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Continuous Flow Synthesis of NHC-Coinage Metal Amido and Thiolato Complexes: A Mechanism-based Process Development

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The first continuous flow syntheses of amido and thiolato families are reported. Our studies focused on [M(NHC)(Cbz)] (Cbz = carbazolyl) and [M(NHC)(SPh)] (NHC = N-heterocyclic carbene) as general proof-of-concepts and has led to a simple protocol with unprecedented short reaction times and high product yields. The scope of supporting ligands and substrates permits to assess the versatility of the process and a one-pot synthesis starting from the imidazolium salt, metal source and carbazole substrate highlights the simplicity and sustainability of this operating design. The process was made possible through a detailed mechanistic understanding of the underlying reaction chemistry.

Introduction

Over the last 30 years, N-heterocyclic carbene (NHC) ligands have revolutionised the field of organometallic chemistry.[1] The NHC's capability to exert considerable steric bulk while maintaining conformational flexibility, combined with their excellent donor properties has helped them transcend the initial reputation of them being mere phosphine mimics. Successful implementations in numerous catalytic, photoluminescence and therapeutic applications have clearly demonstrated their versatility, explaining the broad interest in transition metal-NHC complexes.[2]

Among transition metals, the coinage metals occupy a prominent place as a consequence of their natural availability, exceptional properties and associated reactivity.[3] The chemistry of coinage metal complexes is highly diverse something which is reflected in recent developments in the field, especially with respect to gold.[4] Among the great variety of derivatives, Carbene-Metal-Amido (CMA) complexes of the coinage metals have shown great promise in terms of photophysical properties, which is evidenced by their recent application in highly luminescent organic light-emitting diodes (OLEDs).[5] Their attractiveness for photoluminescent applications originates from the large tunability and diversity of the emission properties combined with a near 100 % internal quantum yield as a function of supporting ligation.[6] Coinage metal-thiolate complexes, for their part, are important targets owing to their biological activity, as is exemplified by *auranofin* which has recently received FDA approval for Phase II clinical trials in cancer therapy.[7] In contrast to many other metallodrugs, gold-thiolato complexes target and inhibit redox enzymes thereby inducing cellular oxidative stress and ultimately apoptosis, thus rendering them potent agonists against *cisplatin*-resistant cancer cell lines.[7b,8] Readily accessible synthetic routes to both families of complexes are vital for spurring innovation in these domains.

Gold-thiolato complexes were among the first metal complexes to be synthesized using a weak base.[9] The reactions, reported by Laguna and co-workers, were fast and could be performed at room temperature, yet dichloromethane was used as the reaction solvent. Baker and Scattolin have made improvements to this protocol by accessing gold(I)-thiolato complexes in ethanol using K_2CO_3 and NaOAc as the weak base, respectively.[10] Recently, the synthesis of copper(I)-thiolato complexes under mild conditions using K_2CO_3 as the base has been reported.[11] Great advances have recently been made by implementing this same *weak base approach* to the synthesis of CMA complexes (Scheme 1).[12] Traditionally, the latter are synthesized using strong bases or lithium/potassium amides, requiring inert atmospheres and toxic solvents.[6a,13] Other, indirect approaches make use of well-defined organometallic synthons but require multiple synthetic steps.[14] The weak base approach generally offers single-step, high-yielding, readily scalable and mild alternatives to such harsher protocols.[15]

Despite the important advances in terms of synthetic ease and sustainability provided by the weak base route, reactivity issues remain a concern. Several equivalents of base are required to drive

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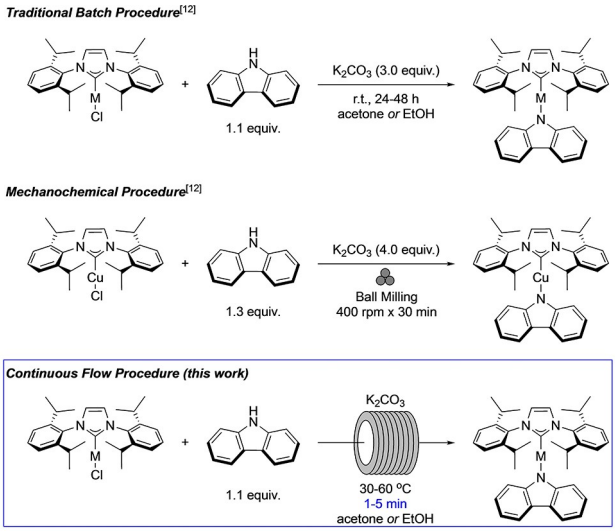


Scheme 1. State-of-the-art synthetic processes for the synthesis of [M-(NHC)(Cbz)] (M = Cu, Ag and Au; Cbz = carbazolyl) complexes.

reactions towards completion, while additionally necessitating reactions to stir for extended periods of time. Via solventless mechanochemical approaches, reaction times have already been greatly reduced, yet substantial excess of base and amine substrates are still required.[12,16] Continuous flow technology offers opportunities to address poor reaction kinetics simply by the nature of its small reactor dimensions which allows for enhanced mass and heat transfer.[17] Additionally, optimized homogeneity ensures increased product selectivity and reductions in waste.

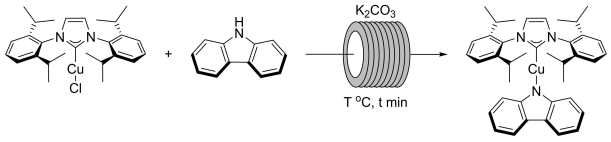
We have recently developed a scalable continuous flow procedure – inspired by the weak base batch protocol – for the synthesis of NHC-copper(I), -gold(I) and -palladium(II) complexes from the corresponding imidazolium salt and metal precursor, in unprecedentedly short reaction times.[18] The efficacy of this process to access other complexes was further assessed in the synthesis of a range of gold(I)-aryl complexes.[19] Encouraged by these initial findings, we hypothesized that the use of continuous flow protocols towards N–H and S–H activation, in a way to further demonstrate the *weak base* versatility and potential, could further capitalize on our mechanistic understanding of the underlying chemistry to provide easy access to complexes possessing catalytic and photochemical potential. We now report on the continuous synthesis of coinage metal-carbazolyl and -thiolato complexes as a proof-of-concept showcasing the synthetic potential of simple, mechanistically based flow processes.

Results and Discussion

Synthesis of M-Amido Complexes (M = Cu, Ag, Au)

The continuous flow synthesis of [Cu(IPr)(Cbz)] (**3**) in acetone was used as an entry point to assess the overall viability of the process (Table 1). Full conversion to the desired product was achieved with a residence time of 5 minutes and a temperature

Table 1. Optimization of the continuous flow protocol for [Cu(IPr)(Cbz)] (**3**).



2 **3**

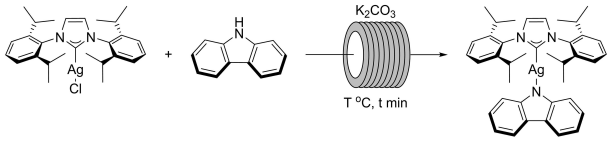
Entry[a]	Solvent	T [°C]	Residence time [min]	Conversion/Yield [%][b]
1[c]	Acetone	50	5	100/83
2	Acetone	50	2	100/81
3	Acetone	50	1	100/77
4	Acetone	40	2	100/78
5	Acetone	30	2	100/81
6	EtOH	50	2	100/74

[a] Conditions unless otherwise stated: [Cu(IPr)Cl] (48.8 mg, 0.10 mmol), carbazole (1.2 equiv.), 5 mL of solvent. [b] Isolated yield. [c] Carbazole (1.1 equiv.).

of 50 °C (Entry 1, Table 1). Addition of a 1.1 equivalent of carbazole to the reagent solution was accompanied by the observation of some minor product impurities which are observed in the batch and mechanochemical synthetic procedures as well. To eliminate such side-reactivity, a slightly larger excess of carbazole was added during parameter optimization. Very short reaction times and low reaction temperatures proved sufficient to reach full conversion to the desired product (Entries 3 and 5, Table 1). Complex **3** was also obtained by employing ethanol as solvent (Entry 6, Table 1). Despite being significantly greener,[20] ethanol is less desirable than acetone due to the manifestation of some process-related complications. Firstly, as the studied metal complexes are only sparely soluble in ethanol, product might be retained on the packed bed reactor column, thus only allowing diluted reagent solutions to be injected. In addition, the viscosity of ethanol is substantially larger as compared to acetone, such that higher internal pressure buildups are observed.

For the synthesis of [Ag(IPr)(Cbz)] (**5**), the use of acetone as the reaction solvent was not successful (Entry 1, Table 2). Changing to ethanol gave direct access to the product

Table 2. Optimization of the continuous flow protocol for [Ag(IPr)(Cbz)] (**5**).



4 **5**

Entry[a]	Solvent	T [°C]	Residence time [min]	Conversion/Yield [%][b]
1[c]	Acetone	60	5	67
2	EtOH	70	5	100/95
3	EtOH	60	5	100/85
4[d]	EtOH	60	5	100/80
5[d]	EtOH	60	2	100/89

[a] Conditions unless otherwise stated: [Ag(IPr)Cl] (30 mg, 0.05 mmol), carbazole (1.2 equiv.), 10 mL of solvent. [b] Isolated yield. [c] Concentration (0.02 M). [d] Solvent (EtOH abs.).

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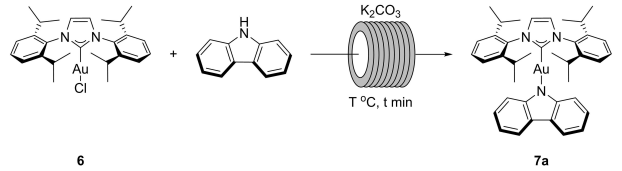
(Entries 2 and 3, Table 2). The use of absolute ethanol is preferred, yet technical grade ethanol suffices to reach desirable results (Entries 3–5, Table 2). Noteworthy are the short residence times that prove sufficient to obtain **5** in high yields.

No trace of product was observed for the synthesis of [Au(IPr)(Cbz)] (**7 a**) in acetone (Entry 1, Table 3). Using ethanol as the solvent resulted in full conversion to the desired product, both with moderately long (i.e., 5 minutes) as well as very short (i.e., 1 minute) residence times (Entries 2–5, Table 3). The usual issues associated with the use of ethanol were encountered for this set of experiments as well. 0.0035 M solutions of [Au(IPr)Cl] (**6**) and carbazole in ethanol still displayed some remaining precipitate, whereas concentrations exceeding 0.005 M proved acceptable for the synthesis of the copper and silver complexes. Using a suitable co-solvent in a 1:1 ratio, the product was obtained with full conversion while increased concentrations could be employed (Entries 4 and 5, Table 3). The use of 2-MeTHF as co-solvent is preferred over THF for sustainability reasons. The solubilizing power of both solvent mixtures is comparable so that the same concentrations can be established.

Table 3. Optimization of the continuous flow protocol for [Au(IPr)(Cbz)] (**7 a**).



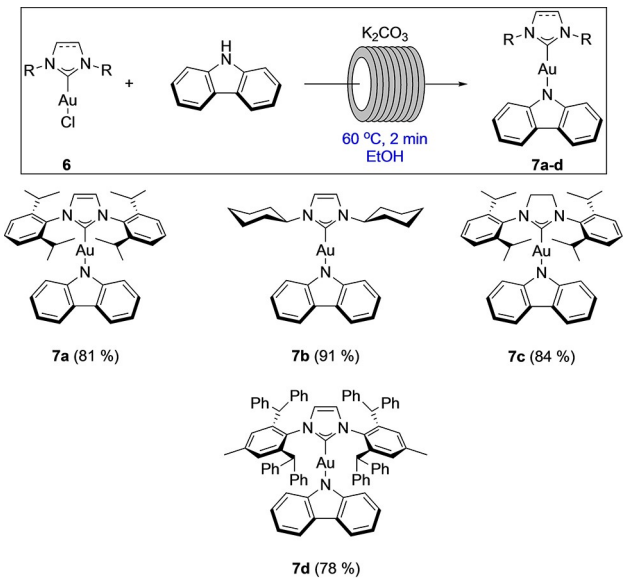
Entry[a]	Solvent	T [°C]	Residence time [min]	Conversion/Yield [%][b]
1[c]	Acetone	60	5	0
2	EtOH	60	5	100/61
3	EtOH	60	2	100/57
4[c,d]	EtOH	60	2	100/81
5[c,e]	EtOH	60	1	100/76
6	EtOH	50	2	80
7[f]	EtOH	60	2	100/87

[a] Conditions unless otherwise stated: [Au(IPr)Cl] (22 mg, 0.035 mmol), carbazole (1.2 equiv.), 10 mL of solvent. [b] Isolated yield. [c] Concentration (0.01 M). [d] Co-solvent (2-MeTHF). [e] Co-solvent (THF). [f] [Au(IPr)Cl] (200 mg).

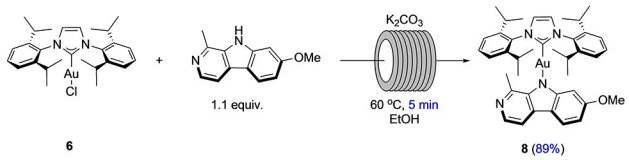
To test the scalability of the developed protocol, a larger scale synthesis of complex **7 a** was performed (Entry 7, Table 3). 210 mg of the desired product was obtained in high yield (87%) and in very short reaction times. This showcases that larger amount of product can be synthesized in very short reaction times, necessitating only minimal workup to deliver the final product.

Following the set of benchmark reactions performed with complex **6**, we set out to explore a brief scope of NHC supporting ligands (Scheme 2). As a proof-of-concept, conditions of 2 minutes residence time and 60 °C were selected to test NHC compatibility. Comparable to the batch synthesis,[12] complex **7 b** bearing an *N*-alkyl substituted NHC was readily afforded in high yields, and significantly shorter reaction times were sufficient to reach these results. Of significant note, great improvements with respect to reaction time were obtained in the synthesis of **7 c** and **7 d**, complexes whose respective batch syntheses required 24 and 48 h, respectively.[12] Especially the synthesis of complex **7 d** is notable as it clearly indicates that the presence of excessive steric bulk on the supporting ligand – a feature rendering batch synthesis often cumbersome – is not an impediment in this continuous flow synthesis. The advantages of flow in terms of mixing appear to overcome the hurdles created by NHC steric bulk observed in batch.

Considering the results obtained for the synthesis of complex **7**, we hypothesized that more elaborate architectures based on this core motif might be accessible in flow. We therefore expanded the scope to the synthesis of complex **8** (Scheme 3). β-carboline harmala alkaloids such as *harmine* (7-methoxy-1-methyl-9H-pyrido[3,4-b]indole) display activity as antituberculosis, analgesic and antimicrobial agents.[21] When bound to metal centers, their activity can be enhanced, as exemplified by the harmine-ligated platinum(II) and palladium(II) complexes that display antiproliferative properties.[22] Complexation to gold is particularly interesting given the historical significance of gold in the treatment of various afflictions.[23] Support by NHC ligands greatly increases stability and bioavailability of the active complexes, thus enhancing their therapeutic potential. Of note, the carbene framework is also essential for any potential photonic application of this carboline-derived CMA. While also being accessible in batch synthesis under our conditions (see the Supporting Information for details),[12] the continuous flow approach proved



Scheme 2. Scope of N-heterocyclic carbene ligands used in this study.



Scheme 3. Continuous flow synthesis of [Au(IPr)(Hrm)] (**8**) (Hrm = harmine).

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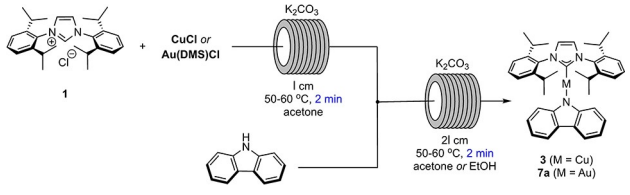
high yielding and expedient, successfully affording the product in short reaction times (Scheme 3).

A major advantage to the use of continuous flow synthesis is the potential to access desired compounds at significantly higher reaction rates compared to batch synthesis. This is clearly illustrated in the numerous examples presented above. Another important advantage, mainly in terms of time management, is provided by performing *one-pot* or *telescoping reactions*.[24] By simple adaptation of the flow setup, multiple reagent streams can be coupled in series. Therefore, multi-step procedures can be established by sequentially interconnecting reactor columns and by introducing new reagents at set intervals in the continuous flow sequence.[25] In addition, flow technology offers the opportunity to perform in-line purification, extending ever more the potential of the outlined technology.[26]

The one-pot reaction for the synthesis of [Cu(IPr)(Cbz)] (**3**) starting from IPr·HCl (**1**) and CuCl was attempted initially since reaction conditions established for both stages are very similar (acetone, 2 min residence time, 50 °C). A first reactor was used for the synthesis of [Cu(IPr)Cl] (**2**), which is in turn immediately fed into a second reactor with concomitant introduction of a carbazole solution (Scheme 4). Conditions of 50 °C and a residence time of 2 minutes for each of the two separate stages proved successful. The desired product was obtained cleanly in unprecedentedly short reaction times, without the need for wasteful intermediate purification steps. In comparison, reaction times of the corresponding batch process easily adds to 48 h.[12] The synthesis of [Au(IPr)(Cbz)] (**7 a**) from imidazolium salt **1** and [Au(DMS)Cl] (DMS = dimethyl sulfide) resulted in the desired complex as well, yet required a plug of silica to be added to the reactor column prior to the injection of the carbazole solution. The necessity for different solvents at the separate stages of the reaction presents no issues since the second reaction step is fully operational with one-to-one ethanol/acetone solvent mixtures. Again, marked improvements have been established when compared to the batch version of the syntheses.[12]

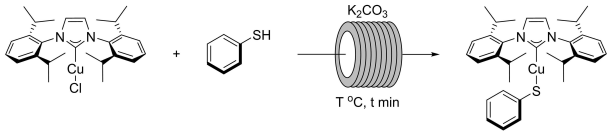
Synthesis of M-thiolato Complexes (M = Cu, Au)

Reactivity of thiols towards coordination with coinage metals is relatively high, as evidenced by the batch processes which only require half an hour in the case of copper.[11] As a consequence, a 2-minute residence time was selected as a reasonably short entry point for the continuous synthesis of [Cu(IPr)(SPh)] (**9**) from complex **2** and thiophenol (Entry 1, Table 4).



Scheme 4. One-pot continuous flow synthesis of [M(IPr)(Cbz)] (M = Cu and Au)

Table 4. Optimization of the continuous flow protocol for [Cu(IPr)(SPh)] (**9**).



2 **9**

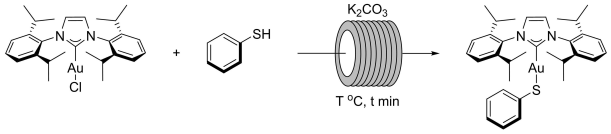
Entry[a]	T [°C]	Residence Time [min]	Conversion [%]	Isolated Yield [%]
1	60	2	100	89
2[b]	60	2	100	>99
3	60	1	100	98
4	30	2	100	94
5	30	1	100	95

[a] Conditions unless otherwise stated: [Cu(IPr)Cl] (48.7 mg, 0.10 mmol), thiophenol (1.1 equiv.), 5 mL of acetone. [b] Thiophenol (1.0 equiv.).

The residence time and reaction temperature could be greatly reduced while maintaining full conversion to the product (Entries 3–5). Adding stoichiometric amounts of thiophenol to the reagent mixture results in full conversion thus eliminating the need for additional workup to remove any additional/unreacted thiophenol (Entry 2, Table 4).

Encouraged by the exceptionally mild conditions established for complex **9**, we set out to explore the synthesis of gold(I)-thiolate complex (**10**) whose batch synthesis required 6 h.[10b] The observations made during the continuous synthesis parallel those obtained for the synthesis of complex **9**. Reduction of the residence time and temperature resulted in the formation of the desired product in high yields (Entries 1 and 3–5, Table 5). Adding equimolar amounts of thiophenol again resulted in full conversion to product (Entry 2, Table 5). This observation is in stark contrast to the batch procedure which requires 2-equivalent excess of thiophenol to reach full conversion.[10b] Synthesis on a 200 mg scale shows scalability while excellent yields remain (Entry 6, Table 5).

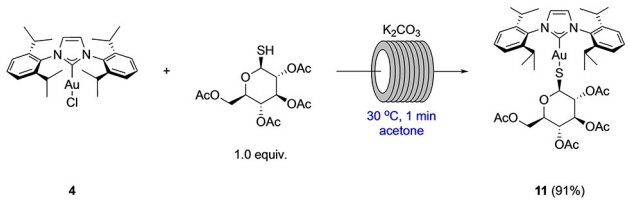
Table 5. Optimization of the continuous flow protocol for [Au(IPr)(SPh)] (**10**).



4 **10**

Entry[a]	T [°C]	Residence Time [min]	Conversion [%]	Isolated Yield [%]
1	60	2	100	95
2[b]	60	2	100	>99
3	60	1	100	97
4	30	2	100	92
5	30	1	100	94
6[b,c]	30	2	100	98

[a] Conditions unless otherwise stated: [Au(IPr)Cl] (37.3 mg, 0.06 mmol), thiophenol (1.1 equiv.), 6 mL of acetone. [b] Thiophenol (1.0 equiv.). [c] [Au(IPr)Cl] (200 mg).



Scheme 5. Continuous flow synthesis of [Au(IPr)(1-thio-β-D-glucose tetraacetate)] (**11**).

The results obtained during parameter optimization incited us to aim for the continuous flow synthesis of the biologically promising [Au(IPr)(1-thio-β-D-glucose tetraacetate)] complex **11**, an *auranofin*-analogue and member of the Au(I)-thiolate glycoconjugate complex family.[27] Batch conditions indicated that reaction times of only 1 h already sufficed to obtain complex **11** in high yields, yet elevated reaction temperatures are required to reach these yields. In line with results obtained for the set of benchmark reactions, complex **11** was readily synthesized under mild conditions and very short reaction times (Scheme 5).

Conclusion

In summary, we have developed a convenient continuous flow procedure for a set proof-of-concept syntheses of coinage metal amido and thiolato complexes. The approach was designed based on our current understanding of the reaction mechanism (**C**oncerted-**M**etallation-**D**eprotonation-like weak base involvement). The previous batch reaction studies along with the mechanism provided the inspiration for the selected process configuration. Via parameter optimization, we have demonstrated that very short reaction times and mild conditions can be readily employed to achieve high yields of product. The benchmark complexes synthesized can all be accessed under exceptionally short reaction times. This short reaction timeframe is showcased by the one-pot synthesis of complexes **3** and **7a**. Syntheses of therapeutically relevant complexes **8** and **11** indicate that more elaborate substrates are fully compatible with the developed protocol. Studies dealing with the implementation of the developed continuous flow approach to the synthesis of valuable complexes/catalysts and molecules are ongoing in our laboratories.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: carbene-metal-amide · continuous flow synthesis · metal-thiolate · N-heterocyclic carbenes · weak base route

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