Continuous Flow Synthesis of Metal-NHC (NHC = *N*-heterocyclic carbene) Complexes

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Abstract: *The use of weak bases and mild conditions is currently the most sustainable and attractive synthetic approach for the preparation of Late-Transition metal complexes, some of which are widely used in catalysis, medicinal chemistry and material sciences.*

Herein, we report the use of cuprate, aurate or palladate species for a continuous flow preparation of Cu(I), Au(I) and Pd(II)-NHC complexes. All reactions examined proceed under extremely mild conditions and make use of technical grade acetone as solvent. The scalability of the process was exemplified in a multigram-scale synthesis of [Cu(IPr)Cl].

N-heterocyclic carbenes (NHCs) have become a most popular ligand family for the synthesis of organometallic compounds with uses in catalysis.[1] The surprising stability of the metal-NHC bond has also permitted the study and use of transition metal-NHC complexes in medicinal chemistry[2] and most recently in material science.[3] The nowadays ubiquitous use of this fascinating class of ligands has been a driving force encouraging the development of sustainable, efficient and user-friendly routes leading to their syntheses.[4]

Although not quite sustainable, the most commonly used synthetic strategy, based on the seminal work of Arduengo,[5] involves the generation of free NHC by deprotonation of the corresponding azolium salt with a strong base (e.g. NaH, KO^tBu) and subsequent coordination to a metal. The most significant drawbacks of the free carbene route lies in the need for strictly anhydrous conditions. Additionally, this route is not suitable for complexes requiring the use of metal precursors sensitive to strong bases.

A synthetic alternative protocol which has been widely used involves the synthesis of Ag(I)- or Cu(I)-NHC species and the subsequent transfer of the carbene ligand to a different metal. This process is known as the *transmetallation route*. The silver and copper carbene complexes used in the transmetallation process are generally prepared, according to the protocols published by Lin and Cazin, in a reaction between the azolium salt and Ag_2O or Cu_2O.[6] The latter act both as bases and as coordinating centers. The use of basic metal precursors such as Ag_2O, Cu_2O or $Pd(OAc)_2$ is known as the *built-in base route*.

Both the transmetallation and the built-in base routes have as their main disadvantage a low atom economy and, considering the transmetallation, the use of Ag(I) species which are notoriously light-sensitive, also represents a resource depleting factor. In order to overcome the limitations highlighted by the three synthetic routes described above, the last decade has seen the development of what we now commonly call the *weak-base route*.[4] This approach involves the use of weak and inexpensive bases such as K_2CO_3, NaOAc or NEt_3, the starting azolium salt and a metal precursor of interest. The main benefits of this synthetic strategy lie in the possibility of carrying out the reactions under air, in a single step, with high atom efficiency and using technical grade, green solvents (e.g. acetone, ethyl acetate or ethanol) at mild temperatures (25-60°C). As we recently disclosed, the key to obtaining NHC complexes with some transition metals is the rapid formation of *-ate* intermediate species that slowly evolves into the final products through a Concerted-Metallation-Deprotonation (CMD)-like mechanism involving the weak base where the free NHC is not generated.[7] The weak-base route represents an attractive alternative to the classical synthetic methods for the preparation of metal-NHC complexes, we hypothesised that an even more sustainable approach could be devised.

A decidedly appealing option, that has yet to be examined for the chemistry discussed here, would be to explore translation of the batch reactions currently performed and move to a continuous flow process. Continuous-flow systems are extensively employed in petrochemical and bulk chemical industries since they allow a safer and automated execution of single- or multi-step processes with high control over the various reaction parameters (e.g. residence time, temperature and pressure) with a significant saving in terms of money, time and space.[8] It is important to remember that this type of technology provides efficient mass and heat transfer rates and allows for the use of small volumes of reagents and in turn enables easy and safe handling of hazardous reagents.[9]

The simultaneous reagent production and consumption enables scale-up without increasing the maximum reagent accumulation. Moreover, it is possible to continuously monitor, unlike batch reactions, the quality of the product and, by virtue of the efficient mixing and accurate control of reaction parameters, to reduce the reaction times and enhance the yield and chemical selectivity of the entire process.[10]

To the best of our knowledge, the only example of continuous flow synthesis of metal-NHC complexes reported in the literature dates back to 2013, when McQuade and co-workers

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documented the possibility of obtaining copper-NHC complexes by passing a solution containing the an imidazolium salt through a bed of Cu_2O (Figure 1).[11] This approach, in addition to suffering from poor atom efficiency as previously stated, involves the use of environmentally deleterious solvents (5% MeOH/ 80% CH_2Cl_2/ 15% toluene) and high temperatures (110 °C) to ensure high conversion of the starting material. Furthermore, the efficiency of the reactor decreases significantly after less than 10 minutes of use.

In the present work, we report the continuous flow synthesis of copper, gold and palladium complexes bearing the 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr), which has been taken as model NHC since it is by far the most used in homogeneous catalysis and, by virtue of its stability and reduced cost, is the most interesting to be developed on a large scale (Figure 1).

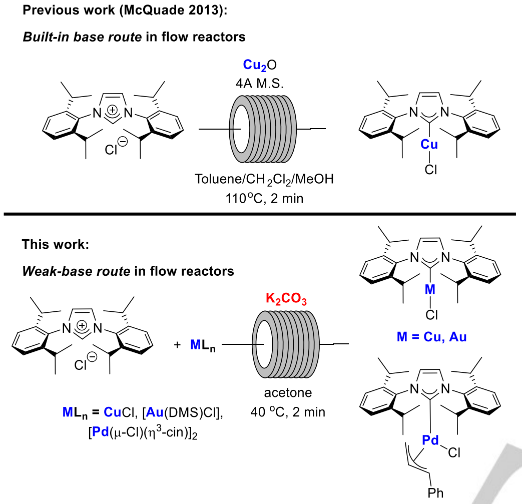


Figure 1. Comparison between built-in base and weak-base routes in flow continuous reactors.

To evaluate the feasibility of the synthesis of metal-NHC complexes taking advantage of both flow technology and the weak base approach, we first investigated the formation of the [Cu(IPr)Cl] complex. The latter can be used as an alternative transmetallating agent to [Ag(IPr)Cl] as well as an efficient well-defined pre-catalyst in hydrosilylation, [3+2] cycloaddition, carbonylation and carboxylation processes.[12]

In analogy with the approach used by McQuade, we first opted for a solution containing the imidazolium salt (1,3 bis(diisopropylphenyl)imidazolium chloride, IPr·HCl) and a solid phase containing both the copper source (CuCl) and the weak base (K_2CO_3). More specifically, a 0.01 M solution of IPr·HCl in technical grade acetone was injected into a microreactor, thermostated at 50 °C and filled with CuCl and K_2CO_3 (1.5 g each, previously mixed), using 5 min as residence time (Figure 2, setup A). With this initial setup, no conversion to product was observed but instead the development of a deep purple colour in the reactor was evident. This is most likely due to the formation of copper (II) salts in the presence of K_2CO_3 under these specific conditions. To confirm this, the same reaction was carried out by filling the microreactor with three plugs containing K_2CO_3, CuCl and the CuCl/K_2CO_3 mixture, respectively, separated from each other by plugs of silica (Figure 2, setup B). Also, in this arrangement, a strong colour change was observed in the K_2CO_3/CuCl layer but, unlike the previous experimental setup, the partial formation of the final product was observed (15% conversion). Based on these observations it can be deduced that a key factor in converting the substrate into the final complex is the separation of the copper source from the weak base as well as the exclusion of oxygen (air) using this design.

The next reactor design evolution made use of a plug of K_2CO_3 and one of CuCl separated by silica. This new design led to a 40% conversion to the desired product (Figure 2, setup C).

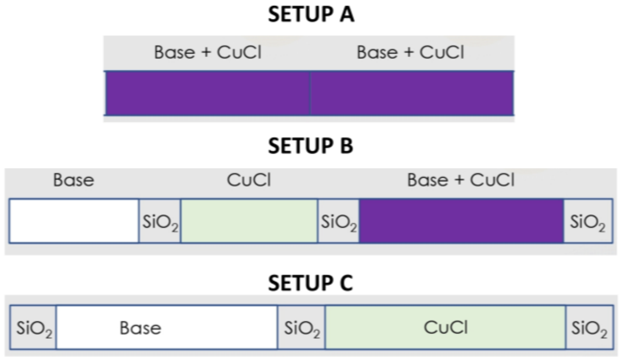
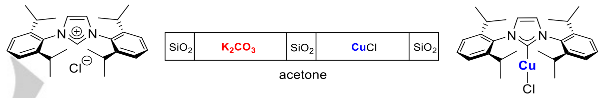


Figure 2. Different reactor configurations used in preliminary tests.

In an attempt to further improve the performance of this reactor design, the residence time and temperature were varied, and the associated outcomes are summarized in Table 1.

Table 1. Optimization of the synthetic protocol for [Cu(IPr)Cl] (Setup C).



Entry	Temperature (°C)	Residence Time (min)	Conversion (%)
1	50	5	40
2	50	15	55
3	60	25	62
4	75	10	71

These data highlight how, with the same base (K_2CO_3), the increase in residence time and/or temperature enhance the conversion but, as evidenced by the ^1H NMR spectra, they also lead to the formation of unwanted by-products.

An approach that has allowed us to significantly increase the efficiency of the reaction, involves an increase in the number of plugs of K_2CO_3 and CuCl, separated by plugs of silica. By alternating the segments in such a way as to create four base/CuCl repeat units, interspersed with plugs of silica or sand, conversions of 85 and 93% were obtained, respectively. The slight increase in conversion when using sand is attributable to the slight acidity of the silica which counteracts the action of the base. If basic alumina or sodium acetate are used instead of K_2CO_3, no conversion to the product is observed. This is intriguing as sodium acetate has recently been used as a weak base for the preparation of several gold(I)-NHC complexes under batch conditions.[13] This is presently being further investigated.

In order to reduce the amount of solvent used, an essential issue in industrial processes, the concentration of the solution containing the imidazolium salt was increased. Using a 0.03 M solution and the setup containing the sand plugs, complete conversion of the starting imidazolium salt into [Cu(IPr)Cl] in a 82% isolated yield was obtained. Furthermore, the microreactor maintains a complete conversion for about 75 minutes of use (see Figure S3, Supporting Information).

Gratifyingly, these results highlight the use of an eco-friendly solvent and very mild operating conditions compared to those used by McQuade.[11] We wondered if the reaction and reactor design could be further simplified leading to further solvent and energy savings. To this end, we took inspiration from mechanistic insights afforded by some of our recent studies[7] focusing on the weak base route. The identification of a very simply formed *ate* complex (when the metal source is placed into contact with the imidazolium salt) raised the possibility of using this cuprate, which can be made by grinding or milling,[14] as a reagent already containing the metal and the imidazolium components in the correct ratio and deploying it in the flow reaction.

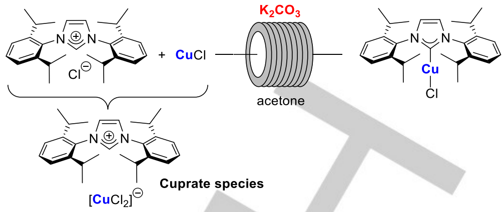
The use of the cuprate does lead to a much simpler reactor design. The next reactor evolution then became operationally basic with the cuprate being flowed through a reactor bed filled with the solid base. Therefore, a microreactor charged only with potassium carbonate was injected with a 0.03 M solution of the cuprate species [IPrH][$CuCl_2$]. Note here that the cuprate obtained by mechanochemistry [14] or by simply pre-mixing the imidazolium salt (IPr·HCl) and CuCl (5 min at RT in green acetone) [7d] are both fit for purpose. Gratifyingly, in both scenarios, the cuprate species was completely converted into the final complex by reaction with potassium carbonate, using the same operating conditions as before (5 min at 50 °C). The final isolated yield was 90% in both cases. In order to optimize the operating conditions of this straightforward route, the conversion and final yields, obtained by varying the temperature and residence time, are shown in Table 2. From these data, the optimal conditions guarantying a complete conversion of the substrate are 40 °C and *2 min of residence time*.

It is worth mentioning that the same approach is applicable to the synthesis of [Cu(IPr)Br], using CuBr as a copper source (see Supporting Info).

Satisfied with the simple reactor design and mild operating conditions, we decided to test the validity of the approach on a larger scale. The multigram synthesis of [Cu(IPr)Cl] was performed using a Buchi Sepacore C-690 Glass Column. The column was filled with 12 g of K_2CO_3 and could easily be attached to the current setup. This allowed the process to be scaled up approximately ten-fold, whilst maintaining its operational simplicity. During the run 2.6 g of product was made with an isolated yield of 89%. Only, 120 minutes of reactor time were required to generate the 2.6 g amount using the small tubular reactor design.

Encouraged by the results obtained for the copper complex, we wondered if this simple flow continuous apparatus could be used under similar/identical conditions for the synthesis of NHC complexes with other Late Transition metals.

Table 2. Optimization of the synthetic protocol for [Cu(IPr)Cl] (procedure B).



Entry	Temp (˚C)	Residence Time (min)	Conversion (%)	Isolated yield (%)
1	50	5	100	89
2	50	2	100	91
3	40	5	100	91
4	40	2	100	92
5	25	5	77	/

We then chose to investigate the synthesis of the gold congener, [Au(IPr)Cl], which is well known for its ability to provide access to a wide range of organometallic complexes with applications ranging from catalysis to medicinal chemistry.[15] In order to obtain this complex, a 0.01 M solution of [Au(DMS)Cl] (DMS = dimethylsulfide) and IPr·HCl, premixed at RT for 5 min (thereby forming *in situ* the aurate species), was injected into the microreactor containing potassium carbonate (T = 50 °C, t = 5 min). Unlike the copper complex, a significant colour change of the column and a slightly lower conversion (84%) were noted. The same result was obtained by injecting into the reactor a solution of the aurate intermediate [IPrH][$AuCl_2$], which was in turn prepared according to the protocol reported in the literature. [7c] This is most likely due to the greater propensity of gold to form nanoparticles, as also evidenced in batch processes. This poisoning significantly alters the performance of the column.

A first attempt to guarantee the complete substrate conversion without altering the operating conditions of the system was made by using a column having a double length compared to the standard one (110 cm vs 55 cm). This change led to the desired complete conversion of the aurate species (yield: 94%), effectively showing significant damage to the first half of the column containing the potassium carbonate. A second attempt to reduce decomposition processes inside the reactor and at the same time to allow high substrate conversion was carried out using a lower operating temperature and residence time for the process. Gratifyingly, using lower temperatures and/or residence time, it was possible to obtain high conversions and yields maintaining the original setup (55 cm column). In this respect, as shown in Table 3, the optimum conditions were to operate at 40 °C using 2 min of residence time.

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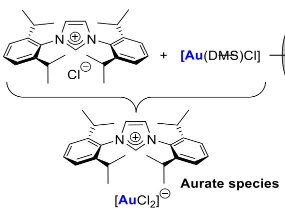
Table 3. Optimization of the synthetic protocol for [Au(IPr)Cl].

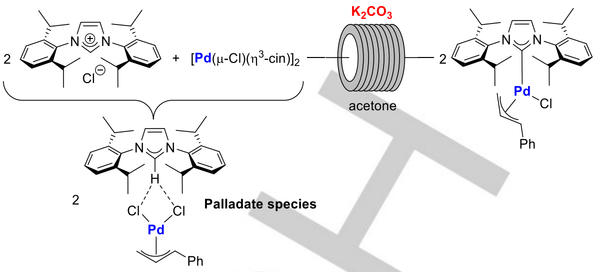


Entry	Temp (°C)	Residence Time (min)	Conversion (%)	Isolated yield (%)
1	50	2	100	93
2	40	2	100	93
3	25	5	98	/
4	25	2	67	/

The last category of compounds considered for evaluation of the generality of this approach is represented by a member of the Pd-NHC family. These compounds have become classics in homogeneous catalysis especially for their ability to promote cross-coupling reactions.[16] These complexes have also very recently exhibited promising anticancer activity, with particular efficacy, from *in vitro*, *ex vivo* and *in vivo* studies, against ovarian cancer.[17] Therefore, both in homogeneous catalysis and in medicinal chemistry, a prominent place is occupied by Pd(II)-η^3-allyl and cinnamyl complexes bearing NHC ligands.[18]

With these reasons in mind, because of our experience in the development and handling of these organometallic complexes, we investigated the preparation of [Pd(IPr)Cl(η^3-cinnamyl)], as a key example of this family.[19] Unlike the gold complex described above, a complete conversion was observed using the same setup of the copper derivatives, by passing through the reactor containing the potassium carbonate a 0.03 M solution of [Pd(Cl)(η^3-cinnamyl)]$_2$ and IPr·HCl.[20] The latter components were pre-mixed at RT for 5 min to form the palladate species *in situ*. An identical result is obtained if an acetone solution containing pre-formed palladate species (prepared separately following to the published protocol)[7e] is injected in the microreactor. An important observation here is the lack of significant signs of alteration of the reactor even after several passages of the substrate. As already achieved in the case of the gold and copper derivatives, the optimization of the process was carried out by varying the temperature and the residence time (see Table 4). From the data reported in Table 4, it is clear that, similarly to the copper complex, the best conditions under which to obtain [Pd(IPr)Cl(η^3-cinnamyl)] in good yields and purity are 40 °C and 2 min of residence time.

Table 4. Optimization of the synthetic protocol for [Pd(IPr)Cl(cin)].



Entry	Temp (°C)	Residence Time (min)	Conversion (%)	Isolated yield (%)
1	50	5	100	86
2	50	2	100	88
3	40	2	100	86
4	25	5	87	/
5	25	2	87	/

In summary, we have reported a general method for the preparation of gold, copper and palladium-NHC complexes taking advantage of continuous flow technology. The experiments carried out suggest that the best experimental setup, which is the same for the different complexes examined, consists of a microreactor filled with potassium carbonate (weak and inexpensive base) into which is injected a technical grade acetone solution of the imidazolium salt (IPr·HCl) and the metal precursor (CuCl, Au(DMS)Cl or [Pd(Cl)(η^3-cinnamyl)]$_2$), pre-mixed for a few minutes in order to obtain the cuprate, aurate or palladate species, respectively, which are the operating starting materials in the reaction. Note that the ultimate simple process design was inspired by the fundamental mechanistic understanding and the role of key air-and moisture stable intermediates along the reaction sequence leading to the M-NHC bond formation using the weak base route.

In all cases, it was possible to completely convert the starting species into the corresponding NHC-complexes using very mild conditions (40 °C, 2 min) and without the need for further purification after solvent removal under vacuum. This solvent can be easily recycled. Noteworthy, the same reactions carried out in batch require more drastic conditions (60 °C for 1-24 h) and an additional purification step. Moreover, in the case of [Cu(IPr)Cl], the synthesis on a multigram scale in flow was successfully achieved.

This is the first study on continuous flow reactions using the *weak-base route*, we believe it may be an encouraging starting point for both industrial and academic researchers dealing with the synthesis of metal-NHC complexes and their numerous applications. Studies aimed at extending this simple protocol to related organometallic systems are ongoing in our laboratories. The present effort will, we hope, help democratise access of these versatile catalysts and materials.

Acknowledgements

The authors like to thank MSc. Pierfrancesco Motti, ir. Reinout Van Kerrebroeck and Dr. Thomas Heugebaert (Department of Green Chemistry and Technology) for helpful discussions. We are grateful to the SBO (D2M to SPN) and the BOF (starting and senior grants to SPN) for financial support. Umicore AG is gratefully acknowledged for generous gift of materials.

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Keywords: Flow continuous synthesis • *N*-heterocyclic carbene ligands • Weak-base route • Cu, Au and Pd complexes • Green solvents

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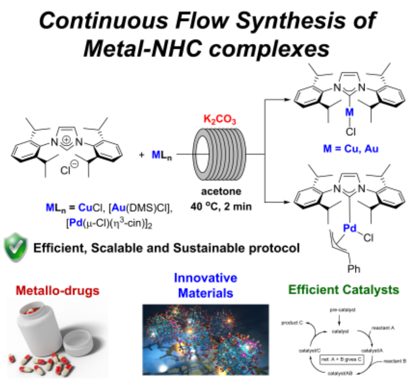

Simplicity is the ultimate sophistication: Taking advantage of the mechanistic understanding of the *weak base route* to access M-NHC complexes, the first continuous flow syntheses of Cu(I), Au(I) and Pd(II)-NHC complexes using very mild conditions (40 °C, 2 min in technical grade acetone) are described.

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