Figure 8. Synthesis and application of NHC complexes with metals of Group 9.**

(A-B) Use of potassium carbonate for the preparation of Mo-, Co-, Rh- and Ir- complexes. (C) [Ir(NHC)(cod)OH] species as powerful synthons for the synthesis of several Ir(I) derivatives.

**Concluding remarks**

As the enormous interest and activity in the field of Transition-metal-NHC chemistry and catalysis evolves, it is of interest to take a pause and evaluate the synthetic methods used to access these fascinating well-defined complexes. This evolution has taken us from the brute force approach of generating the free NHC at whatever the cost to using transmetalation routes that uses easily accessible agents to now use weak bases and very mild conditions. Whether this approach is truly as general as we hope is something to be explored. We are endeavouring to identify the cases where the *weak base route* can be successful success. We have so far been surprised by the generality of the approach and hope that simpler, more eco-friendly and sustainable conditions will help further democratise the use of these versatile and robust transition-metal complexes.

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**Glossary**

**Azolium salts:** salts obtained for the protonation or substitution at nitrogen of imidazoles and their derivatives.

**Free NHC route:** a synthetic approach that leads to carbene complexes using free carbene (isolated or generated *in situ*).

**Heteroleptic:** a complex with two or more types of ligands.

**Homoleptic:** a complex with all ligands identical.

**Ligand displacement**: the exchange of one ligand for another, with no change in oxidation state at the metal center.

**Metallate species:** any anion or salt containing a metal bind to one or more atoms/molecules (i.e. *aurate*, *palladate* and *cuprate* intermediates).

**Synthon:** astructural unit within a molecule which by means of a chemical reaction is convertible into the desired product.

**Transmetallation:** a reaction that involves the transfer of a ligand from a metal to another.

**Weak base:** a base that does not ionize fully in an aqueous solution.

**Weak base approach:** use of weak bases, mild conditions and green solvents for the preparation of Metal-NHC complexes.