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The "Weak Base Route" Leading to Transition Metal-N-Heterocyclic Carbene Complexes

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*Dedicated to the memory of Professor Paul C. J. Kamer*

N-heterocyclic carbenes (NHCs) are nowadays ubiquitous in organometallic chemistry and catalysis. Recently, a synthetic method which makes use of weak bases and desirable solvents has emerged as a simple, widely applicable and cost-effective pathway to well defined M-NHC complexes. Herein, recent studies devoted to the weak base approach are examined in detail, in order to showcase the simplicity, scope and variations of the method with regards to the azolium salts, bases and the metal sources, as well as the reaction conditions used. Mechanistic investigations are presented,illustrating the formation of intermediates which are air and moisture stable, prior to the metallation step. Finally, the importance, limitations and future prospects of the weak base route are discussed.

Introduction

The vast potential of N-heterocyclic carbenes (NHCs) as ancillary ligands in transition metal catalysis has been demonstrated and thoroughly explored during the last decade.[1–3] In any catalytic method, the access to the catalyst is a crucial factor in determining its overall utility. Consequently, sustainable routes for the synthesis of transition metal-based catalysts are highly desirable to stock the synthetic chemist's toolbox.

Historically, there have been three main approaches for the synthesis of transition metal-NHC complexes (Scheme 1).[4] The first involves the formation of a free carbene as the initial step (Scheme 1a).[5–9] Such species are usually obtained by the addition of a strong base to an azolium salt. The next step of this "free carbene route" is the introduction of a transition metal source to the reaction mixture (of the *in situ* generated NHC) or to the isolated NHC. It is worth mentioning that besides being a two-step procedure, the free carbene route is carried out under inert atmosphere, using strictly anhydrous conditions and strong bases, which are usually expensive and potentially hazardous. The second approach – the "transmetallation route" – is also a two-step procedure (Scheme 1b).[6,10–12] The first step is the reaction between an azolium salt and copper or silver oxides, in order to obtain the corresponding Cu- or Ag-NHC complexes. The next step consists of a NHC transfer to a desired second transition metal. Despite the advantageous features of this approach, such as the use of air-stable starting materials and the generation of water as by-product in the first step, it also has significant drawbacks. This route is limited to the use of

only copper and silver oxides, usually requires high temperatures or toxic solvents, while it generates non-trivial amounts of waste. It is also troublesome when attempting to access metal complexes bearing bulky NHC ligands.
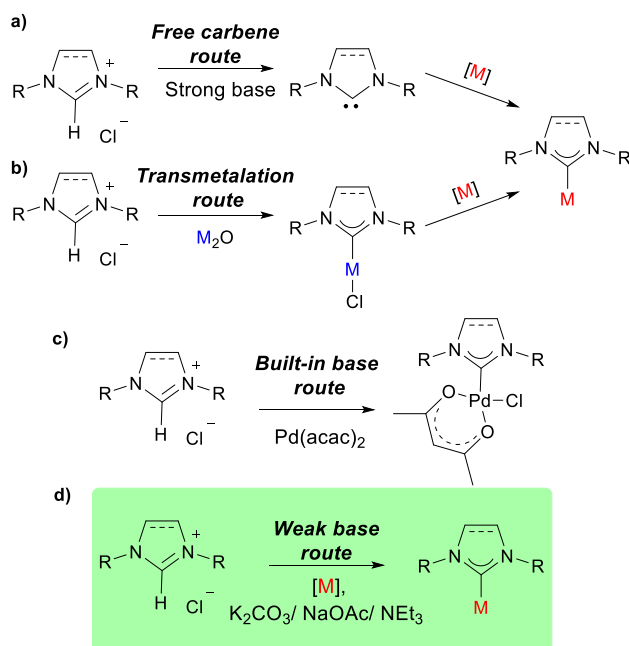
Scheme 1. Methods for the synthesis of metal-NHC complexes.

Importantly, these limitations render the scale-up of these routes challenging and not sustainable in terms of waste and resource management. The third approach, the "built-in base route" [13,14], is not as general as the other two and requires the prior installation of a ligand onto the metal precursor that can act as a base (Scheme 1c). Some examples make use of

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commercially available precursors already possessing such ligands. A simple, one-pot synthetic procedure has been reported,[14] where $Pd(acac)_2$ and excess of an NHC salt were refluxed in 1,4-dioxane for 24 hours; after which time the desired compound, [Pd(acac)(NHC)Cl], was obtained in almost quantitative yield.

A limited number of works devoted to the synthesis of various M-NHC complexes (M=Rh, Ir, Au, Ni, Pd, Cu, Ag, etc.) via the reaction between metal sources and azolium salts in the presence of weak bases, such as NaOAc, K_2CO_3 and NEt_3 have also been described in the literature during the period from 2002 until 2012.[15–22] It is worth mentioning that the reported procedures require high temperatures (80-200 °C), microwave irradiation, long reaction times (9-24 hours) and toxic solvents (xylenes, 3-chloropyridine and acetonitrile). In addition, there are examples of using the weak base approach to obtain a cationic Pt-NHC complex by stirring a triazolium salt and Karstedt's catalyst in the presence of NaOAc in THF, at room temperature.[23] Unfortunately, these procedures cannot be applied to many NHC ligands or azolium precursors.

The groups of Nolan and Gimeno,[24,25] in 2013, independently reported an approach using a weak base (K_2CO_3, among others), imidazol(in)ium salts and gold or silver sources, which allows the one-step synthesis of the corresponding metal-NHC complexes (Scheme 1d). These were some of the earliest systematic reports on the topic, describing the metallation of the most commonly used NHC salts under environmentally benign conditions and provided an in-depth investigation of the methodology, highlighting its importance for coinage metals specifically and also in general. This "weak base route" led to several significant improvements namely to the use of aerobic conditions, the prospect of using greener solvents, such as acetone and ethanol, and to the use of weak bases that are less toxic and cost-effective.

The objective of this contribution is to highlight the weak base approach as the state-of-the-art procedure for the synthesis of numerous metal-NHC complexes. An up-to-date overview of studies on the "weak base route" is presented herein. Particular attention is paid to key aspects of this chemistry including its large-scale applications and mechanistic understanding, highlighting the future prospects and limitations discovered thus far. Throughout this review, the term "weak base" refers to typically inorganic bases and triethylamine (with a pK_a value of their conjugate acid being less than 11 in water). Even though pK_a values depend on the solvent, comprehensive classification of the bases examined is not the objective and the reagents which will be encountered herein are typically regarded as mild or "weak" bases.

The weak base route in the synthesis of Group 11 complexes

Gold-NHC complexes are valuable to the wide research community because of their various applications in catalysis[26,27] medicinal chemistry and material science.[28–30] For these reasons, complexes of the coinage metal have become a key point of interest during the last two decades. In 2011, Zhu and
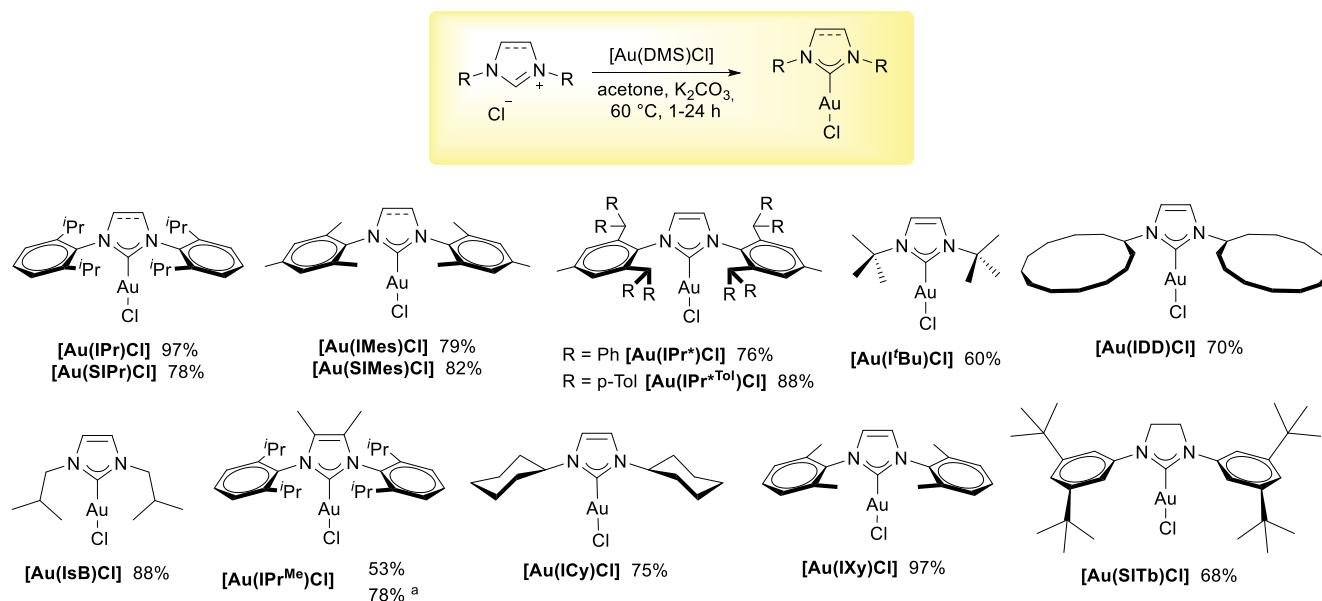
co-workers reported a new synthetic approach for gold-NHC complexes using a weak base route.[31] It was shown that [Au(NHC)Cl] complexes can be obtained directly by heating $[M][AuCl_4]\cdot 2H_2O$ (M = Na, K) and various NHC ligands in 3-chloropyridine with potassium carbonate as a base. $[Au(NHC)Cl_3]$ species were considered as intermediates for this reaction, which can be transformed into the desirable gold-NHC complexes by re-exposing the reaction conditions. The use of a toxic solvent and high temperature are among the main drawbacks of this route which are reminiscent of the approach used for Organ's palladium system (see the Pd-NHC chapter below). The Ananikov group attempted to obtain gold complexes containing ring-expanded NHC ligands using the same procedure, but did not succeed.[32] Their work has demonstrated the unsuitability of this approach in the case of bulkier ligands (THP-Dipp, THD-Dipp).

The Nolan[24] and Gimeno groups,[25] independently reported an alternative approach implementing the use of weak bases for the synthesis of such complexes. This method allows the one-step synthesis of gold-NHC complexes using imidazol(in)ium salts and metal sources. The procedure reported by Gimeno requires an excess (15 eq.) of base and is carried out in dichloromethane. The same reaction conditions were also tested for the synthesis of Ag-NHC complexes (Scheme 2a). The reaction conditions described by Gimeno and co-workers were not applicable to NHC ligands bearing both very bulky and very small substituents, the latter compounds were observed to decompose to metallic gold under these conditions. In order to find a more versatile procedure, Gimeno reported the "acac method" in 2016.[33]

THT = tetrahydrothiophene; DMS = dimethylsulfide
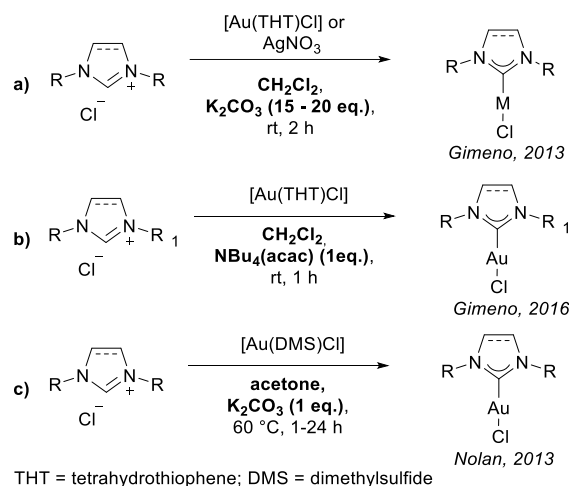
Scheme 2. Various reaction conditions for weak base route.

Tetrabutylammonium acetylacetonate, $NBu_4(acac)$, was used as the deprotonating reagent in this approach, however it is worth mentioning that $NBu_4(acac)$ requires synthesis prior to use, thus adding a step in the M-NHC synthetic procedure. Reactions were carried out in DCM, a non-desirable solvent for sustainability reasons (Scheme 2b). The Nolan method makes use of only 1 equivalent of potassium carbonate and of the more sustainable acetone as solvent (Scheme 2c). The

Scheme 3. General synthetic procedure for [Au(NHC)Cl] complexes using optimized conditions. Scope of obtained gold-NHC complexes.

Reaction conditions: 1 eq. of NHC·HCl salt, 1 eq. of [Au(DMS)Cl], 1 eq. of K$_2$CO$_3$., ^{a} 2 eq. of K$_2$CO$_3$

optimization of this route was carried out on an example of IPr·HCl as the imidazolium salt and [Au(DMS)Cl]. Different solvents (among them acetonitrile, acetone, THF and iPrOH), bases (such as NaOAc, K$_2$CO$_3$, NaHCO$_3$, Na$_2$CO$_3$, NEt$_3$ and pyridine) and temperatures (from 25 to 60 °C) were tested. The best result was obtained in acetone with 1 eq. of potassium carbonate at 60°C after 1 hour. To highlight the versatility of this approach, reactions with various saturated and unsaturated NHC ligands under the same user-friendly conditions were performed (Scheme 3). Both saturated and unsaturated Au-NHC complexes were obtained in good to excellent yields. In some cases, improved performance in comparison with previously reported methods was observed.[6] [Au(IPr)Cl] was prepared in 97% yield in comparison to 76% yield while using the free carbene route. The yield was also improved for [Au(IMes)Cl] from 63% (using the transmetallation route) to 79%. It is worth mentioning that [Au(IPr*)Cl], bearing the very bulky IPr* ligand, which could not be obtained by transmetallation,[34] was successfully prepared in 76% yield using the weak base route.[24] However, although the yields for gold complexes bearing ICy, IDD and I^{t}Bu were good (60-88%), the reactions did not reach completion. Substituents on the backbone of IPr^{Me} decreased the yield to 53%, but this can be improved to 78% by the addition of 2 eq. of potassium carbonate. Usually for saturated NHC ligands, longer reaction times (24 hours) are required to reach full conversion.

The scalability of this approach was also tested.[24] Gram-scale experiments with various NHC salts (IPr·HCl, IMes·HCl, ICy·HCl, IPrMe·HCl, SIMes·HCl) demonstrated excellent results with 1 eq. of base. In order to shorten the reaction time, excess potassium carbonate (3 eq.) can be used. The desired gold complexes were obtained in high yields (77-94%) (Table 1)).

The Cisnetti group investigated the weak base route with the use of aqueous ammonia in order to obtain Cu-NHC complexes.[35] Despite the reaction proceeding under mild conditions, it has some drawbacks, for example, 6 eq. of NH$_3$ (aq.) are essential to reach full conversion. Also, the desired Cu-NHC complexes can be isolated from the aqueous solution only after numerous filtrations or extractions. Water appears cumbersome here as it is in numerous other workups. In addition, this route is not applicable to IAd·HCl due to its higher pK$_a$ value. So, the described synthetic procedure is restricted to NHC salts with lower pK$_a$ values (pK$_a \approx 21$).

Table 1. Large-scale reactions.

NHC·HCl (g)	Yield % (g)
IPr·HCl (21.7)	94 (29.8)
IMes·HCl (23.1)	87 (31.6)
ICy·HCl (3.0)	75 (3.9)
IPrMe·HC (1.22)	77 (2.1)
SIMes·HCl (3.0)	79 (3.7)

In order to find a more versatile approach to Cu-NHC complexes using milder bases, Cazin and co-workers investigated the weak base synthetic approach for copper-NHC complexes,[36] as simple access to such compounds would significantly streamline their use. Moreover, being in the same group, copper and gold were expected to both be amenable to such simple conditions. However, the exploration of appropriate reaction conditions for
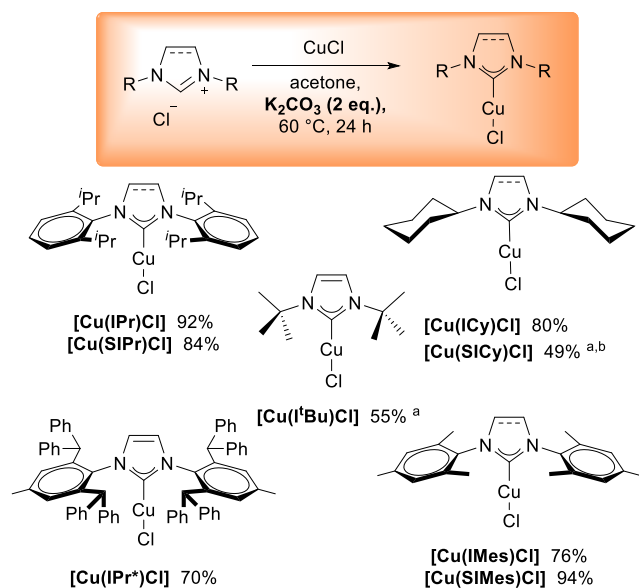
Reaction conditions: 1 eq. of NHC·HCl salt, 1 eq. of CuCl, 2 eq. of K₂CO₃; [a] under Ar; [b] in CH₂Cl₂.

Scheme 4. General synthetic procedure for [Cu(NHC)Cl] complexes using optimized conditions. Scope of obtained copper-NHC complexes.

the [Cu(IPr)Cl] complex revealed that 1 eq. of K_2CO_3 was not enough to reach full conversion (only 80 % was achieved), while doubling the amount of the weak base allowed to isolate the desired compound in a 92% yield. In order to reduce the reaction time to 1 hour, 10 eq. of K_2CO_3 were employed. The weak base route with modified reaction conditions was tested on a large scope of Cu-NHC complexes, bearing both saturated and unsaturated NHC ligands. All the desired copper-NHC complexes were obtained in moderate to high yields (Scheme 4).

Noteworthy is that the formation of side-products such as $[Cu(NHC)_2]^+$ was never observed, in contrast with free carbene route.[37] The described procedure allowed to isolate very bulky copper-IPr* complex without use of microwave irradiation as it was previously reported.[34] The use of the weak base approach improved the yield for [Cu(ICy)Cl] complex from 70% [37] to 80%. The synthesis of [Cu(I^{t}Bu)Cl] was carried out under inert atmosphere as it is known to be air- and moisture-sensitive.[37] It was revealed that [Cu(SICy)Cl] complex cannot be obtained under batch conditions. The only reported procedure includes using of a continuous flow system.[38] As it was shown by the Cazin group, attempts to obtain the [Cu(SICy)Cl] complex from the appropriate NHC salt using the transmetallation route led to decomposition of the complex and concomitant formation of 1,3-dicyclohexylimidazolidin-2-one.[12] The copper complex bearing the SICy ligand was synthesized using the weak base approach in 49% yield. Under the optimized conditions, a mixture of the desirable [Cu(SICy)Cl] complex and 1,3-dicyclohexylimidazolidin-2-one was obtained. To avoid the formation of the by-product, DCM was used instead of acetone. The obtained results demonstrated the scalability and versatility of the weak base route both for gold- and copper-NHC complexes.

In order to gain insight into possible intermediates involved in this synthetic route, [Au(DMS)Cl] and IPr·HCl were stirred in acetone in the absence of base. The formation of a new compound was observed, an imidazolium aurate, which was isolated and fully characterized by ^{1}H, ^{13}C NMR and elemental analysis. Its formation in solution can be determined by the significant upfield shift of the imidazolium C2 proton in the ^{1}H-NMR spectrum. This shift is indicative of metallate formation in most cases examined as part of investigation of the weak base route. The structure of the intermediate was determined unequivocally using X-ray diffraction as [IPrH][AuCl] (Fig. 1).[24]
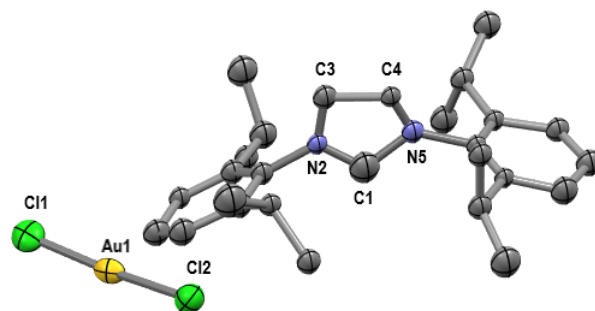

Figure 1. Thermal ellipsoid representation of [IPrH][AuCl₂] at 50% probability. A counterion [AuCl₂] with a Cl(1)-Au(1)-Cl(2) angle of 175.0(4)°.

The same procedure was repeated for copper compounds: the reaction between CuCl and IPr·HCl salt without K_2CO_3 was carried out, and a product of similar structure [IPrH][CuCl₂] was isolated.[36] The formation of both aurate and cuprate intermediates occurs at room temperatures, while the desired metal-NHC complexes can be obtained by adding the corresponding amount of base to these.

The unusual structure of isolated intermediates prompted the authors to perform experiments with NHC salts containing various halides (Br, I, Cl). The authors investigated which halide would be included in the structures of intermediates and established the structures of the corresponding complexes in each case. Reactions of [Au(DMS)Cl] or CuCl with IPr·HBr, IPr·HI salts were carried out under the usual mild conditions. The desirable intermediates [IPrH][MClBr] and [IPrH][MICl] (M = Au, Cu) were isolated in high yields. The addition of 1 eq. of K_2CO_3 for gold compounds and 2 eq. of K_2CO_3 for copper compounds led to only one type of metal-NHC complex in each case. For copper complexes, the reactions between IPr·HCl and CuX (X = Br, I) were also explored, it was established that the same intermediates and Cu-IPr complexes were obtained (Scheme 5). It is worth mentioning that a chloride-containing metal complex was never observed if IPr·HBr or IPr·HI was used. While the reaction between IPr·HBr and CuI was carried out, a new intermediate [IPrH][CuBrI] was isolated in 94% yield. After the addition of potassium carbonate to this intermediate, only one copper complex [Cu(IPr)I] was obtained. We assumed that the trans effect of halides (I ≥ Br > Cl) is the main reason for this observed phenomenon.[39]

The Nolan group tested the described weak base approach on a

large scope of different both saturated and unsaturated NHC
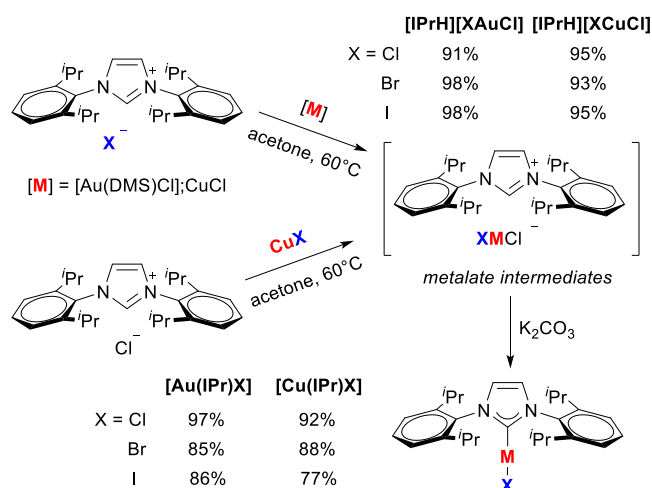
Scheme 5. Formation of [Au(IPr)X] and [Cu(IPr)X] complexes including intermediates [IPrH][XAuCl] and [IPrH][XCuCl].

ligands. The influence of different NHC ligands on the reaction time was examined. For example, complexes [Au(IPr)Cl] and [Au(IMes)Cl] were obtained in 1 hour and 3 hours, respectively, whereas the corresponding saturated compounds [Au(SIPr)Cl] and [Au(SIMes)Cl] required 24 hours under the same reaction conditions. In order to decrease the reaction time for saturated NHC ligands, the same weak base approach using SIPr·HCl salt and [Au(DMS)Cl] with large excess (namely 6 equivalents) of potassium carbonate was tested.[40] Unexpectedly, a mixture of two different complexes, the desirable [Au(SIPr)Cl] and a new [Au(SIPr)(CH$_2$COCH$_3$)] was obtained in 1.3:1 ratio. The same reaction using unsaturated NHC salts led exclusively to the acetonyl compounds. Full conversion in the reaction between IPr·HCl salt and [Au(DMS)Cl] was obtained in 48 hours and the product [Au(IPr)(CH$_2$COCH$_3$)] was isolated in 80% yield (Scheme 6).
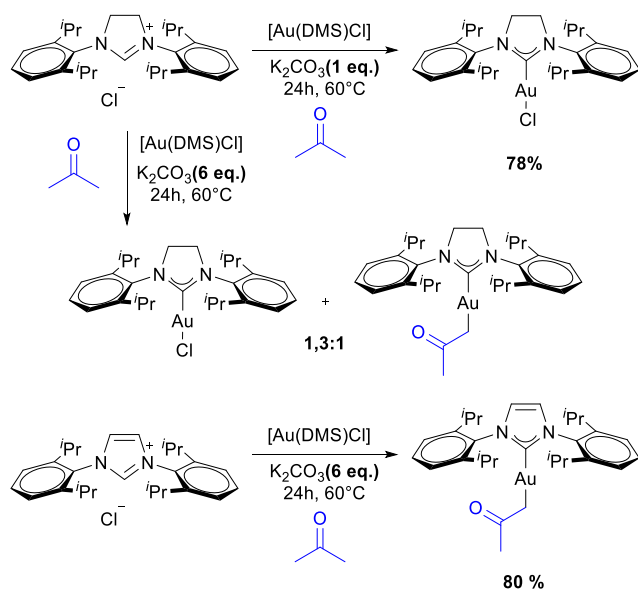
Scheme 6. The formation of acetonyl complexes.

The authors suggested the following reaction mechanism (Scheme 7): the base being in large excess assists in the deprotonation of both the NHC salt and acetone, producing [Au(NHC)Cl] and generating an enolate. The latter reacts with the soft electrophilic gold center, leading to the acetonyl complex and releasing potassium chloride.
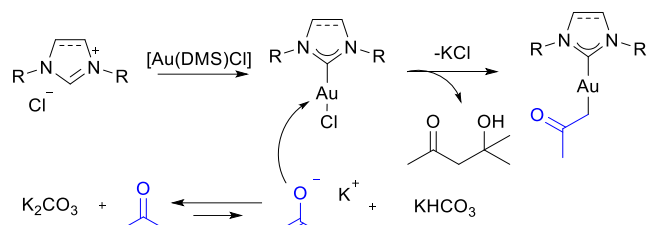
Scheme 7. The proposed mechanism of the acetonyl complex formation.

4-Hydroxy-4-methyl-2-pentanone, which is the product of aldol condensation of acetone in the presence of base, was found to be a side-product under these conditions, which supports the proposed mechanism.

This approach was proven to be efficient for various NHC ligands, namely IMes, SIMes, IPr, SIPr, IPr*, IAd. All complexes with the common structure [Au(NHC)(CH$_2$COCH$_3$)] were isolated in good to high yields (65-97%) (Scheme 8). Moreover, [Au(IPr)(acetonyl)] complex showed high activity for the hydration of alkynes and intramolecular rearrangement/hydroarylation of propargylic acetates.[38] Importantly, the potential of these compounds as organometallic synthons for the installation of various molecular fragments on NHC-ligated gold was also demonstrated.
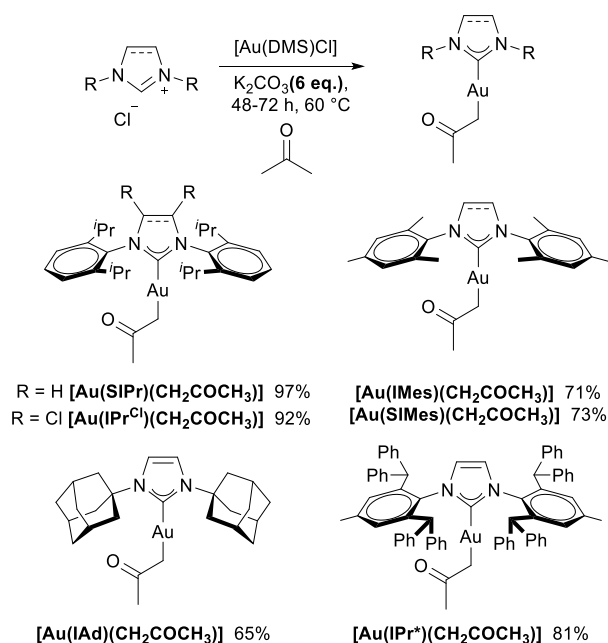
Scheme 8. Scope of [Au(NHC)(acetonyl)] complexes.

Our group also investigated the versatility of weak base approach to unsymmetrical NHC ligands bearing bulky

dibenzotropylidenyl (Trop) as one of substituents on nitrogen.[41] The free carbene route is not applicable for this type of ligands because of difficulties associated with the free carbene isolation. Rapid rearrangement occurs due to reaction between the carbene lone pair and the double bond of the dibenzotropylidene ring.[42] We reported a new synthetic approach for these compounds, by the use of weak base and technical grade acetone at 60 °C.[41] It is worth mentioning that the weak base route is also applicable to the synthesis of gold complexes based on dibenzotropylidene-functionalized NHC ligands (Scheme 9).
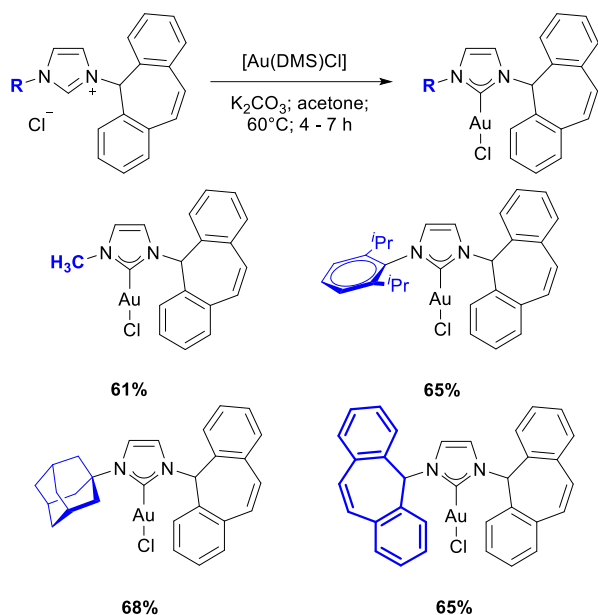
Scheme 9. Synthesis of Trop-NHC Au(I)-complexes.

Due to the growing interest in homogeneous gold catalysis, gold complexes in the higher oxidation state III were also investigated. The high redox potential of gold makes gold (III) compounds oftentimes tend to be reduced into gold (I) or gold (0) complexes.[43] Despite the facile synthesis of [Au(NHC)X$_3$] (X = Cl, Br) complexes, these were found to be photolytically unstable. Cationic gold (I)-bis(NHC) complexes then attracted attention due to the higher stability provided by the presence of a second NHC ligand. These compounds were then thought to be suitable precursors to obtain stable Au(III)-bisNHC complexes. The most frequently encountered synthetic approaches to Au(I)-bisNHC are the transmetallation and free carbene routes.[44,45] Inspired by previous results and proven efficiency of the weak base route, we explored the applicability of this approach to Au-bis(NHC) complexes.[46] [Au(IPr)Cl] in the presence of IPr·HBF$_4$ and 2 eq. of K$_2$CO$_3$ was transformed to the desirable homoleptic gold complex [Au(IPr)$_2$][BF$_4$]. The investigation of the scope for this reaction showed applicability of this procedure for both saturated and unsaturated NHC ligands of different steric and electronic properties to obtain heteroleptic complexes. Moreover, different counterions were tested to prove the versatility of the method (Table 2).

The reaction between [Au(IPr)Cl] and SIMes·HBF$_4$ requires

longer reaction times in comparison with other complexes. It was mentioned above that for [Au(NHC)Cl] complexes bearing saturated NHC the reaction proceeds more slowly compared to their unsaturated counterparts. Moreover, full conversion has not been reached even in six days. However, a modified strategy was implemented for that compound. Using [Au(SIMes)Cl] and IPr·HBF$_4$ for the synthesis of [Au(IPr)(SIMes)]BF$_4$ complex proved successful. Full conversion was reached in 72 hours and the desired compound was isolated in excellent yield.[46]

Table 2. Application of weak base route to the synthesis of gold-bis(NHC) complexes, bearing NHC ligands with various electronic and steric properties.

Au-bis(NHC) complex	Yields (%)
[Au(IPr)$_2$][BF$_4$]	95
[Au(IPr)(IMes)][BF$_4$]	52
[Au(IPr)(SIMes)][BF$_4$]	98[a]
[Au(IPr)(I^{t}Bu)][BF$_4$]	82
[Au(IPr)(ICy)][BF$_4$]	73
[Au(IPr)(BMIM)][BF$_4$]	96
[Au(IPr)(BMIM)][PF$_6$]	79
[Au(IPr)(BMIM)][Cl]	62

[a] [Au(SIMes)Cl] as a precursor, IPr·HCl, in the presence of K$_2$CO$_3$.

Two small NHC ligands on gold are favourable for oxidation reactions in gold(I)/gold(III) catalytic processes. The gold-bis(NHC) complex containing two small and flexible BMIM ligands was synthesized by our group. With the same procedure starting from [Au(BMIM)Cl] and BMIM·HBF$_4$, a mixture of various complexes was obtained, but [Au(BMIM)$_2$][BF$_4$] could not be isolated. Nevertheless, the one-pot modification of the reaction starting from [Au(DMS)Cl] and mixture of BMIM salts led exclusively to the desired gold complex in high yield (Scheme 10).[46]
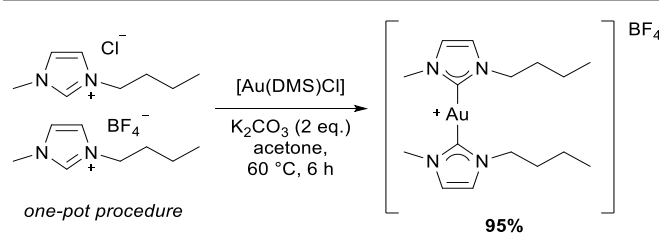
Scheme 10. One-pot procedure of the synthesis of [Au(BMIM)$_2$][BF$_4$].

In addition, the reaction of the synthesized gold complexes with hypervalent iodine in order to obtain the corresponding Au(III) compounds were explored, which is an important step in gold redox catalysis.[46] Further investigations of steric and electronic effects of NHC ligands were carried out. Small and more electron donating NHC ligands were found to be more desirable for the gold (I) center. The weak base approach was proven to be effective for the synthesis of Au(I)-bis(NHC) complexes both
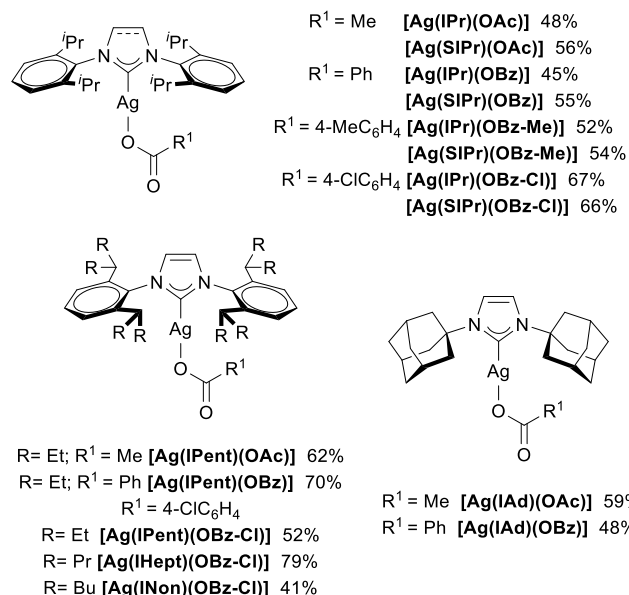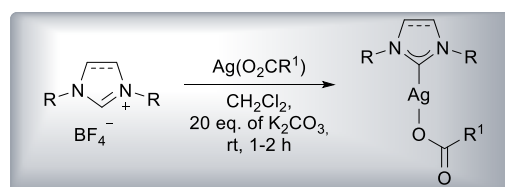
homo- and heteroleptic, bearing NHC ligands possessing various electronic and steric properties. The discussed weak base route was also proven to be efficient in the synthesis of dinuclear NHC-Au complexes.[47]

Another highly important metal in NHC chemistry is silver. It is worth mentioning that Ag-NHC complexes are highly viewed in medicinal chemistry due to their anticancer and antimicrobial properties,[28,48,49] but applications of Ag-NHC complexes in catalytic reactions remains relatively rare.[1,50,51] The main reason for this can be the weakest M-C bond in Ag-NHC complexes among other metals in Group 11.[52] The ability of [Ag(NHC)X] complexes to form bis-Ag (NHC) complexes of the formula [Ag(NHC)$_2$][X] in solution, is widely used in organometallic chemistry.[53] The described tendency has allowed Ag-NHC complexes to be employed as carbene-transfer reagents for the transmetallation route. Nowadays researchers are particularly interested in catalysts based on cheaper metals, such as silver. These catalysts can be used to facilitate the intermolecular addition of N-H and O-H bonds to alkynes to yield substituted oxazolines.[54–56] Another significant application of silver complexes is in enantioselective transformations such as the aldol-type condensation, Mannich reactions, Michael reactions, 1,3-dipolar cycloadditions, among others.[57] In addition, Ag-NHC complexes are widely used as NHC transfer agents to copper, Cu-NHC complexes are essential catalysts for a large number of reactions.[58] This use is intriguing in view of the more efficient and direct route disclosed by Cazin.[12]

It was established that complexes such as [Ag(NHC)Cl] (NHC = IPr, SIMes), [Ag(IPr)$_2$]PF$_6$ and [Ag(SIPr)(OTf)] are inefficient as catalysts in cyclisation reactions involving propargylic-amide oxazoline derivatives.[59] In attempts to find active silver catalysts, the Nolan and Hii groups investigated the activity of [Ag(NHC)(O$_2$CR)] complexes.[59] There are several independent sites in the structures of Ag-NHC carboxylate complexes that assist in optimizing catalytic activity. In order to accommodate steric and electronic properties of a potential catalyst, the degree of saturation in the NHC ligand that modifies σ donation properties can be changed. Bulky N-substituents also influence the properties of NHC ligands, as they prevent catalyst decomposition. The carboxylate ligand itself stabilizes these complexes and makes them more reactive, as the dissociation rate is higher for Ag-carboxylates than for Ag-halides.[59]

Usually there are two possible approaches for the synthesis of Ag-NHC carboxylate compounds. The first one includes reaction between a Ag-carboxylate and the corresponding [Ag(NHC)X] (X = Cl, Br, I) complex.[60] According to the second approach, the NHC precursor salt and 2 eq. of Ag(O$_2$CR) are used in the reaction.[61] Notably, these approaches have disadvantages, as AgX is generated during these reactions and also an excess of silver carboxylate is required. Both factors render the isolation of the desired compound difficult.

To overcome the described difficulties, the Hii group tested the weak base approach with previously described reaction conditions on silver-NHC compounds.[59] This synthetic procedure was adapted to a series of [Ag(NHC)(O$_2$CR^1)] complexes, bearing various saturated and unsaturated NHC

R^1 = Me	[Ag(IPr)(OAc)]	48%
	[Ag(SIPr)(OAc)]	56%
R^1 = Ph	[Ag(IPr)(OBz)]	45%
	[Ag(SIPr)(OBz)]	55%
R^1 = 4-MeC$_6$H$_4$	[Ag(IPr)(OBz-Me)]	52%
	[Ag(SIPr)(OBz-Me)]	54%
R^1 = 4-ClC$_6$H$_4$	[Ag(IPr)(OBz-Cl)]	67%
	[Ag(SIPr)(OBz-Cl)]	66%

R= Et; R^1 = Me [Ag(IPent)(OAc)]	62%
R= Et; R^1 = Ph [Ag(IPent)(OBz)]	70%
R^1 = 4-ClC$_6$H$_4$	
R= Et [Ag(IPent)(OBz-Cl)]	52%
R= Pr [Ag(IHept)(OBz-Cl)]	79%
R= Bu [Ag(INon)(OBz-Cl)]	41%

R^1 = Me [Ag(IAd)(OAc)]	59%
R^1 = Ph [Ag(IAd)(OBz)]	48%

Scheme 11. Scope of silver-NHC carboxylate complexes [Ag(NHC)(O$_2$CR^1)].

ligands (IPr, IPent, IHept, INon, IAd, SIPr) and diverse substituents on the carboxylate fragment (Me or substituted Ph). The authors underlined that the key to success is the use of NHC·HBF$_4$ instead of NHC·HX (X = Cl, Br, I) salts. The desired compounds were obtained in moderate to good yields (41-79%) (Scheme 11).

To obtain acetate complexes (R^1 = Me), an excess (namely 20 eq.) of potassium carbonate is essential.[59] The reason for using a large excess of the base is to prevent the formation of homoleptic Ag-NHC complexes [Ag(NHC)$_2$][X]. This amount of K$_2$CO$_3$ is enough to assist in the deprotonation the generated acetic acid and to form the counterion. The catalytic activity of these silver-NHC complexes was tested in the cyclisation of propargylic amides. Compared with the Ag-pyridyl complexes,[56] NHC Ag-carboxylate catalysts proved efficient for amides with electron-deficient substituents. Thus, the weak base route proved to be an efficient, scalable and versatile approach towards the synthesis of these coinage metal-NHC complexes as well.

The application of the weak base route to Palladium- and Platinum-NHC complexes

Pd-NHC complexes have been widely explored during the last decades and ubiquitously used in catalytic chemistry, especially in cross-coupling reactions.[62–64] Complexes of the type [Pd(NHC)(η^3-R-allyl)Cl] (R-allyl = allyl, methyl allyl, cinnamyl, indenyl) revealed to be useful pre-catalysts in reactions

generating C-C and carbon-heteroatom bonds.[65–68] The most widespread approach to the synthesis of Pd-NHC complexes is using of a strong base in order to generate a free carbene, followed by the addition of Pd precursors, for example dimers such as [Pd(η^3-allyl)(μ-Cl)]$_2$ or [Pd(η^3-cin)(μ-Cl)]$_2$.[5,9] Another approach, making use of a "built-in" base, does not require inert conditions, nevertheless high temperatures and 1,4-dioxane as a solvent are essential.[69] Taking into consideration the previously described disadvantages of the free carbene route, the development of more facile and cost-effective approach was highly desirable.

Ying and co-workers reported a one-pot procedure for the synthesis of palladacycle NHC complexes using a weak base.[70–72] Although the described procedure allowed the synthesis of the desired palladacycle NHC compounds, bearing unsaturated NHC ligands in high yields, it required high temperatures and a toxic solvent (Scheme 12).
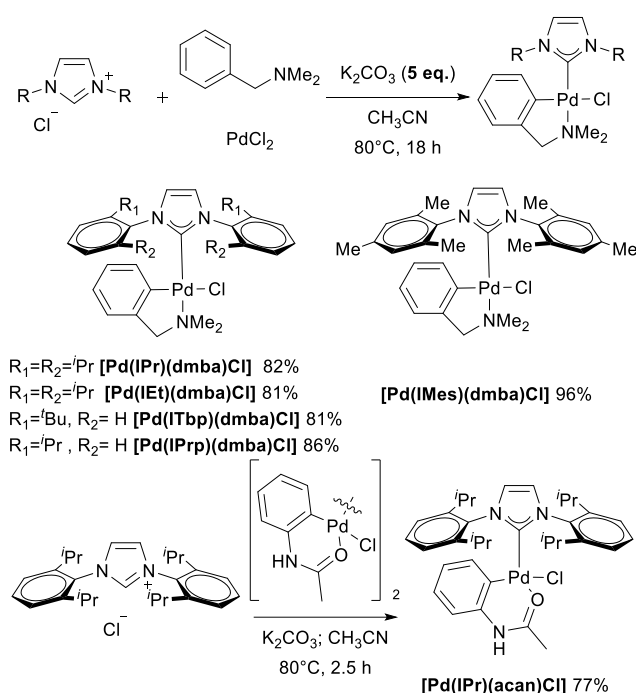
Scheme 12. Weak base route for the synthesis of palladacycle NHC complexes, bearing unsaturated NHC ligands.

The same approach was also implemented for complexes with saturated NHC ligands.[71] In the reaction of the commercially available SIPr·HCl salt, PdCl$_2$, N,N-dimethylbenzylamine and 5 eq. of K$_2$CO$_3$, the desired complex [Pd(SIPr)(dmba)Cl] was observed, with the concurrent formation of several other compounds. These side-products were unreacted NHC precursor salt and N,N'-bis(2,6-diisopropylphenyl)-N-formylethylenediamine, which is the ring opened product of the carbene precursor (Scheme 13).

The formation of by-product can be explained by lower acidity of saturated NHC salts in comparison to the unsaturated counterparts and a tendency of saturated salts to hydrolyse. Using the more expensive Cs$_2$CO$_3$ instead of K$_2$CO$_3$ decreases the amount of by-product to appropriate level.
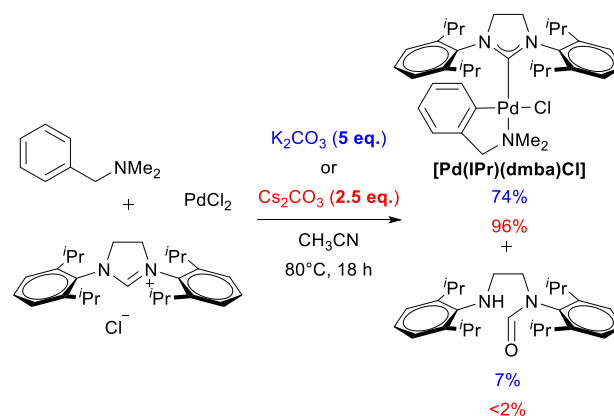

Scheme 13. The synthesis of palladacycle NHC complexes, bearing saturated NHC ligands.

As it was previously discussed, our groups successfully established the weak base approach for Cu- and Au-NHC complexes. The experimental data revealed the existence of similar intermediates in both cases. In attempts to probe if the existence of such an intermediate, which is an "ate" complex, was more widespread than expected, Zinser et al. obtained a series of Pd-NHC complexes using the same reaction conditions as for the Cu- and Au-NHC compounds.[73,74]

The palladium dimers [Pd(η^3-allyl)(μ-Cl)]$_2$, [Pd(η^3-cin)(μ-Cl)]$_2$[73,74] and [Pd(η^3-2-Me-allyl)(μ-Cl)]$_2$[74] were reacted with various saturated and unsaturated NHC salts in acetone in the presence of K$_2$CO$_3$. While common NHC salts reacted well when simple heating of mixture in acetone at 60°C for 5 hours, bulkier NHC ligands (namely IPr*, IPr*^{OMe}, IPr*^{2Np}, IPent, IHept) required a modified procedure. The mixture of the corresponding NHC salt and palladium dimer in acetone was heated at 60° C for 1 hour, to initially form the "ate" complex, then K$_2$CO$_3$ was added and the mixture was stirred for 24 hours. All the desired Pd-NHC complexes were obtained in good to excellent yields (78-98%) in this manner (Scheme 14).

The optimization of reaction conditions on the example of IPr complex revealed that 2.4:1 ratio for IPr·HCl and [Pd(η^3-cin)(μ-Cl)]$_2$ was optimal to reach full conversion. Noteworthy, while increasing the amount of the base leads to a decrease in reaction time, the amount of by-products however increases. Two equivalents of K$_2$CO$_3$ are enough to obtain [Pd(IPr)(η^3-cin)Cl] in excellent yield (98%). The obtained results demonstrated the correlation between steric bulk of the NHC ligands and reaction conditions (time and the equivalents of a base) which are required for the formation of products and intermediates. The generation of Pd-NHC complexes, containing bulky ligands such as IPr*, IPr*^{OMe}, IPr*$^{2-Np}$, IPent and IHept, requires longer reaction time (namely 24 hours in comparison to less bulky ligands needing only 5 hours) and the excess of the weak base 4 eq.[73]

The scalability of the weak base route for the synthesis of such complexes was demonstrated in the case of [Pd(IPr)(η^3-cin)Cl], [Pd(IPr)(η^3-allyl)Cl] and [Pd(IPr*)(η^3-cin)Cl]. The desired compounds were obtained in excellent yields of 97%, 92% and 98%, respectively, on gram-scale reactions without any
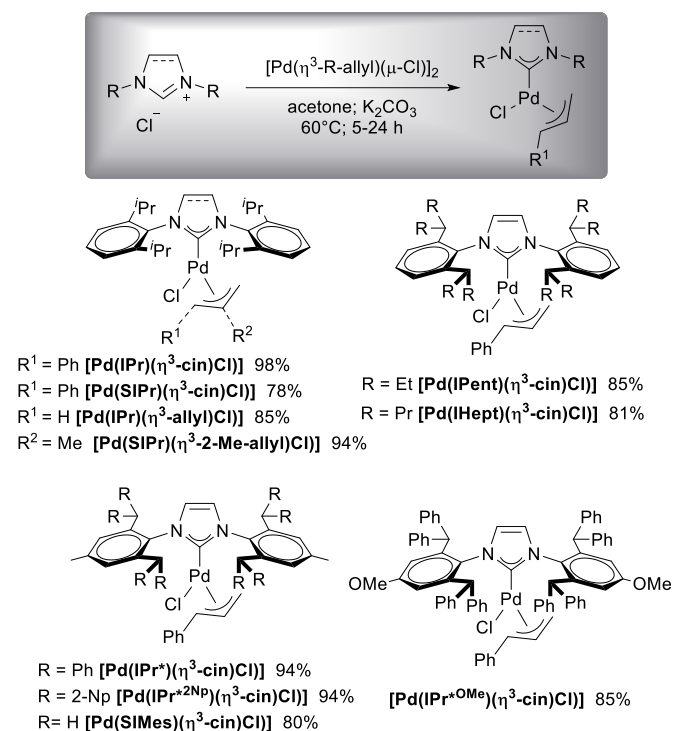
Scheme 14. General synthetic procedure for [Pd(NHC)(η3-R'-allyl)Cl] complexes using optimized conditions. Scope of obtained palladium-NHC complexes.

modification of the smaller-scale reaction conditions.[73]

To establish the structure of the palladate intermediate in the reaction between IPr·HCl and [Pd(η3-cin)(μ-Cl)]2, the reaction was carried out without the addition of K2CO3.[73] A new compound was isolated and characterized by NMR spectroscopy and elemental analysis. The structure of the intermediate was determined using X-ray diffraction as [IPrH][Pd(η3-cin)Cl2] (Fig. 2).
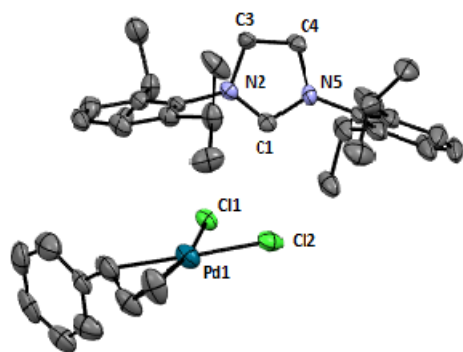

Figure 2. Thermal ellipsoid representation of [IPrH][Pd(η3-cin)Cl2] at 50% probability.

The interaction between the most acidic proton of the imidazolium salt (H1) and both chloride atoms of the palladate counterion was observed. This stabilizing interaction hints at the formation of a strong ion-pair in the solid state, while it also prevents the palladate intermediate from decomposing. Reactions without the addition of base, in order to isolate palladates [IPrH][Pd(η3-allyl)Cl2], [IPr*H][Pd(η3-cin)Cl2] and

[SIPrH][Pd(η3-cin)Cl2], were also carried out. The desired compounds were obtained in almost quantitative yields. The formation of Pd-NHC complexes including the formation of intermediates is illustrated in Scheme 15.
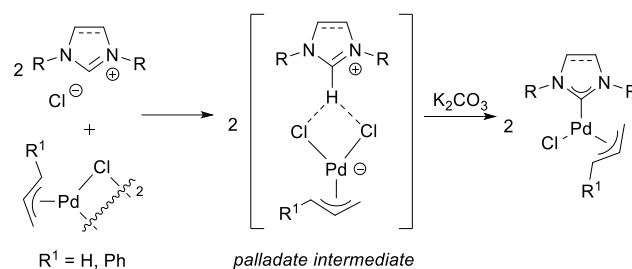
Scheme 15. General synthetic procedure for Pd-NHC complexes, including the formation of intermediate.

It is worth noting that the obtained palladate intermediates are air- and moisture-stable, and these properties render them potentially valuable pre-catalysts. The use of inorganic bases in the Suzuki–Miyaura reaction in the presence of Pd-NHC complexes was previously reported.[75] Zinser et al. investigated the possibility of using potassium carbonate as a multi-functional component in this catalytic reaction. The palladate intermediates [IPrH][Pd(η3-allyl)Cl2], [IPr*H][Pd(η3-cin)Cl2] and [IPrH][Pd(η3-cin)Cl2] were tested as pre-catalysts. The catalytic results were compared with that using well-defined Pd-NHC complexes such as [Pd(IPr)(η3-cin)Cl], [Pd(IPr)(η3-allyl)Cl] and [Pd(IPr*)(η3-cin)Cl]. Two different reaction conditions were tested and palladates were inactive in both cases. The authors suggested that palladates should be converted into neutral Pd-NHC complexes prior to addition of the cross-coupling partners (phenylboronic acid and 4-chloroanisole). To activate the palladates, these were added into the reaction with 1.1 eq. of K2CO3 and then stirred in ethanol at 60° C for 1 hour, after that time, phenylboronic acid and 4-chloroanisole were added and the mixture was stirred without heating for 20 hours. The modification of reaction conditions helped to obtain the desired cross-coupling product in high yield.[73] It is interesting that no reaction was observed while using NHC salts and palladium dimers, for example [Pd(η3-cin)Cl]2. This highlights the importance of using pre-formed, well defined palladates, as this ensures the formation of the desired Pd-NHC complexes under the reaction conditions. When the activation time was changed from 1hour to 30 minutes, lower yields for [IPrH][Pd(η3-allyl)Cl2] and [IPrH][Pd(η3-cin)Cl2] were observed. It was found that the steric bulk of the NHC ligand affects the activation step. [IPrH][Pd(η3-cin)Cl2] was also tested as a pre-catalyst in the Suzuki–Miyaura reaction with various coupling partners, among them were 2-chloropyridine, 2-bromopyrimidine and 2-chloro-6-trifluoromethylpyridine. All the desired compounds were obtained in high yields (85-99%). The applicability of the described palladates was also shown for the Mizoroki‑Heck,[73,74] the Buchwald-Hartwig arylamination and ketone arylation reactions.[76] The scalability of the weak base approach was also showcased. The reaction between IPr·HCl and the Pd source [Pd(η3-cin)(μ-Cl)]2 with K2CO3 was carried out. The desired Pd-

NHC complex was isolated in excellent yield (98%) (Scheme 16).[77]
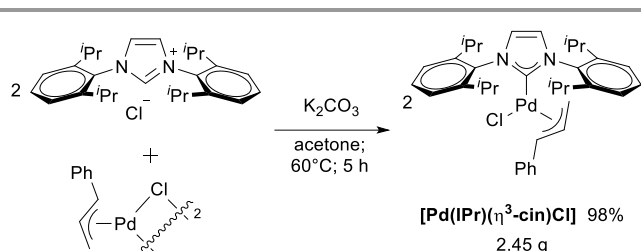
Scheme 16. Large-scale synthesis of [Pd(IPr)(η³-cin)Cl].

Hazari and co-workers investigated the activity of various Pd-NHC complexes in the Suzuki–Miyaura cross-coupling.[78] The obtained data showed the influence of allyl group substitution on the conversion of neutral Pd-NHC complex to Pd(I) allyl dimer. [79,80]
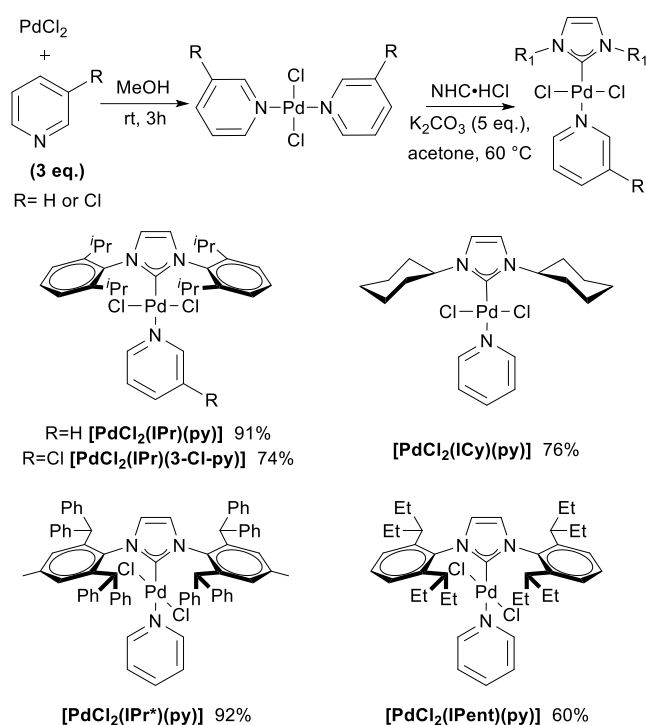
The substitution of the backbone of the NHC ligands provides an opportunity to modify the electronic and steric properties of these ligands and the corresponding NHC-metal complexes and thus affect the catalytic activity.[81–83] The catalytic activity of Pd-NHC complexes, containing IPr^{Cl} and IPr^{Br} ligands has been explored in the Suzuki–Miyaura cross-coupling reaction and compared to that of [Pd(IPr)(η³-cin)Cl].[84] Both palladium compounds, bearing halogen substituents in the C^{4,5} – positions of imidazol-2-ylidene ring were obtained using the weak base route in high yields. (Scheme 17).

X=Cl [Pd(IPr^{Cl})(η³-cin)Cl)] 92%
X=Br [Pd(IPr^{Br})(η³-cin)Cl)] 90%
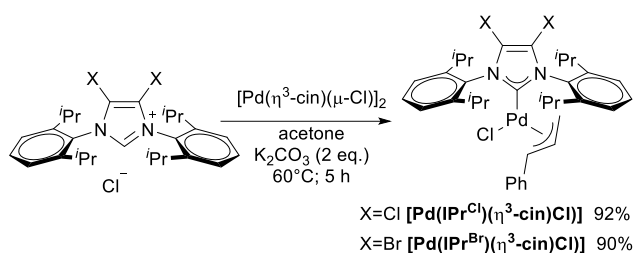
Scheme 17. General synthetic procedure for [Pd(IPr^X)(η³-cin)Cl] complexes using optimized conditions.

In 2006, Organ and co-workers reported the air-stable palladium "PEPPSI" (PEPPSI = pyridine-enhanced precatalyst preparation, stabilisation and initiation) pre-catalysts.[20] The catalytic activity of the described complexes was tested in a large variety of cross-coupling reactions, including the Suzuki–Miyaura, Negishi, and Kumada-Tamao-Corriu reactions as well as in various carbon-heteroatom coupling reactions.[5,85,86] The simple synthetic procedure leading to their isolation by action of a weak base is one of the most significant advantages of these complexes. Using potassium carbonate, various NHC salts, PdCl$_2$ and pyridine (or its derivatives), the desired PEPPSI complexes were obtained in high yields. Pyridine is used both as a solvent, and as a ligand in this procedure, so a large excess of pyridine is required. Of note, the use of high temperatures (80 °C) also proves essential.

While attempting to understand the mechanism of formation at play in Organ's synthetic procedure, Nolan and co-workers made use of the weak base route to obtain PEPPSI-type

R=H [PdCl$_2$(IPr)(py)] 91%
R=Cl [PdCl$_2$(IPr)(3-Cl-py)] 74%

[PdCl$_2$(ICy)(py)] 76%

[PdCl$_2$(IPr*)(py)] 92%

[PdCl$_2$(IPent)(py)] 60%

Scheme 18. General synthetic procedure for PEPPSI-type compounds.

compounds. In a simpler and more environmentally acceptable approach, only 3 eq. of pyridine were used, high temperature was not essential, and acetone was used as a solvent.[87] The modified procedure was tested on various NHC ligands (IPr, IPr*,ICy, IPent), and all the desired compounds were obtained in good to high yields (Scheme 18). Two intermediates were isolated and investigated, which shed light on the mechanism of the reaction and confirmed that 3 eq. of pyridine are enough to obtain the desired Pd-PEPPSI complexes.

As a continuation of the previous work regarding the development of general and robust synthetic methodologies towards transition metal-NHC complexes, Nolan and co-workers performed the first systematic study in the case of platinum.[88] This provided a new method for accessing a variety of well-defined Pt-NHC complexes that are active in the hydrosilylation of alkenes and alkynes, a field in which Pt-NHC complexes hold a prominent position.[89,90]

Despite the existence of sporadic reports mentioning the use of a weak base in order to generate Pt-NHC complexes, this proves to be the first general and in-depth investigation (Scheme 19) of such a route in platinum systems.[91–93] The development of the new methodology was enabled by the use of the platinum source [Pt(DMS)$_2$Cl$_2$] in the presence of an imidazolium salt and potassium carbonate in acetone, which was a system that had proven successful in past studies focusing on gold, copper and palladium. IPr·HCl was used in order to obtain proof of concept and optimize the reaction conditions. It was found that ethyl acetate is also a suitable, green solvent in which this reaction can be carried out. A profound effect of the base amount on the rate of the reaction was also found, while the carbonate base proved to be far more efficient than triethylamine in the case of
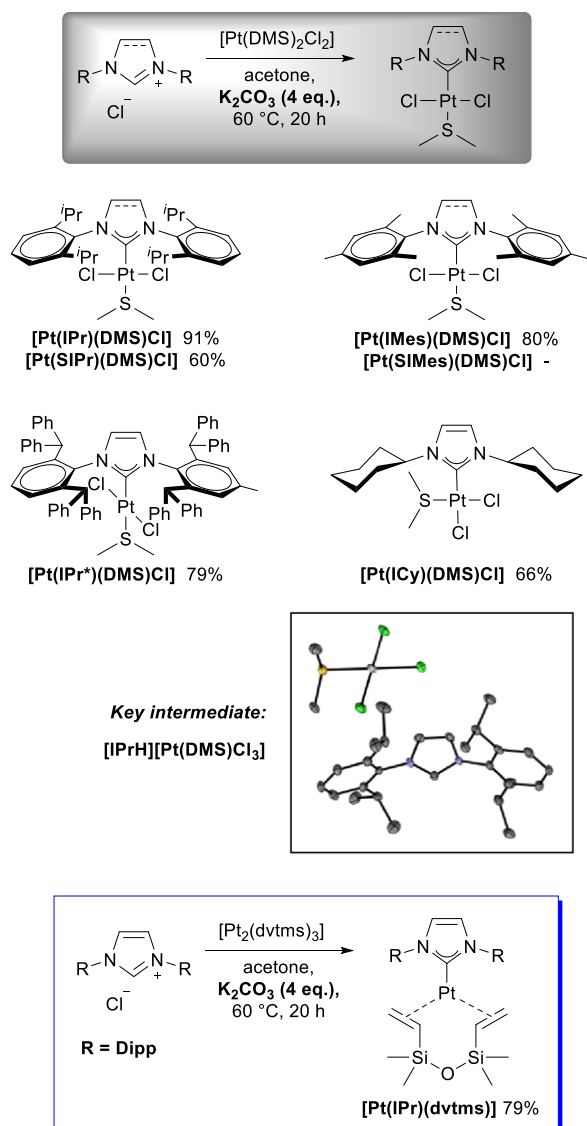
Scheme 19. General synthetic procedure for Pt-NHC complexes using optimized conditions.

platinum. The protocol was applied for a variety of imidazol(in)ium salts and led to satisfactory yields for the new complexes (Scheme 19). Structural investigation of the complexes revealed that only in [Pt(ICy)(DMS)Cl₂], which bears the least sterically demanding NHC, the chloride anions are mutually cis. Limitations of the protocol were also encountered, as PEPPSI-type and DMSO-coordinated platinum complexes could not be obtained under these conditions when suitable platinum sources were used. Furthermore, SIMes·HCl and IAd·HCl did not react under the operational conditions.

Importantly, when the reaction was carried out in the absence of base with IPr·HCl, an imidazolium platinate was observed and isolated as a key intermediate (Scheme 19).[88] Its molecular structure was unequivocally determined by single crystal X-ray diffraction analysis, and it is reminiscent of the aurate, cuprate and palladate salts reported previously. In the presence of a base, this intermediate is transformed into the desired Pt-NHC complex. Finally, the versatility of the weak base approach was

demonstrated, when a Pt(0)-NHC complex was synthesized in 79% yield, using the standard conditions and Karstedt's catalyst as the platinum source (Scheme 19).

The application of the weak base route to the synthesis of Rhodium and Iridium-NHC complexes

The catalytic applications of Rh and Ir-NHC complexes were widely explored. These compounds proved to be efficient catalysts in numerous reactions, such as in the borylation of arenes, the hydrogenation of ketones, imines and olefins, the isomerization of allylic alcohols to ketones and the hydrosilylation of ketones.[94–99] An important application of [M(NHC)(CO)₂Cl] complexes (M=Rh or Ir) is for the measurement of the Tolman Electronic Parameter (TEP) for novel ligands.[83,100,101] The use of these compounds for that purpose is a good alternative to previously used [Ni(NHC)(CO)₃] complexes.

Early examples of using a mild base (NaOAc) to obtain Rh and Ir-NHC complexes were explored by Crabtree and Peris.[18,19] In this manner, a series of bidentate NHC compounds were obtained, containing various NHC ligands. The influence of steric properties of NHC ligands was demonstrated. On the example of bulky ᵗBu substituents, using the same reaction conditions, the possibility of isolating only one NHC complex [Ir(COD)(NHC)I] (cod = 1,5-cyclooctadiene) was shown (Scheme 20). The addition of various bases (K₂CO₃, NaOAc, KOtBu) or prolongation of the reaction time did not lead to formation of the chelated bis-NHC complex.[18] The described procedures require refluxing for 16 hours in acetonitrile, the addition of 4 eq. of NaOAc and purification by column chromatography. The desired complexes were isolated in moderate to good yields, and the obtained compounds are air- and moisture-stable (Scheme 20).
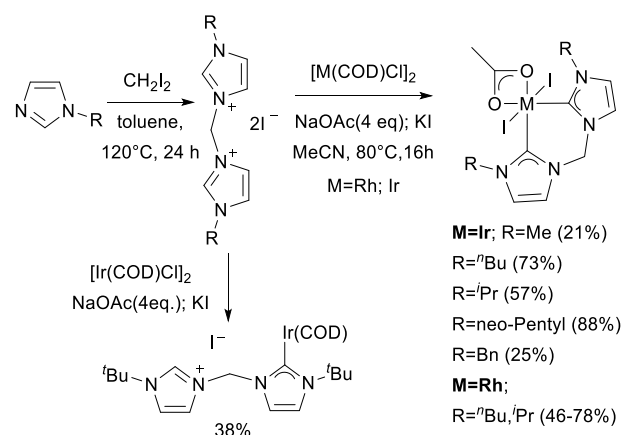
Scheme 20. General synthetic procedure for the synthesis of bidentate Rh and Ir-NHC complexes.

Inspired by the work of Gimeno, the group of Plenio investigated the use of a simple and user-friendly procedure for the synthesis of [M(NHC)(COD)Cl] and [M(NHC)(CO)₂Cl] (M=Rh or Ir) complexes.[102] The procedure involves the use of potassium carbonate as a base and acetone or DCM as a

solvent. Various NHC precursor salts, bearing both saturated and unsaturated backbones, were examined in the reaction with [Rh(COD)Cl]$_2$ as the metal source in the presence of K$_2$CO$_3$ in acetone. All the desired complexes were isolated in high yields (Scheme 21). It is worth mentioning that more than 90 % of conversion was observed for the described compounds, but lower isolated yields were obtained in some cases. Then experiments with [Ir(COD)Cl]$_2$ as a metal source under the same reaction conditions were also carried out and lead to Ir-NHC complexes containing unsaturated ligands in high yields. Here, for saturated NHCs, the base amount was found to be the most important parameter. In those cases, 1.2 eq of K$_2$CO$_3$ were required in comparison to 3 eq. for Rh-NHC compounds. Various NHC·HX (X=Cl, I) salts were also tested. The formation of only one complex [M(NHC)(COD)X], containing either Cl or I, depending on the counterion of the corresponding imidazolium salt was observed (Scheme 21).
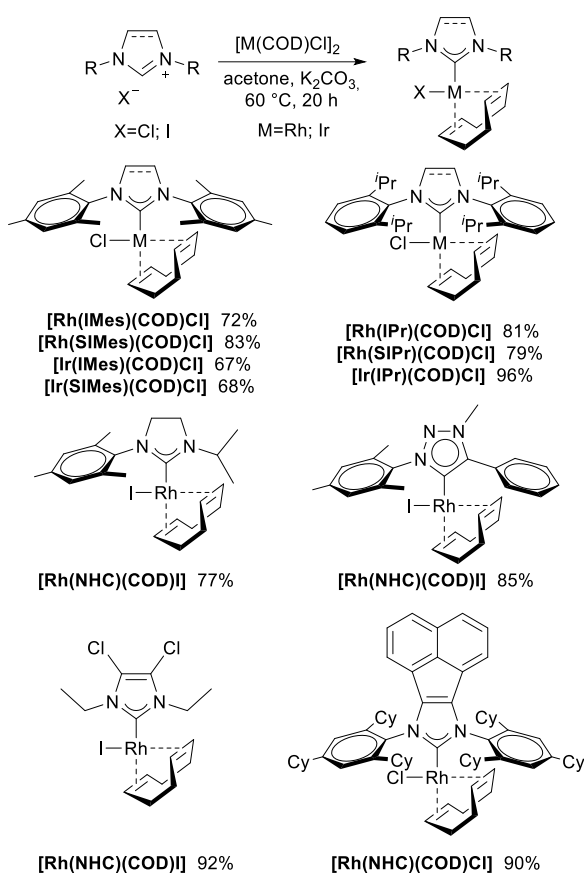

Scheme 21. General synthetic procedure for the synthesis of [M(NHC)(COD)Cl] (M=Rh or Ir) complexes.

According to mechanistic investigations performed with SIMes·HCl and K$_2$CO$_3$ in the absence of a metal source, formamides were formed. These compounds are known to be the hydrolyzed products from free NHC ligands.[103] Despite this fact, the authors insisted that the formation of the free carbene during weak base route can be excluded as they decompose in acetone. Next, the reaction with [Rh(COD)Cl]$_2$ and potassium carbonate was carried out and it was established that the spectra of the obtained product was the same as the hydroxo

complex [Rh(COD)(OH)]$_2$. The authors assumed that a hydroxo complex is formed in the first step, which reacts with an NHC precursor leading to the formation of the desired M-NHC complexes.

Plenio and co-workers also studied the possibility of obtaining [M(NHC)(CO)$_2$Cl] complexes directly from [M(COD)Cl]$_2$ and CO.[102]
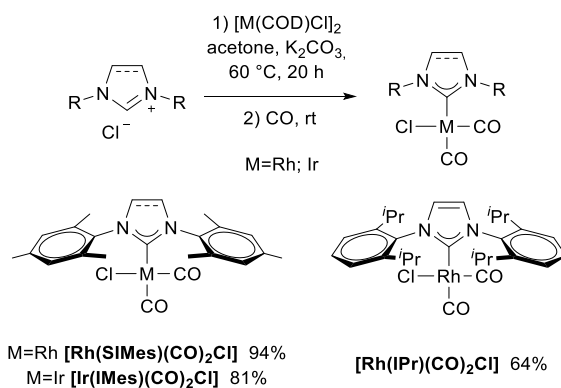
Scheme 22. One-pot procedure for [M(NHC)(CO)$_2$Cl] complexes.

The desired compounds were obtained in good to high yields (Scheme 22). The authors underlined that isolated yields in the case of complexes bearing CO were higher compared to those of compounds bearing COD ligands, because of the lower solubility of the former. Lower solubility in non-polar solvents resulted in minimized product loss during purification. A one-step, simple route to Rh systems enabling the TEP determination for the NHC ligand is highly desirable.

The application of the weak base route to the synthesis of Ruthenium-NHC complexes

Ru-NHC complexes have been widely explored during the last decade, due to their high catalytic activity in a number of reactions, such as hydrogenation, alkene metathesis and amidation. [104,105] Simplification of the synthetic access to well-defined Ru-NHC complexes is an important goal and has been sought after in sporadic reports, particularly through the application of the weak base route.[106]

Özdemir and co-workers reported the synthesis of a series of [Ru(NHC)Cl$_2$] and [Ru(NHC)(p-cymene)Cl$_2$] complexes using caesium carbonate as a base, in toluene.[107,108] Ru-NHC complexes with bulky substituents were obtained in good to high yields (Scheme 23). Of note, the described procedure required a high temperature and a toxic solvent.

In 2004 Peris and co-workers reported the synthesis of Ru(II)-p-cymene complexes with mono- and bidentate ligands with the use of NEt$_3$ as a base.[109] The authors underlined that the use of NaOAc and Na$_2$CO$_3$ gave mixtures of products, which were difficult to identify. The formation of mono- or biscarbene complexes was found to be dependent on the steric bulk of the azolium precursor, as in the case of the larger neo-pentyl ligand only the monocarbene complex was formed. All the compounds were obtained in low yields and the reactions were carried out
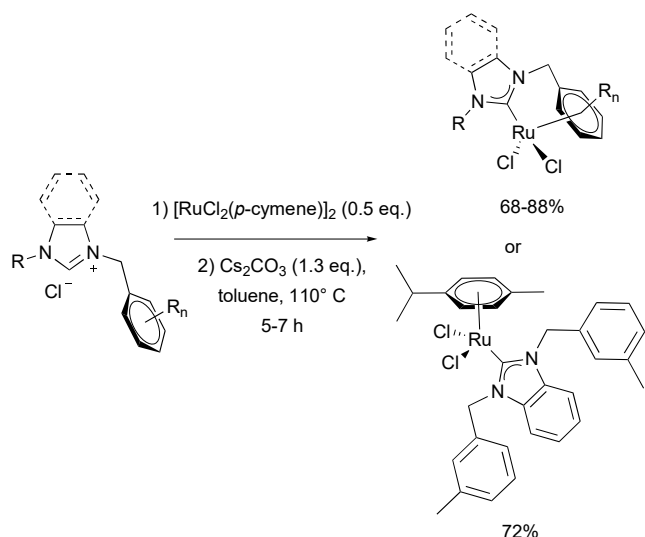
Scheme 23. General synthetic procedure for the synthesis of [Ru(NHC)Cl$_2$] and [Ru(NHC)(p-cymene)Cl$_2$] complexes

under an inert atmosphere (Scheme 24).

In some recent reports, synthetic routes to Ru(II)-p-cymene complexes containing various NHCs, through the use of a weak base, namely Cs$_2$CO$_3$, were discussed (Scheme 25).[110,111] The yields for the obtained Ru-NHC complexes range from low to good. It is worth noting that in these works, inert atmosphere and/or toxic solvents (THF) were required. Also, Cs$_2$CO$_3$ is more significantly more expensive than K$_2$CO$_3$, an important factor for large scale synthesis.
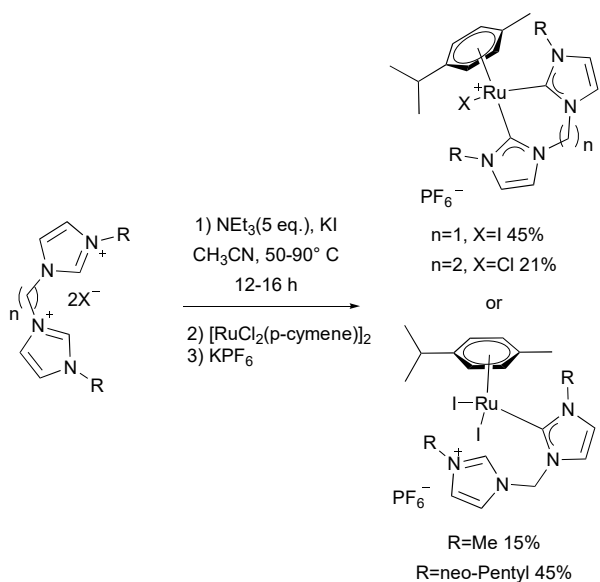
Scheme 24. General synthetic procedure for the synthesis of Ru-arene-monocarbene and biscarbene complexes.

In 2019, the research groups of Verpoort and Chen reported a simple synthetic pathway to the highly efficient in dehydrogenative amidation of alcohols Ru-NHC catalysts.[112,113] In this work,[112] the authors used in situ generated Ru species in amide and amine synthesis. They also tested various bases for

these catalytic reactions such as, K$_2$CO$_3$, KOAc, KO^{t}Bu and NaH, but only Cs$_2$CO$_3$ led to high yields of desired products and was
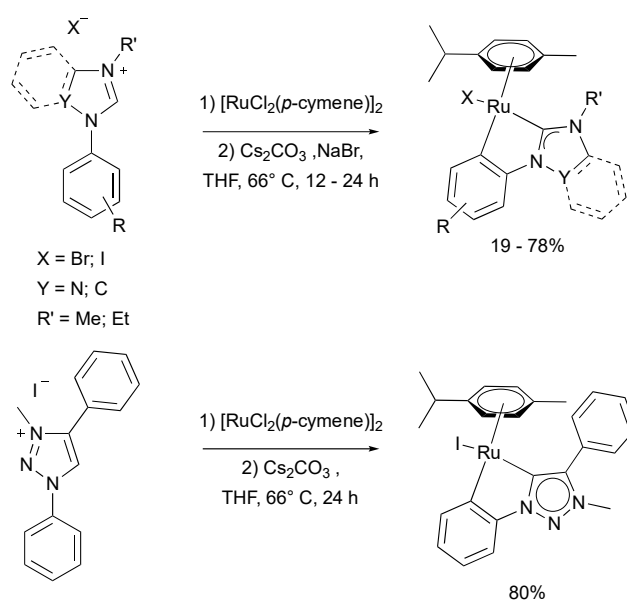
Scheme 25. General synthetic procedure for the synthesis of Ru-NHC- complexes.

effective for the selective amide formation. With these results in mind, the authors tried to isolate and characterize Ru species, which were formed during the catalysis. They described the synthesis of these Ru-NHC complexes from various NHC salts and [Ru(p-cymene)Cl$_2$]$_2$ in the presence of Cs$_2$CO$_3$ in toluene and under inert atmosphere. Of note, in both cases column chromatography was used for the purification of the desired complexes and yields of the isolated compounds were low (22% and 29% respectively, Figure 3). Moreover, these groups reported other Ru-NHC complexes, which were obtained with the use of the described weak base route. The desired Ru-NHC
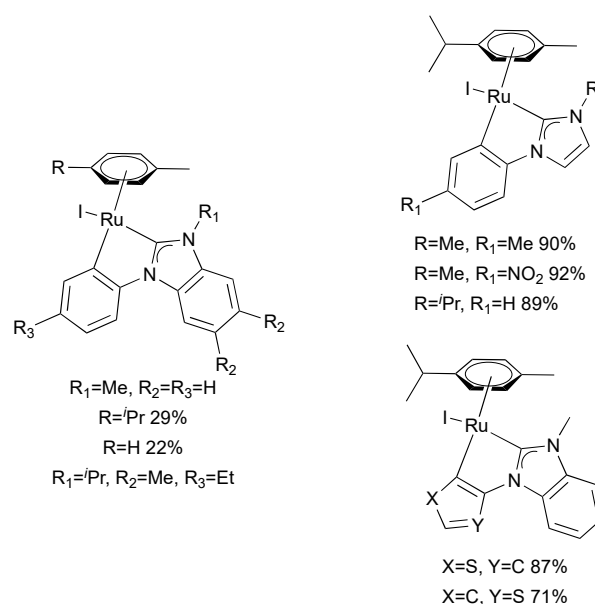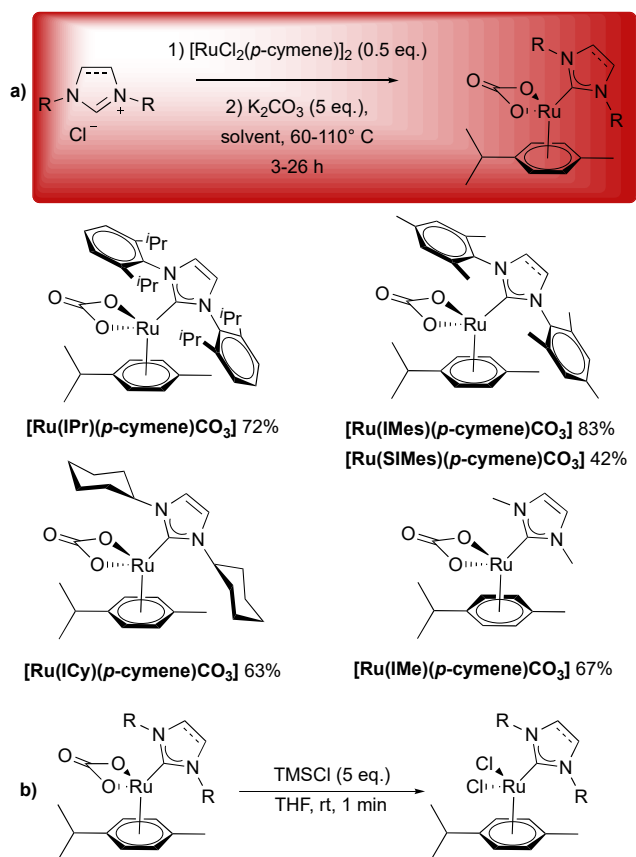

Figure 3. Scope of Ru-NHC complexes via weak base route with the use of Cs$_2$CO$_3$ as a base.

complexes were obtained in good to excellent yields (Figure 3)[113].

Recently, Ma et al. investigated the previously described weak base route with NHC precursor salts and [RuCl$_2$(p-cymene)]$_2$ in the presence of K$_2$CO$_3$ in acetone to obtain [Ru(NHC)(p-cymene)Cl$_2$] complexes, but this reaction led to the formation of [Ru(NHC)(p-cymene)CO$_3$] complexes instead through anion metathesis.[114] The weak base route was tested with various NHCs, both saturated and unsaturated, and proved to be highly efficient for the synthesis of the carbonato-Ru complexes (Scheme 26a). The authors also reported an easy way to convert [Ru(NHC)(p-cymene)CO$_3$] complexes into [Ru(NHC)(p-cymene)Cl$_2$] complexes, using TMSCl. After 1 minute, 100% conversion was observed and the desired compounds were isolated in high yields (74-84%) (Scheme 26b). It was demonstrated that these procedures can be carried out in one pot, thus simplifying the synthesis of [Ru(NHC)(p-cymene)Cl$_2$] complexes.

[Ru(IPr)(p-cymene)CO$_3$] 72%

[Ru(IMes)(p-cymene)CO$_3$] 83%
[Ru(SIMes)(p-cymene)CO$_3$] 42%

[Ru(ICy)(p-cymene)CO$_3$] 63%

[Ru(IMe)(p-cymene)CO$_3$] 67%

Scheme 26. ^{a} General synthetic procedure for the synthesis of [Ru(NHC)(p-cymene)CO$_3$] complexes via the weak base route. ^{b} General synthetic procedure for the synthesis of [Ru(NHC)(p-cymene)Cl$_2$] complexes.

Mechanistic investigations of the weak base route

The versatility of the weak base route has been shown for various metals, but the mechanism of the metallation is still unclear. Despite the fact that experimental results and thermodynamic values (pK$_a$) clearly show that free carbene

formation is unlikely when weak bases (K$_2$CO$_3$ or NEt$_3$) are used, its formation should not be completely excluded.[115] Perhaps a more practical and relevant approach than simply debating whether free carbene formation is feasible, would be to investigate the events that may occur in the presence of metal sources or other substrates in the reaction. Such studies would be more closely aligned with real reaction systems in both organocatalysis and M-NHC complex synthesis, providing a valuable perspective. The first report examining such systems concerned the role of azolium salts and weak bases in organocatalysis, and hypothesized/demonstrated that a concerted mechanism in which the base, the imidazolium salt and the substrate react simultaneously, is much more favourable than a stepwise free carbene generation and subsequent reaction with the substrate.[116] A similar, concerted mechanism was proposed in the case of a study concerning deuterium exchange of azolium salts, in which there is no free carbene intermediate.[117] A more recent study for the case of organocatalysis, further supported the concerted mechanism, in which the azolium salt interacts directly with the substrate without the involvement of a free carbene.[118] Importantly, the study showed that the exact conditions of the system, including the solvent used, may determine whether or not the path involving a free carbene is favourable.
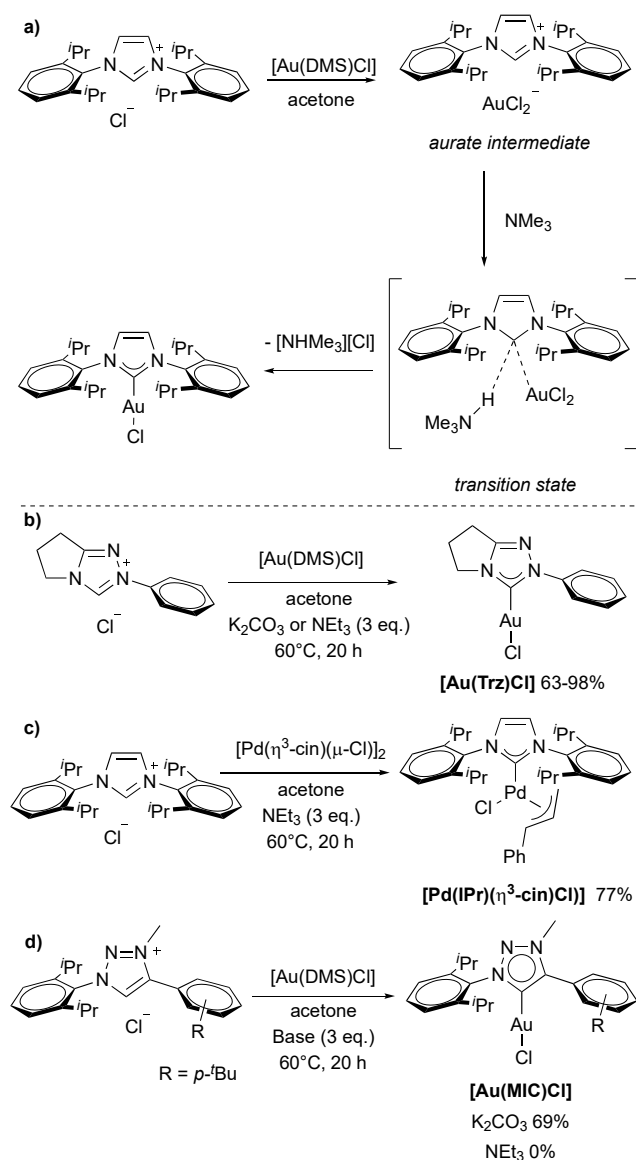
During the development of the weak base methodology for Au, Cu and Pd, observation and isolation of the metallate intermediates were common features. Later on, the same type of intermediate was isolated in the case of Pt. We reported mechanistic investigations on the role of the weak base in transition metal-NHC complex synthesis, using the metallate intermediate as a starting point.[119] In the beginning, the counterion in the aurate intermediate was suspected to be essential for the removal of the azolium proton while using a weak base, because of a decrease of the pK$_a$. However, further investigations revealed that pK$_a$ values were the same for both IPr·HCl and the corresponding aurate intermediate.[120] Based on the results, the authors discounted an azolium deprotonation step from the transformation.

Another pathway of the reaction was tested with the aid of DFT. It included the simultaneous creation and scission of bonds in contrast to the previously discussed route, which consisted of deprotonation and subsequent metallation. For these investigations IPr·HCl and [Au(DMS)Cl] were chosen in the presence of NMe$_3$ as the base. The formation of the aurate intermediate was confirmed and shown to be energetically favourable. It is worth noting that the energy barrier when going from the metallate intermediate to the transition state depends on steric factors both for the base and NHC ligand. The transition state is followed by the dissociation of a chloride ion and formation of the ammonium salt [Me$_3$NH]$^+$[Cl]$^-$ which leads to the formation of the desired [Au(IPr)Cl] complex (Scheme 27a). Another pathway which includes deprotonation of IPr·HCl leads to a species which is higher in energy in comparison to the reactants and that is why a two-step route is not appropriate for the described process.

To address the influence of ligand structures on the energy barrier, the percent buried volume, %V$_{Bur}$, as steric descriptor

and the snapping energy of the NHC-H bond were calculated for various ligands. The results showed that the energy barrier

Scheme 27. Synthetic pathway for [Au(IPr)Cl] using DFT calculations and experimental results with NEt$_3$.

increases while using bulkier ligands (for IPr ligand $\Delta G^{\neq}_{Tr.s.}$= 28.2 kcal mol^{-1}, for IMes ligand $\Delta G^{\neq}_{Tr.s.}$= 24.9 kcal mol^{-1}). In addition, correlation between the strength of the NHC-H bond and energy barrier was found. TPT-Me (1,3,5-trimethyl-1,3,4-triazol-2-ylidene) (%V$_{Bur}$ = 24.0) involved an energy barrier of 18.9 kcal mol^{-1} and IMe (%V$_{Bur}$ = 25.8) - 25.6 kcal mol^{-1}. These differences in energy barrier values can be explained with weaker NHC-H bond, therefore the energy is lower for TPT-Me in comparison to IMe.

In order to establish whether the computational model had predictive value, reactions with a 1,2,4-triazolium salt and [Au(DMS)Cl] in the presence of both triethylamine (which closely resembles trimethylamine) and potassium carbonate were performed. The desired [Au(Trz)Cl] complex was efficiently obtained in all cases, while the yields were

substantially higher when the corresponding aurate was subjected to the reaction conditions (Scheme 27b). These results confirmed the computationally predicted ease with which the triazolium salt should react under the conditions of the weak base approach. In order to probe the generality of the triethylamine-assisted protocol, the synthesis of a palladium-allyl-type NHC complex was attempted. Remarkably, the dimer-cleaving approach led to the desired complex in 77% yield without modification of the conditions (Scheme 27c). Furthermore, to test the limits of this protocol, the reaction between a mesoionic carbene (MIC) precursor and [Au(DMS)Cl] was carried out in the presence of both weak bases. The computational model predicted that this metalation should not be favoured, and indeed the reaction was unsuccesful with triethylamine. However, potassium carbonate was able to facilitate this transformation, highlighting the importance of the identity of the weak base (Scheme 27d). The precise reasons behind the superiority of the carbonate base still remain unclear, although it is now evident that the pK$_a$ of the base has little effect on the energy barrier of the reaction, as was demonstrated in a later work on the use of NaOAc for the synthesis of Au-NHC complexes.[121] In fact, NaOAc led to a lower energy barrier than trimethylamine, despite having a significantly lower pK$_a$. The results suggest that although triethylamine is competent enough for some cases, in a synthetic scenario, the inorganic bases would be more reliable and robust. Lastly, the weak base approach was used to synthesize thiourea and selenourea derivatives of NHCs. This is possible with both triethylamine and potassium carbonate as demonstrated recently by Nahra and co-workers.[122]

Application of weak base route in mechanochemistry

In the context of the greener nature of the weak base approach, Cazin and co-workers have recently disclosed a solid state, solvent-free mechanochemical protocol that enables the access to complexes of the type [Cu(NHC)Cl] which drastically reduces reaction times and solvent use (Scheme 28).[123]

By means of an automated device (namely, a planetary ball mill) and by leveraging on previously unreported reactivity of the NHC salt precursor, the Cazin group was able to assemble seven different complexes (including **[Cu(MIC)Cl]**) in good to excellent yields and in short reaction times (only 1.5 hours). Under these conditions, solvent usage is limited to workup phase (simple filtration over a SiO$_2$ plug) and to acetone (a solvent listed among the "preferred" ones in many solvent selection guides - Pfizer, GSK, Sanofi, etc.). As in the solution-based chemistry, the reaction proceeds through the formation of a *cuprate* species, which is subsequently converted to the desired metal complexes upon addition of an excess of K$_2$CO$_3$ (3 eq.). No particular trend was observed regarding the steric properties of the employed NHC precursors, as opposed to the solution-based variant where long reaction times are observed for more encumbered NHC salts.[36]

Principles of scalability of the protocol were also provided:

mixing of 5 g of IPr·HCl, in the presence of CuCl (1 eq.) and K₂CO₃ (3 eq.), delivered 4.3 g of [Cu(IPr)Cl] (75% yield) in only 10 min:
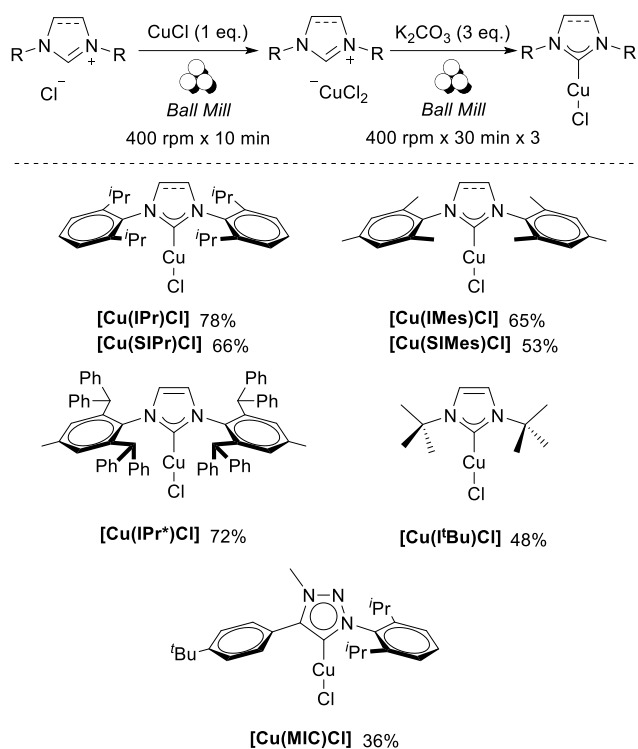
Scheme 28. Mechanochemical synthesis of [Cu(NHC)Cl] complexes.

this further reduction of reaction time was attributed to an increase in temperature inside the reaction ball-mill vessel, observed to concomitant increase with the number of milling bodies (which in turn increases the frequency of collisions during the milling process and therefore the energy transferred to the reactor).

Concomitantly to this early communication, Udvardy, Czégeéni & co-workers published a report reporting the mechanochemical synthesis of a small number of methylene bridged dinuclear rhodium(I)-NHC complexes of the type [{RhCl(COD)}₂(μ-di-NHC)] using K₂CO₃ as operational base (Scheme 29).[124] Again, as for the case of Cu(I)-complexes, the
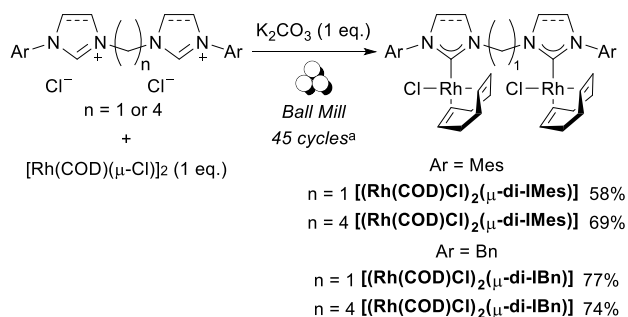

ᵃ 1 Cycle = milling for 2 min at 550 rpm, followed by 2 min resting

Scheme 29. Mechanochemical synthesis of [{RhCl(COD)}₂(μ-di-NHC)] complexes.

main features of such an approach were the short reaction times and the (partial) exclusion of solvents (only for the workup), thus eliminating the need of heating flammable acetone or toluene for prolonged periods of time.[102,124]

In light of these early reports, Cazin and co-workers further expanded on the repertoire of metal-NHC complexes assembled using K₂CO₃ route under mechanochemical conditions, publishing an account in which general conditions for the assembly of different NHC-containing metal complexes are reported.[125] The synthetic approach adopted is simple and straightforward and consists of mixing the NHC salt together with the metal salt precursor of interest in the presence of an excess amount of the base.
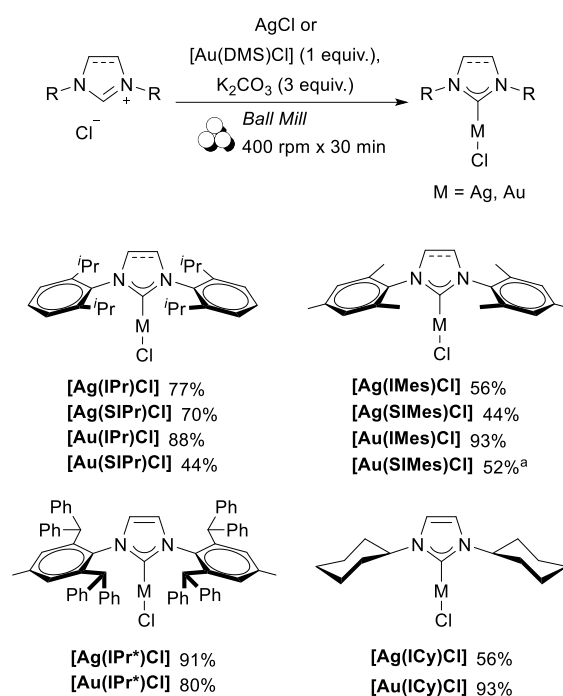
Scheme 30. Mechanochemical synthesis of [Ag(NHC)Cl] and [Au(NHC)Cl] complexes. ᵃK₂CO₃ (6 eq.).

Using this approach, the Cazin group was able to complete the series of coinage metals describing the assembly of complexes of the type [M(NHC)Cl], with M = Ag(I), Au(I), by simple interchanging of the metal precursor (Scheme 30). Again, the most striking feature of such approach is that 30 min were sufficient to deliver these complexes in good to excellent yields, while limiting the use of (green) solvents (acetone and *n*-heptane) to the workup phase (thus, enhancing the E-factor for the overall process). Again, no particular trend is observed correlating the steric of the NHC salt precursors and the reaction time (trend that is observed in solution, as for the assembly of the [Au(X)NHC] complexes, with X= Cl, Br, I, reported by Nolan and co-workers).[24] Of note, the synthesis of the complex [Au(Cl)SIMes] could only be accomplished in 52% yield only when 6 equiv. of the K₂CO₃ base were used: the addition of 3 equiv. of K₂CO₃ invariably led to the formation of the corresponding *aurate* intermediate [IMes·H][AuCl₂].

The conditions reported were shown to be suitable also for the assembly of Pd(II)-complexes (Scheme 31). Simple exchange of
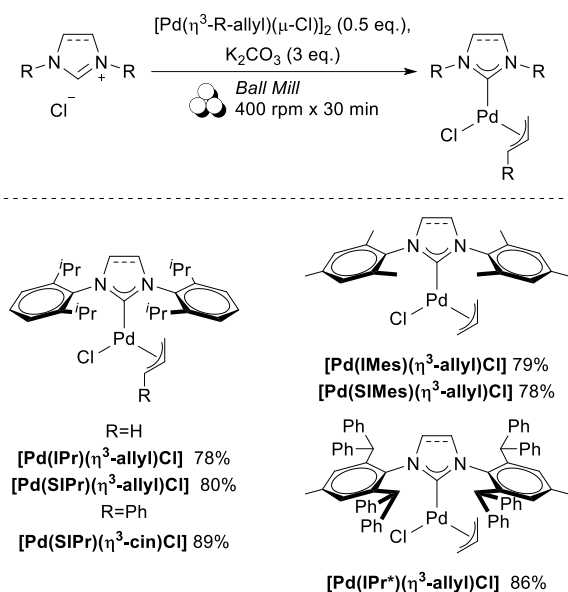
Scheme 31. Mechanochemical synthesis of [Pd(NHC) (η^3-R-allyl)Cl] complexes.

the metal precursors to [Pd(η^3-allyl)(μ-Cl)]$_2$ and [Pd(η^3-cin)(μ-Cl)]$_2$, was sufficient in delivering the complexes of the general formula [Pd(η^3-R-allyl)(Cl)(NHC)], in good to excellent yields, again, after only 30 min. As for the synthesis of Cu(I) and Au(I) complexes, the formation of these complexes involves the formation of a *palladate* intermediates, which have already been shown to be accessible by Nolan and Cazin, in the solid state by simple griding of 0.5 equiv. of the dimeric Pd(II) precursor to the NHC·HCl salt using mortar and pestle.[76] Again,
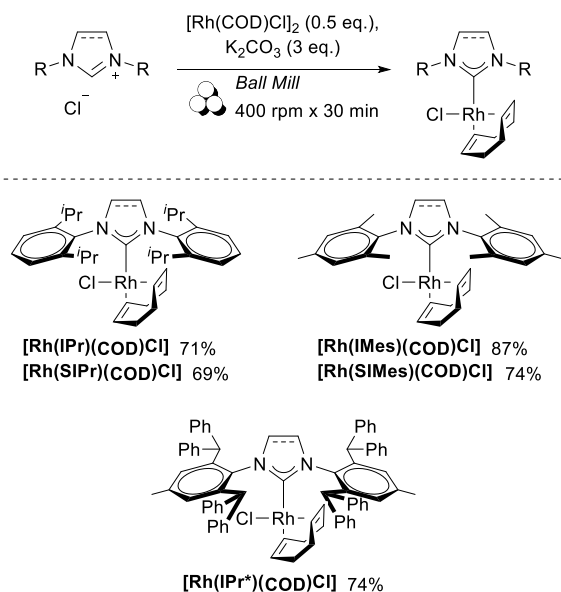
Scheme 32. Mechanochemical synthesis of [Rh(cod)(Cl)(NHC)] complexes.

under mechanochemical conditions, no particular trends were observed with respect to the bulkiness of the NHC·HCl salt or the allyl moiety (allyl or cinnamyl). Also in this case, proofs of

scalability of the methodology were accomplished: 5.0 g of IPr·HCl were easily converted into 5.1 g (77% yield) of [Pd(η^3-allyl)(Cl)IPr]. In the same report, Cazin and co-workers also successfully translated the protocol developed by Plenio and co-workers[102] for the synthesis of [Rh(NHC)(COD)Cl] complexes into a mechanochemical version (Scheme 32). This was, again, accomplished by simple interchanging of the metal salt precursor to [Rh(COD)Cl]$_2$.

From the viewpoint of green chemistry, this development (the previously unreported reactivity of the NHC precursors in the solid state and the use of mechanical forces to enable the assembly of NHC-metal complexes) is of great interest as this approach drastically reduces energy costs as well as waste production, by eliminating the need for heating highly flammable (although green) solvents and limiting their use in workups.

Conclusions and Outlook

This feature article provides an overview of a simple and efficient route to the synthesis of various NHC-metal complexes, using a weak base. All advantages of this approach were fully described and illustrated with many specific examples. The versatility of this route was also shown to occur under mechanochemical conditions. The mechanistic aspects of the described process are also described. We strongly believe this simple procedure can be successfully deployed as a method of choice to access a large variety of metal-NHC complexes and non-metal-NHC adducts. Given our continuous interest in the synthesis of well-defined M-NHC complexes and their use in organometallic synthesis and catalysis, we will pursue further advancements regarding the use of the weak base route in the near future. The contribution of our research groups, in addition to those of many others, has thus far highlighted the practicality and generality of this approach. As a result, we expect to encounter its use more frequently in the future, as it certainly renders the synthesis of various, highly useful M-NHC complexes a facile, routine operation. Moreover, the detailed reports in the literature which now cover most catalytically relevant transition metals, in combination with critical analysis provided in recent reviews,[4,126] including the present one, are expected to provide a strong foundation for organometallic chemistry practitioners and researchers practicing M-NHC catalysis. A specific aspect of the weak base approach which has been emphasized by our groups is scalability. This aspect is highly important in our view, especially since it is a prerequisite for industrial applications, and has been demonstrated recently through the disclosure of detailed protocols for multigram scale (up to 200 grams) syntheses of Au-NHC complexes.[127] Of course, the various routes towards M-NHCs display complementarity in many cases and none should be disregarded, however the weak base route is the simplest and most user-friendly route so far, in addition to being superior in some cases, with the synthesis of [Au(IMes)Cl] being one example.[127]

Keeping the recent advancements in mind, there are still challenges ahead on various frontiers of M-NHC synthesis. Currently, the weak base route is mainly applied for

imidazol(in)ium salts as carbene precursors with few exceptions which can be found in the present review.[102,112,113,119] Therefore, this route has to be extended towards other types of azolium salts, leading to the generation of metal-carbene complexes.[128] Additionally, other types of metal-NHC complexes can be targeted for each metal, with Pd being a case which may act as an example. In many cases, the scope limitations of the weak base route need to be investigated and overcome if possible, for example in the case of Pt-NHC complexes. Finally, the mechanistic aspects of this facile metalation have begun to emerge, however many questions remain unanswered, particularly regarding the superiority of carbonate bases over NEt_3 and the details concerning the mechanistic pathways and intermediates in the case of each transition metal.[119]

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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