

Rapid and Mild Synthesis of Au-NHC Complexes in a Simple Two-Phase Flow Reactor

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Abstract

We describe a simple two-phase flow reactor which allows for the efficient and rapid synthesis of several Au(I)-NHC complexes under mild conditions, with minimal workup, and avoiding common problems with decomposition to Au(0). An optional second stage allows for direct synthesis of Au(III)-NHC complexes, without isolation of the Au(I)-NHC intermediate.

Introduction

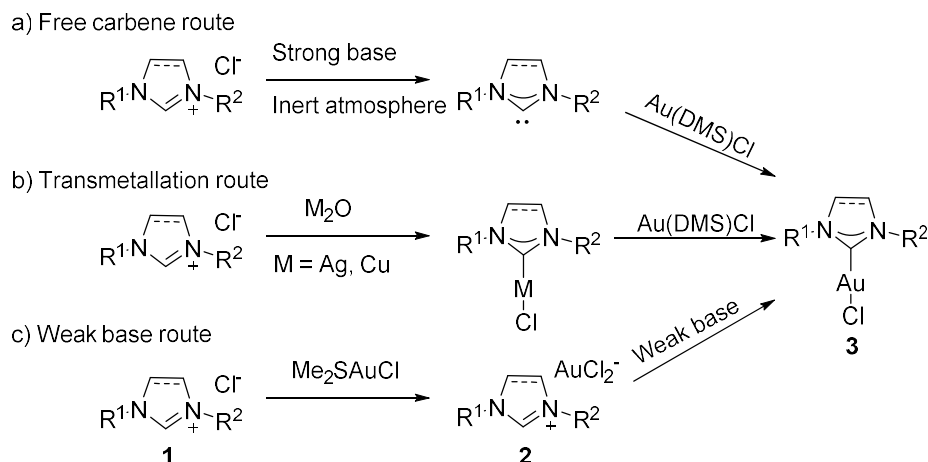
N-Heterocyclic carbenes (NHCs) are one of the most widely used classes of ligands for organometallic complexes. The strength of the metal-carbene bond as well as the ease of modification of both the backbone as well as the *N*-wingtip substituents make this ligand class especially attractive.^{1,2} NHC complexes of gold have been shown to catalyse a wide variety of reactions, and Au(I)-NHC complexes especially are important in gold catalysis.^{3,4} Au(III) has found considerably less use than Au(I)-NHC complexes, despite being readily available from the Au(I) precursors by a simple oxidation. This is most likely due to Au(III)'s propensity towards reduction to Au(I) or Au(0).⁵ Both Au(I)- and Au(III)-NHC complexes have also shown promise as anticancer agents and their potential application in medicinal chemistry has been widely studied.⁶

There are three main methods to synthesise Au(I)-NHC complexes; the free carbene route (Scheme 1a), the transmetallation route (Scheme 1b), and the weak base route (Scheme 1c).⁷ All the routes start with the imidazolium chloride salt and a gold precursor with a labile ligand, such as Me₂SAuCl. Both the free carbene route and the transmetallation route suffer from several disadvantages. In the free carbene route, generation of the carbene requires a strong base, such as KHMDS, *n*-BuLi, or NaH. Additionally, the instability of the free carbene makes rigorously inert conditions a necessity, usually requiring the use of a glovebox. The transmetallation route, on the other hand, requires the synthesis of either the Ag(I)- or Cu(I)-NHC complex ahead of time. The higher cost and lower atom economy of this reaction route, as well as the light sensitivity of Ag(I)-NHC complexes are significant downsides.

The weak base route has in recent years shown to be an easy and efficient alternative to synthesise Au(I)-NHC complexes. The use of weak, inexpensive bases such as K₂CO₃, NEt₃ and NaOAc, alongside DCM or acetone as the most common (single-phase) solvents, all under ambient atmospheric conditions makes this route attractive.⁸

Mechanistic studies indicate that the reaction proceeds via an aurate intermediate **2**, which is formed rapidly by displacement of Me₂S by the chloride anion upon mixing of the imidazolium chloride and the Au(I) precursor. These aurate salts are generally stable, and selected examples have been isolated and fully characterised.^{9,10} The Au(I)-NHC complex formation is then postulated to go through a concerted metallation-deprotonation process, at least when NEt₃ is used as the base. Spectroscopic

evidence indicates that the free carbene is not generated during the reaction.¹¹ As these reactions are typically performed in a single solvent phase over an insoluble base, workup involves at least one filtration step. Additionally, the long reaction times which are often required result in the reduction of a proportion of the Au(I) precursor to Au(0), potentially harming reaction yields and complicating workup.



Scheme 1. Synthetic routes towards Au(I)-NHC complexes.

We have recently reported a study on alcohol functionalised Au(I/III)-NHC complexes, which were synthesised *via* the weak base route.¹² Compared to a typical reaction performed in a single DCM phase, we found that performing the reaction in a two-phase DCM:H₂O system sped up the reaction significantly; full conversion was usually observed in under 2 hours, compared to only 35% after 12 hours in the single-phase system. However, in that batch process, we still noted a significant presence of Au(0) contamination, requiring filtration of the product through a silica plug to acquire the pure Au(I)-NHC complexes.

Droplet-based microfluidic flow reactors offer several advantages over batch reactors for performing multiphase reactions. In two-phase chemistry, reaction rates are often limited by the interfacial area (per unit volume) between the two phases. By splitting the phases into microlitre-scale droplets in intimate contact, this interfacial area-to-volume ratio is typically much greater than in an equivalent bulk reaction, greatly increasing the amount of phase mixing. Additionally, as each droplet is generated identically (at least for stable flows), mixing and heating are highly reproducible, avoiding much of the batch-to-batch variation typical of batch processes.¹³ This property of flow reactors is also beneficial during scale-up; in batch processes, scale-up requires use of larger reaction volumes, reducing the contacting surface area between phases, as well as larger reaction vessels which exhibit different heat transfer characteristics. In a flow reactor, however, the reaction stream can simply be split into multiple parallel streams, each with the same flow conditions as the reaction optimised at the smaller scale. For two-phase batch reactions, phases are generally manually separated using a separation funnel or the like, whereas flow reactors can make use of simple in-line separators that perform this step without requiring human input.^{14,15} This reduces the amount of workup that must be performed manually, but is also particularly useful for multi-step reactions where new reagents need to be added to the reaction volume downstream. With these advantages in mind, we explored the synthesis of several Au(I)-NHC complexes in a simple two-phase flow reactor, with the aim of improving the total reaction time and simplifying workup. This is, to the best of our knowledge, the

first example of a segmented flow reactor being used for the synthesis of metal-NHC complexes. Simoens et. al. have recently reported a methodology using a continuous flow solid-phase reactor for the synthesis of Au(I)-, Cu(I)- and Pd(II)-NHC complexes.¹⁶

A schematic of the flow reactor is shown in Figure 1. Matched syringes containing an aqueous base solution (S1) and a DCM solution of the relevant NHC-aurate **2a-g** (S2) are connected to the inputs of a y-shaped mixer (Y1, see Fig S1 in SI), and mounted within a dual-channel syringe pump. The co-injection of immiscible liquids at a stable flow rate into Y1 generates a stable, uniform segmented flow, which is directed into a 5 m length of coiled tubing (Zone A) where the aurate intermediate in the DCM reacts with the aqueous base, forming the desired Au(I)-NHC complex **3a-g**. The tubing in Zone A is held at 35 °C by submersion in a temperature-controlled water bath. For all experiments listed here, the flow rate of each solution was held at 200 $\mu\text{l}/\text{min}$, yielding a total flow rate in Zone A of 400 $\mu\text{l}/\text{min}$. The internal diameter of the tubing in Zone A was 1 mm, which corresponds to a total internal volume of 3.925 ml. At a total flow rate of 400 $\mu\text{l}/\text{min}$, the total transit time within Zone A is 9.8 min. The segmented flow exits Zone A into a previously-described liquid-liquid phase separator PS (see SI), which physically separates the two phases and stops the reaction.¹⁵ The DCM phase, which contains the newly formed Au(I)-NHC complex, is collected for analysis by ^1H NMR, whereas the aqueous phase containing the partially depleted base is discarded as waste. Prior to ^1H NMR analysis, the solvent was simply removed under reduced pressure, and the crude product redissolved in deuterated chloroform.

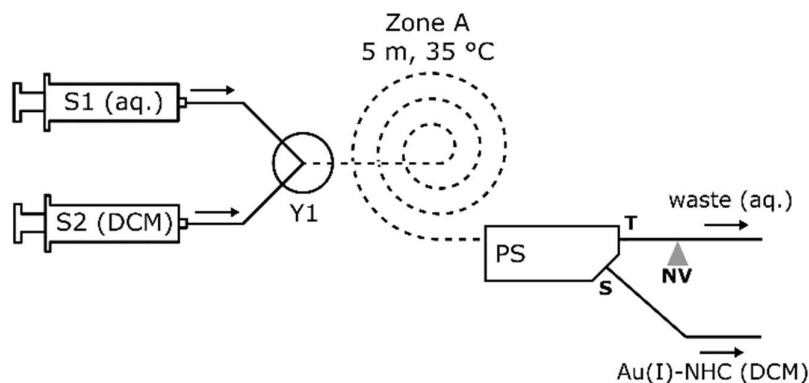
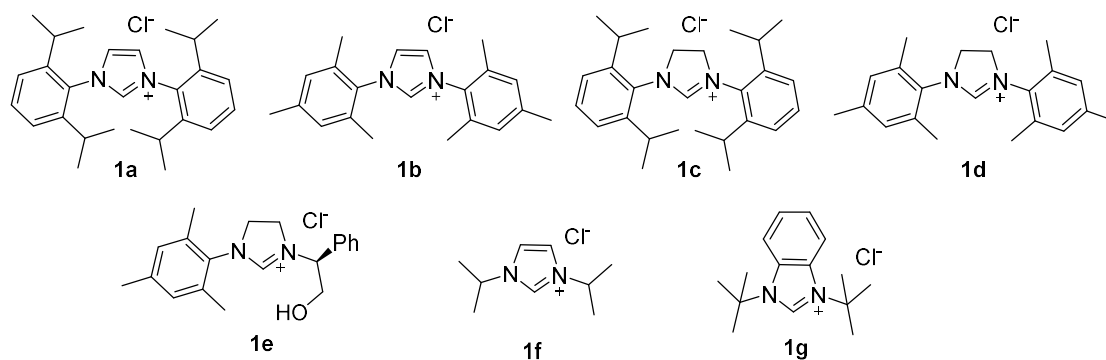


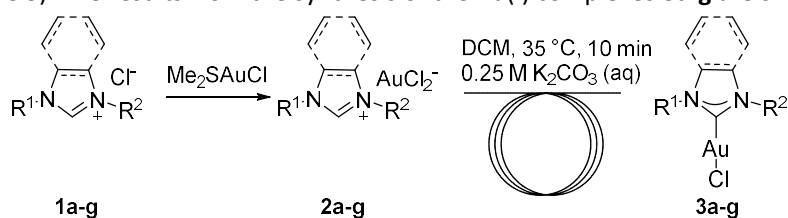
Figure 1. Schematic of flow reactor used for synthesis of Au(I)-NHC complexes. An aqueous base solution and a solution of an imidazolium aurate salt **2** in DCM are injected at equal flow rates into a y-shaped mixer (Y1) using a matched pair of syringes (S1 and S2). The mixer generates a 1:1 segmented flow of the aqueous and DCM solutions, which enters a 5 m length of coiled tubing (Zone A) where the aurate intermediate **2a-g** in the DCM reacts with the aqueous base, forming the corresponding Au(I)-NHC complex **3a-g**. The segmented flow then enters a liquid-liquid phase separator (PS). The aqueous phase containing partially depleted base exits the separator at the through-port T, then passes through a micro-metering needle valve NV, before being discarded as waste. The DCM phase containing the Au(I)-NHC complex is collected at the side port S.

A wide range of imidazolium-based salts **1a-g** (Scheme 2) were chosen for this study. These include the two most common NHC ligands IPr and IMes (**1a,b**) as well as their saturated counterparts SIPr and SIMes (**1c,d**) along with our previously reported alcohol functionalised NHC **1e**. We also included a less sterically hindered ligand **1f**, and benzimidazolium salt **1g**.



Scheme 2: Imidazolium-based salts **1a-g** used in this study.

The azolium salts **1a-g** were mixed with equimolar amounts of Me_2SAuCl in DCM and sonicated to form 0.012 M solutions of the corresponding aurate salts **2a-g**. The aurate solutions were then reacted under the segmented flow conditions described above with a 0.25 M aqueous K_2CO_3 solution acting as base (Scheme 3). The results from the synthesis of the Au(I) complexes **3a-g** are shown in Table 1.



Scheme 3: Synthesis of Au(I)-NHC complexes **3a-g** in the segmented flow reactor described in Figure 1.

Table 1: Synthesis of Au(I)-NHC complexes **3a-g** as shown in Scheme 3.^a

Entry	Preligand	Conversion to Au(I)-NHC ^b
1	1a	100%
2	1b	100%
3	1c	97%
4	1d	100%
5	1e	100%
6	1f	— ^c
7	1g	38%
8	1a	88% ^d

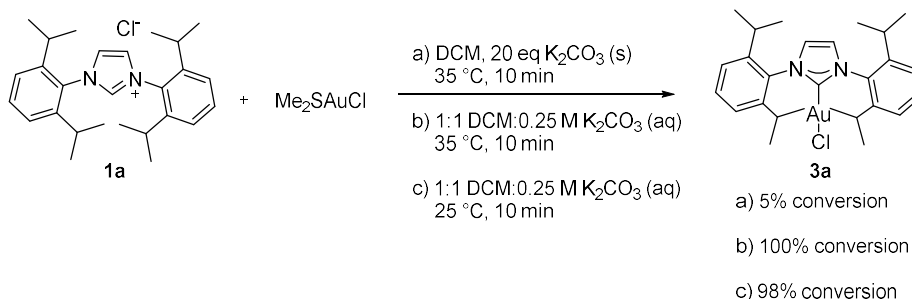
^a0.012 M DCM solutions of aurates **2a-g** were reacted with 0.25 M aqueous solution of K_2CO_3 at 35 °C in the flow reactor described in Figure 1. ^bConversion determined by ^1H NMR spectroscopy. ^cFast decomposition to elemental gold. ^d0.25 M NaOAc solution was used as base.

For imidazoli(ni)um salts **1a-e**, with bulky aryl sidegroups, our conditions were extremely effective, giving full conversion to gold complexes **3a-e** (Table 1, entries 1-5), apart from SIPr•Cl **1c**, which still showed an excellent 97% conversion to the Au(I)-NHC complex **3c**. This method is therefore well suited for the coordination of both imidazolium and imidazolinium chlorides, the latter of which have been reported to require longer reaction times.⁹

Au(I)-NHC complexes with sterically unencumbered ligands are challenging to synthesise with the weak base route, usually showing decomposition to elemental gold. An exception is a method reported by Johnson et. al. which uses $\text{NBu}_4(\text{acac})$ as the base.¹⁷ To test our method on this type of substrate, we attempted the coordination of *N,N*-dialkylimidazolium chloride **1f**. Unfortunately, this led to almost instantaneous formation of elemental gold (see Fig S3) and no complex was obtained (Table 1, entry 6). This method is therefore clearly not suited for less sterically hindered imidazolium salts. Finally, *N,N*-dialkylbenzimidazolium chloride **1g** was found to give only 38% conversion to Au(I)-NHC complex **3g**. This could perhaps be improved by increasing the reaction time, either *via* increasing the length of the tubing (at the cost of an increased dead volume) or reduction of the flow rate, at the cost of separator performance.¹⁵

NaOAc has also been reported to be an alternative to K_2CO_3 for this reaction.¹⁸ We therefore attempted to synthesise complex **3a** by using a 0.25 M aqueous solution of NaOAc instead (Table 1, entry 8). This led to a reduced 88% conversion to Au(I)-NHC complex **3a**, compared to 100% for K_2CO_3 .

To compare our flow reaction with the conventional batch reaction we conducted the reaction of imidazolium chloride **1a** with Me_2SAuCl in both the commonly used single-phase system, as well as our two-phase reaction system (Scheme 4).



Scheme 4: Batch synthesis of Au(I)-NHC complex **3a** in a) single-phase b), c) two-phase solvent systems.

Performing the reaction in just DCM, with 20 eq of K_2CO_3 as base, led to extremely poor conversion. Only 5% conversion (Scheme 4a) was observed after 10 min at 35 °C (c.f. 100% in the two-phase flow reaction). Meanwhile, the two-phase batch reaction also gave full conversion to Au(I)-NHC complex **3a** under otherwise identical reaction conditions (Scheme 4b). The two-phase batch reaction at room temperature is also effective, giving 98% conversion (Scheme 4c). The reason for this dramatic increase in reaction rate with the two-phase system is likely due to more efficient mixing between the aurate salt **2a** and the base in the two-phase system compared to the heterogeneous reaction. Comparing the two-phase flow and batch reactions, the batch reaction resulted in greater decomposition of the Au(I)-NHC complex; within minutes the aqueous phase had turned a dark grey and under evaporation of the separated organic phase the resulting solid was grey, requiring a silica plug filtration to acquire the pure gold complex. In the flow reaction, however, both the phases remained clear and colourless throughout. Evaporation of the organic phase resulted immediately in a white solid which was shown to be pure according to ^1H NMR spectroscopy. Whilst we do not fully understand the mechanism behind this improvement, as the decomposition of Au(I) to Au(0) in such

syntheses is poorly understood, we suggest that the more uniform and efficient phase mixing offered by the microfluidic flow reactor is likely to be a factor. The advantage that this brings in the reduction of necessary workup, as well as the inherent scalability of the flow reaction, is likely to be useful in environments where Au(I)-NHC complexes are synthesised regularly.

Au(III)-NHC complexes are readily available from Au(I)-NHC complexes *via* oxidation by PhICl_2 .¹⁹ We envisioned an easy route towards Au(III)-NHC complexes by adding a second reaction step to our flow apparatus, oxidising the formed Au(I)-NHC complex without isolation. A schematic of the second reaction stage is shown in Figure 2, and a schematic of the full two-stage reactor is shown in Figure S4. The single-step reactor used for synthesis of the Au(I)-NHC complexes **3a-g** was extended by connecting an input port of a second y-shaped mixer Y2 to the separator's side channel **S**. A third syringe (S3) containing a DCM solution of the oxidant PhICl_2 was connected to the second input port of Y2. The output port of Y2 was connected to a second 5 m length of tubing (Zone B), which was kept at 35 °C by submersion in the same water bath as the tubing in Zone A. The flow rate from S3 was set at 100 $\mu\text{l}/\text{min}$, generating a continuous flow in Zone B with a flow rate of 300 $\mu\text{l}/\text{min}$, corresponding to a residence time of 13.1 min. Here, the Au(I)-NHC complex **3a** emitted from the separator at **S** is oxidised by PhICl_2 to form the Au(III)-NHC complex **4a**, which, after passing through Zone B, is collected into pentane. The pentane causes both Au-NHC complexes **3a** and **4a** to precipitate, ensuring that the reaction does not proceed further once the reaction mixture has left the reactor. The reaction scheme is shown in Scheme 5.

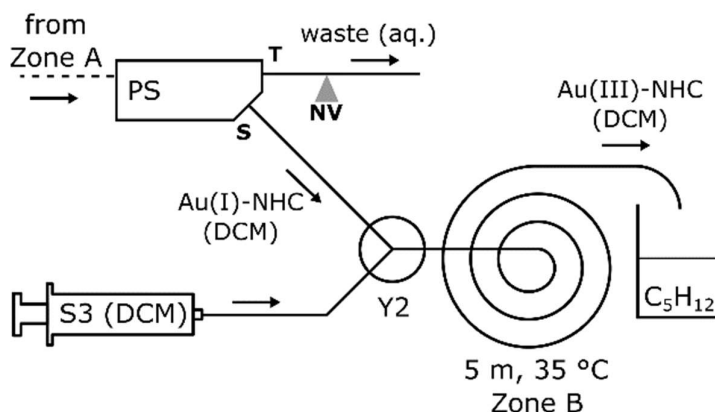
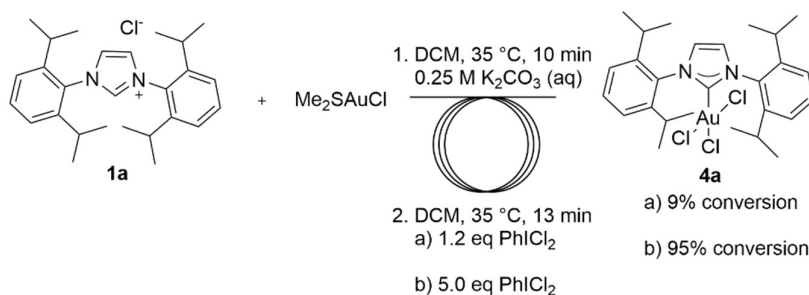


Figure 2. Schematic of second stage of the flow reactor used for synthesis of the Au(III)-NHC complex **4a**. The first stage of the reactor consists of the single-step reactor used for synthesising the Au(I)-NHC complexes **3a-g** (see Figures 1 and S4). The DCM stream emitted from **S**, containing the Au(I)-NHC complex **3a** is directed into one input of a second y-shaped mixer Y2. A DCM solution of the oxidant PhICl_2 is injected into the other input port from a third syringe (S3), forming a continuous flow which enters a second 5 m length of tubing (Zone B). The oxidised Au(III)-NHC complex **4a** is collected at the output of Zone B in a beaker of pentane.



Scheme 5: Synthesis of Au(III)-NHC complex **4a** directly from imidazolium salt **1a** in the two-stage flow reactor described in Figure 2.

Performing the reaction with 1.2 equiv. PhICl_2 (Scheme 5a) led to poor conversion (9%) to the Au(III) complex **4a**, as determined by ^1H NMR. However, increasing the amount of oxidant to 5 equiv. (Scheme 5b) gave 95% conversion to **4a**. This two-stage reactor therefore greatly simplifies the synthesis of **4a** from the starting imidazolium salt **1a** – once the reactor is started, the 95% pure Au(III)-NHC complex can be collected after around 25 minutes, without isolation or purification of any intermediates. The only workup required is washing of the acquired solid with diethyl ether.

Conclusion

In summary, we have presented a simple and efficient route to Au(I)-NHC complexes from imidazolium salts by use of a two-phase version of the weak base route under segmented flow conditions. This method allows the synthesis of the most common Au(I)-NHC complexes under mild conditions and short reaction times. The important benefits of the flow conditions are reduced decomposition to elemental gold, simple scalability, and minimal workup, with only evaporation needed to acquire the 100% pure Au(I)-NHC complexes. This method is excellent for both imidazolium and imidazolinium chlorides with bulky groups, but is less effective for *N,N*-dialkylbenzimidazolium chlorides and ineffective for less hindered *N,N*-dialkylimidazolium chlorides. We have also shown that performing the coordination in a two-phase $\text{H}_2\text{O}:\text{DCM}$ system greatly increases the reaction rate for the batch reaction.

The flow reaction was expanded to include a second, oxidation step. This allowed for the synthesis of a Au(III)-NHC complex directly from the parent imidazolium salt, without isolation or purification of the intermediate Au(I) complex. This proves to be a rapid and user-friendly approach towards Au(III)-NHC complexes, making research into their properties more accessible.

We believe this method provides simple access to Au-NHC complexes of importance to both catalysis and medicinal chemistry, and could potentially be applied to the synthesis of NHC complexes of other metals.

HFJ and AJH conceived the study, performed experiments, and wrote the manuscript. HFJ analysed data. AF assisted with conceptualisation and reviewed the manuscript. There are no conflicts of interest to declare.

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