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Continuous Flow Synthesis of [Au(NHC)(Aryl)] (NHC = N-Heterocyclic Carbene) Complexes

Thibault Cauwenbergh,[a] Nikolaos V. Tzouras,[a] Thomas Scattolin,[a] Subhrajyoti Bhandary,[a] Andreas Simoens,[b] Kristof Van Hecke,[a] Christian V. Stevens,*[b] and Steven P. Nolan*[a]

Abstract: The use of weak and inexpensive bases has recently opened promising perspectives towards the simpler and more sustainable synthesis of Au(I)-aryl complexes with valuable applications in catalysis, medicinal chemistry, and materials science. In recent years, continuous manufacturing has shown to be a reliable partner in establishing sustainable and controlled process scalability. Herein, the first continuous flow synthesis of a range of Au(I)-aryl starting from widely available boronic acids and various [Au(NHC)Cl] (NHC = N-heterocyclic carbene) complexes in unprecedentedly short reaction times and high yields is reported. Successful synthesis of previously non- or poorly accessible complexes exposed fascinating reactivity patterns. Via a gram-scale synthesis, convenient process scalability of the developed protocol was showcased.

Gold-aryl complexes occupy a prominent place in the panorama of organometallic compounds owing to their involvement in many gold-catalyzed reactions, both as efficient pre-catalysts as well as reactive intermediates.[1,2] In addition, various gold-aryl derivatives have found application in the fields of medicinal chemistry and materials science by virtue of their fascinating bioactive and photophysical properties.[3,4] In recent years, N-heterocyclic carbenes (NHCs) have emerged as powerful ancillary ligands in the stabilization of organometallic complexes and have thereby successfully secured their place among their illustrious phosphine counterparts. Their large structural diversity and rich coordination behavior to various transition and main group elements have made them important tools in organometallic chemistry.[5] Increased stability and ease of handling of the associated metal complexes have rendered them indispensable in modern organic synthesis.[6]

Simple synthetic access to gold-aryl complexes has long been hampered by the requirement for inert conditions, high temperatures, toxic solvents or multistep procedures alongside limited functional group tolerance.[4a,7] In a recent report, we have disclosed an operationally simple and mild procedure for the synthesis of various NHC- and phosphine-bearing Au(I)-aryl complexes.[8] This protocol revolves around the use of a weak base such as K_2CO_3 allowing for room temperature synthesis in air using green solvents (e.g. acetone, ethanol, ethyl acetate or water). The efficacy of this so-called *weak base route* has been demonstrated in the synthesis of various other valuable transition metal complexes as well.[5a,9]

Notwithstanding the many assets brought about by the weak base approach, reactivity issues remain the largest concern. Reaction times may easily amount up to 20 h while only substantial excesses of base allow for reaching full conversion to the product. As evidenced by recent reports on the synthesis of [Cu(NHC)Cl] and [Cu(IPr)(Cbz)] (Cbz = carbazolyl), mechano-chemistry might assist in lowering reaction times yet multiple equivalents of base are still required to reach full conversion.[9f,10]

Continuous flow synthesis is considered an attractive alternative to traditional batch synthesis, not in the least as it represents an ideal tool in the pursuit for more sustainable chemical processes.[11] Mainly as a direct consequence of small reactor dimensions, continuous manufacturing has much to offer. Efficient heat and mass transfer allow for reduced reaction times, enhanced product selectivity and a lowered energy demand.[12] Precise control over reaction parameters is enabled through simple reaction automation and in situ monitoring, all increasing product quality, ensuring greater operational safety, and a reduction in waste generation.[13]

We have recently developed an operationally simple and readily scalable continuous flow procedure for the preparation of NHC-supported copper, gold and palladium complexes from the imidazolium salt and appropriate metal source.[14] A solution of the corresponding *-ate* complex in technical grade acetone was hereto injected into a packed bed reactor charged with triturated K_2CO_3, yielding the desired product in no time. Fostered by these fascinating results, we were incited to extend this protocol to the synthesis of various other organometallic species. In the present work, we report the continuous flow synthesis of a range of gold(I)-aryl complexes, to further evaluate the efficacy of the developed setup (Scheme 1).

[a] T. Cauwenbergh, N. V. Tzouras, Dr. T. Scattolin, Dr. S. Bhandary, Prof. Dr. K. Van Hecke, Prof. Dr. S. P. Nolan
Department of Chemistry and Centre for Sustainable Chemistry
Ghent University
Krijgslaan 281, S3, 9000 Ghent (Belgium)
E-mail: steven.nolan@ugent.be

[b] A. Simoens, Prof. Dr. C. V. Stevens
Department of Green Chemistry and Technology Synthesis
Biosources and Bioorganic Chemistry (SynBioC) Research Group
Ghent University
Coupure Links 653, 9000 Ghent (Belgium)
E-mail: chris.stevens@ugent.be

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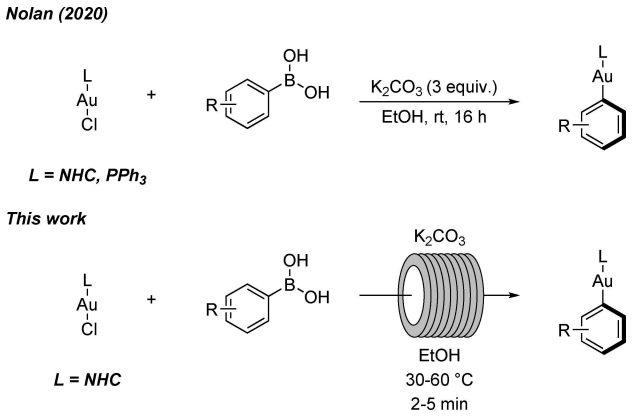


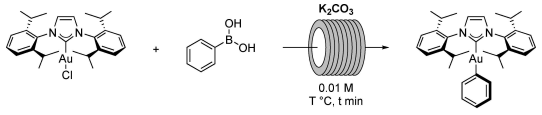
Scheme 1. Batch and reported continuous flow protocol for the synthesis of [Au(NHC)Ar] (Ar = aryl).

As a general proof-of-concept, the continuous transmetalation of [Au(IPr)Cl] (**1**) and phenylboronic acid was attempted. Reaction in acetone with a residence time of 5 minutes at 60 °C resulted in a low conversion to the product (Entry 1, Table 1). Changing the solvent to ethanol gave access to the desired product in a 100% conversion (Entry 2, Table 1). Even though ethanol is a greener alternative to acetone, there are several issues related to its use in the continuous flow synthesis protocol reported here. First, changing the solvent to ethanol entails a considerable increase in viscosity (1.095 cP as compared to 0.316 cP for acetone, measured at 300 K). For microreactors of any type, this implies a significant pressure buildup with all associated process-related consequences. These issues can partly be addressed by using more durable, yet also more expensive, equipment. Most importantly, the reported starting materials and products are only sparely soluble in ethanol. While being of no major concern to the batch process, suspensions are inherently incompatible with continuous flow technology, mainly due to the risk of reactor clogging. Besides these inconveniences – which are of mere practical nature – product might be retained on the packed bed column, which negatively affects reaction yields. One simple way to circumvent the latter is to increase the solubility by using a co-solvent. THF was chosen as the most suitable solvent for this purpose given the enhanced solubility of the studied complexes, as generally observed in batch. As exemplified by the synthesis of complex **3a**, results have however indicated that 2-MeTHF and acetone, generally considered as greener alternatives to THF, perform equally well (Entries 7 and 8, Table 2).[15] Parameter optimization for the synthesis of [Au(IPr)Ph] (**2**) showed that low temperatures (30 °C) or short residence times (2 minutes) can be established with preservation of high reaction yields (Entries 4–6, Table 1).

Batch conditions have revealed the propensity of some boronic acid reagents to undergo *protodeboronation*, referring to undesired protonolysis of organoborane compounds in the presence of a proton source.[16] Especially reactions performed at high temperatures in an acidic or alkaline medium prove problematic. In this context, boronate esters have shown to be less prone to protonolysis reactions and are therefore frequently applied in batch synthesis where long reaction times are typically required.[8a,17] For the synthesis in continuous flow, no notable signs of side-reactivity were observed, indicating that – even though the reagents are exposed to an extremely large base excess – the short residence times prove beneficial in suppressing protodeboronation. Nonetheless, the synthesis of [Au(IPr)Ph] was tested starting from the boronic acid pinacol ester (BPin) as a comparison to the reaction performed with the analogous boronic acid (Entries 2–3, Table 1). Reaction conditions of 5 minutes residence time at a temperature of 60 °C only resulted in a conversion of 43%. The lower reactivity of the associated pinacol boronate ester requires longer reaction times and higher temperatures. Faster reactions, milder conditions and a lower reagent cost all favor the boronic acid approach, a clear asset provided by continuous flow synthesis.

Encouraged by the results obtained for complex **2**, the focus was directed to the synthesis of the gold(I) complex **3a** bearing an electron-donating methoxy group in the *para* position, a valuable precursor in the synthesis of various active gold

Table 1. Optimization of the continuous flow protocol.

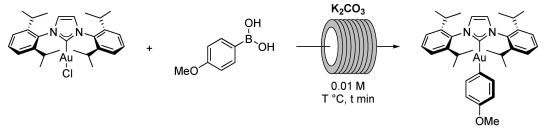


1 2

Entry[a]	Solvent	T [°C]	Residence Time [min]	Conversion [%]	Isolated Yield [%]
1	Acetone	60	5	18	–[b]
2	EtOH	60	5	100	95
3[c]	EtOH	60	5	43	–[b]
4	EtOH	30	5	100	86
5	EtOH	50	2	100	96
6	EtOH	40	2	45	–[b]

[a] Conditions unless otherwise stated: [Au(IPr)Cl] (31 mg, 0.05 mmol), Phenylboronic acid (1.1 equiv.), 5 mL of solvent (1:1 EtOH/THF). [b] Incomplete conversion. [c] From the corresponding pinacol acid boronic ester.

Table 2. Optimization of the continuous flow protocol.



1 3a

Entry[a]	Co-solvent[b]	T [°C]	Residence Time [min]	Conversion [%]	Isolated yield [%]
1	THF	60	5	100	77
2	THF	60	2	100	79
3[c]	THF	60	2	100	82
4	THF	45	2	100	89
5	THF	30	5	100	77
6	THF	30	2	65	–[d]
7	2-MeTHF	60	2	100	88
8	Acetone	60	2	100	90

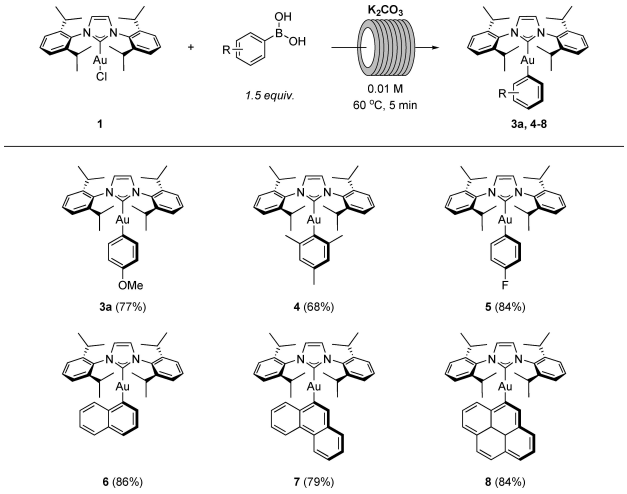
[a] Conditions unless otherwise stated: [Au(IPr)Cl] (31 mg, 0.05 mmol), 4-methoxyphenylboronic acid (1.1 equiv.), 5 mL of solvent. [b] EtOH (eluent). [c] 4-methoxyphenylboronic acid (1.0 equiv.). [d] Incomplete conversion.

complexes.[8a,18] The established conditions allowed access to the product in full conversion, except for the mildest reaction conditions of 2 minutes residence time at 30 °C (Entry 6, Table 2). In contrast with the established batch conditions, adding an equimolar amount of 4-methoxyphenyl boronic acid still resulted in full conversion to the desired product (Entry 3, Table 2). Next, a gram synthesis of complex **3 a** was performed to assess the scalability of the reported continuous flow setup. Over the course of 2 h, 1.075 g of product was obtained in a near quantitative yield (96 %), indicating that continuous flow synthesis can easily rival the batch process. Even though the latter allows for the synthesis of larger amounts of product at once, reaction times are significantly longer as compared to the reported continuous flow process.[8a]

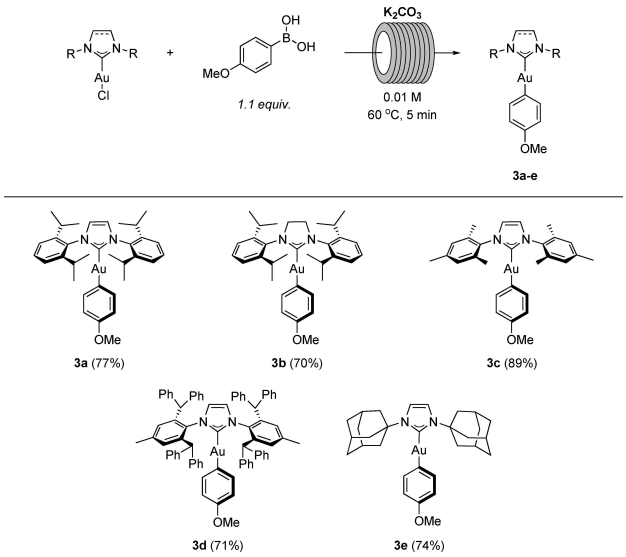
To explore the versatility of the continuous flow setup in synthesizing gold(I)-aryl complexes, the boronic acid scope was further expanded (Scheme 2). Sterically demanding boronic acids gave clean access to the desired complex under the established conditions (**4**). Electron-deficient boronic acids have shown to be compatible as well (**5**). Complex **5** could both be accessed through reaction with the boronic acid as the boronic acid neopentyl glycol ester in comparable yields, under the same set of reaction conditions. Additionally, a series of polyaromatic hydrocarbon (PAH) ligated complexes has been synthesized (**6** to **8**). Due to the presence of extended π-conjugation, these complexes are photochemically active – or are expected to be – and are therefore valuable in the field of OLED technology.[5b–d,19]

The compatibility of a series of supporting NHC ligands was assessed in a next stage (Scheme 3). Complex **3 b** bearing a carbene ligand with a saturated backbone was obtained in a 70 % yield. Other complexes bearing aromatic NHCs with distinctly different steric surroundings were cleanly obtained under the established reaction conditions (**3 c** and **3 d**). As a last example, complex **3 e** stabilized by the electron rich *N*-adamantyl-substituted NHC was obtained in appreciable yields.

Complex **3 d** bearing the highly sterically encumbered IPr* (*N*,*N*′-bis-[2,6-bis(diphenylmethyl)-4-methylphenyl]imidazol-2-ylidene) was synthesized for the first time and its X-ray molecular structure is depicted in Figure 1. Its synthesis has already been attempted using the weak base route under traditional batch conditions, yet we could only obtain maximal conversions of 90 %. When compared to related complexes reported in the literature, complex **3 d** has a C_{NHC}-Au bond length which is on average smaller while the Au-C_{Ar} bond length is elongated.[8a] The bond angle about the gold center is comparable to the one reported for [Au(IAd)(C_6H_5)] which is slightly larger than is the case for complexes such as [Au(IPr^{Cl})(C_7H_7O)] or [Au(I^tBu)(C_7H_7O)].



Scheme 2. Scope of boronic acid reagents used in this study.



Scheme 3. Scope of N-heterocyclic carbene ligands used in this study.

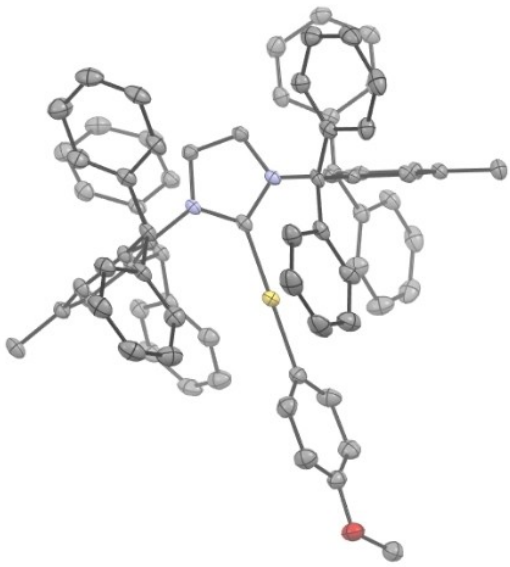


Figure 1. X-ray molecular structure of [Au(IPr*)(C_7H_7O)] (**3 d**) showing thermal displacement ellipsoids at the 50 % probability level, hydrogen atoms omitted for clarity (C_{NHC}-Au = 2.026(3) Å, Au-C_{Ar} = 2.052(3) Å, C_{NHC}-Au-C_{Ar} = 178.73(1)°) CCDC: 2093663.[20]

In conclusion, we have developed an operationally simple procedure for synthesizing Au(I)-aryl complexes in continuous flow. Parameter optimization for the synthesis of complexes **2** and **3a** indicated that very short residence times and low reaction temperatures suffice to reach full conversion to the product. Therefore, the targeted Au(I)-aryl complexes can be accessed in unprecedentedly mild conditions, which was showcased in the large-scale preparation of complex **3a**. Through variation in the nature of the supporting NHC ligand and the boronic acid substrate, we demonstrated the versatility of the outlined procedure. Studies regarding the implementation of the developed continuous flow setup in the synthesis of other valuable complexes are ongoing in our laboratories.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: continuous-flow synthesis · gold(I)-aryl · N-heterocyclic carbenes · sustainability · weak-base routes

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[20] Deposition Number 2093663 (**3d**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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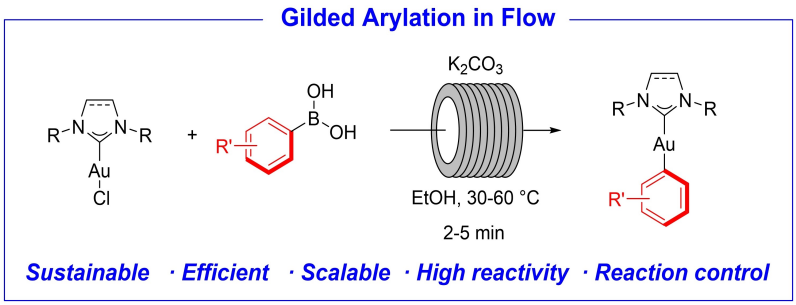

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The continuous synthesis of a range of gold(I)-aryl complexes is reported for the first time. The recently showcased weak base route is successfully implemented into an operationally simple and readily scalable continuous flow procedure. The reported protocol allows for high reaction rates and mild reaction conditions, all in favor of more efficient and sustainable access to products which are valuable in catalysis, materials science and medicinal chemistry.