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# In Situ Brønsted Acid Activated Cyclometalated N-Heterocyclic Carbene-Au(III)-Sulfonamide Complexes as Precatalysts for Alkyne Activation in Benzofuran Synthesis

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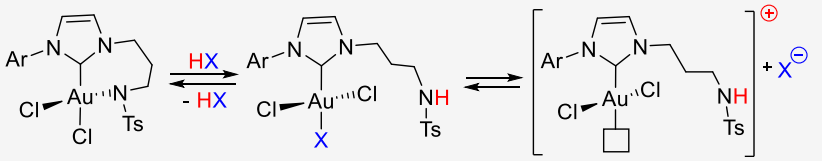


**ABSTRACT:** Cyclometalated N-heterocyclic carbene (NHC)-NTs-$AuCl_2$ complexes of type [(NHC)Au(N)$Cl_2$] are presented as a stable precatalyst, easily activated in situ by an acid (HX) for cationic [(NHC)$AuCl_2$]X catalysis. The "ethyl-and propyl-tosylamide arm" tethered NHC-Au(III)$Cl_3$ complexes can be smoothly converted to cyclometalated (-HCl) analogues by $K_2CO_3$ treatment, and, via the addition of a stoichiometric amount of Brønsted acid (HX), can be further converted to [NHC-Au(III)$Cl_2$]X carrying various counteranions (X = $CCl_3CO_2^-$, $CF_3CO_2^-$, $MsO^-$, $TsO^-$, $BF_4^-$, $TfO^-$, and $Tf_2N^-$). We studied this concept in catalysis using the cycloisomerization of 2-alkynylphenol to benzofurans as a probe reaction. Excellent yields were obtained in 2 h with an equimolar 1 mol % loading of the Mes-NHC-propyl-NTs-$AuCl_2$ precatalyst and MsOH as the acid additive under ambient conditions in $CHCl_3$. The single crystal structure for a cyclometalated NHCAu(III)-complex was characterized by X-ray analysis. $^1$H NMR monitoring of reaction kinetics suggests that the in situ formed Au(III) complex is the catalytically active species.

## INTRODUCTION

Homogeneous gold catalysts have become a valuable tool in modern organic synthesis due to their ability to selectively activate $\pi$-bonds as electrophiles under mild conditions.[1] In the early days of homogeneous gold catalysis, ligand-free Au(III) halide salts dominated the field, overshadowing air-sensitive Au(I) salts in similar transformations,[2] and in some cases, different oxidation states of the metal can promote divergent reaction pathways.[3] However, with the development of phosphine and N-heterocyclic carbene (NHC) ligands,[4] [LAu(I)Cl] complexes reached supremacy as precatalysts as they allow the exploitation of the soft alkynophilic $\pi$-acid properties of Au(I) with improved stability, activity, and selectivity. The active cationic species $[LAu(I)]^+$ are typically prepared by exchanging the tightly coordinated chlorine anion to weakly or noncoordinative counterions by metathesis with silver salts. This anion exchange, however, does not only constitute an additional cost, but the silver residues may also contribute to the catalytic activity.[5] Additionally, the counterion itself can have an impact on catalysis.[6] At the dawn of gold catalysis, the use of Brønsted acid to produce cationic gold species has made it possible to avoid these complications. In the pioneering work by Teles et al., $Ph_3PAuMe$ was activated for alkyne hydroalkoxylation with 10 equiv of MsOH.[7] Although the use of large excess of acid is still common, the loading can be lowered by using a stronger Brønsted acid, or imidogold precatalysts, which are also easier to synthesize as they do not require the employment of moisture-sensitive Grignard-reagents.[8] An even more facile strategy makes use of LAuCl compounds as precatalysts, but in this case, a strong acid such as TfOH is required, which decreases the practicality of the method by making it incompatible with acid labile substrates.[9]

Despite several reported protocols for the synthesis of phosphine[10] and NHC-Au(III) complexes,[11] their catalytic application has been dominated by their Au(I) counterparts. Due to the facile reduction of Au(III) to Au(I), the investigation of the active species and reaction pathways is an important aspect in modern Au(III) research.[12] As a pioneering example of liganded gold(III) application in catalysis, Cinellu and co-workers activated a *N*-(2-hydroxyethyl)picolinamide [Au(N,*N*′,O)$Cl_2$] complex for styrene polymerization by alkoxo group displacement with a strong acid ($HBF_4$ and HOTf).[13] In the past decade, an effective method for the displacement of chloride anions from LAu(III)$Cl_3$ complexes has been the use of functionalized coordinative NHC ligands, which take advantage of the square-

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planar geometry of the Au(III) center (Figure 1). We and others have established that this approach is viable for pyridine

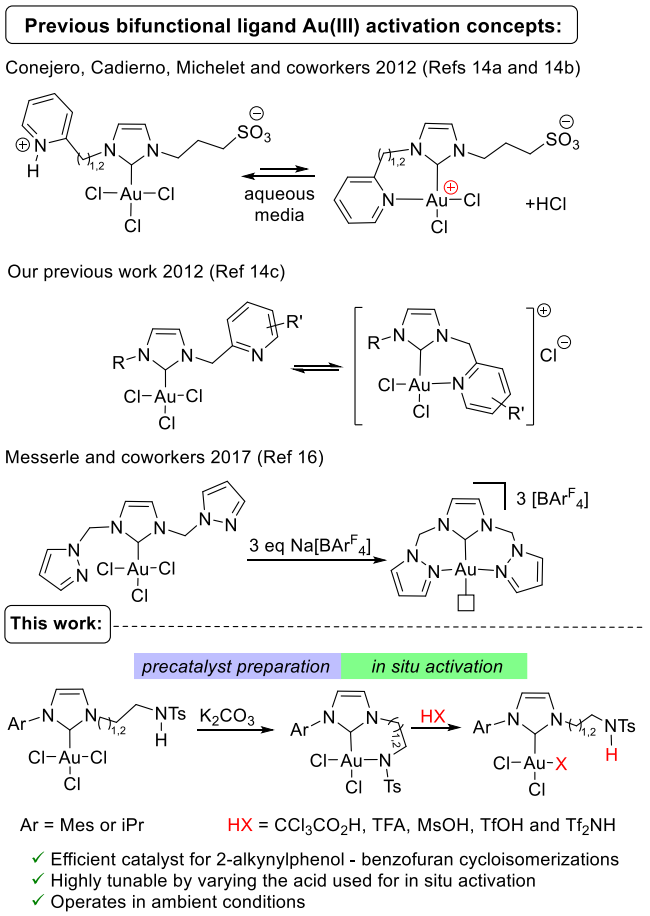



**Figure 1.** Silver-free activation concepts for Au(III) complexes.

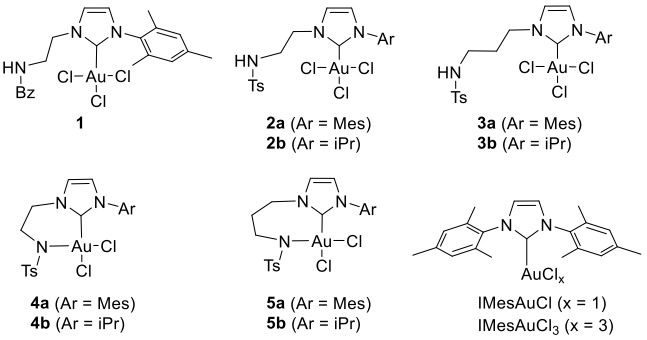
functionalized NHC Au(III)Cl$_3$ ligands (Figure 1).[14] Undeniably, the advantages of NHCAu(III) are less apparent if the cationic gold is formed by using the same additives that are commonly employed in Au(I) chemistry, such as silver salts or NaBAr$_4^F$.[11b,15] However, Messerle's group successfully combined the counteranion exchange to the square-planar geometry of Au(III) with NHC ligands carrying hemilabile ancillary coordinative moieties, which bring stability and efficiency to Au(III) catalysis (Figure 1).[16] Even though these complex and expensive additives can be very effective, Brønsted acids are overlooked as an activation method for Au(III) catalysis and thus worth studying due to their availability and versatility.

We reported previously that [NHC-Au(I)-Cl] complexes with amide functionalized side-arms can catalyze the cycloisomerization of hydrogen-bond-donating *N*-propargylamides to oxazolines without additives or the exchange of a tightly coordinative [Cl$^-$] counterion to a less coordinative one.[17] However, for enyne substrates, in the absence of a H bond donor, an acid additive (CCl$_3$CO$_2$H, TFA, MsOH, or TsOH) was needed to promote the reaction. Combining this with our earlier Au(III) research efforts motivated us to examine the acid activation of amide arm-tethered NHC-Au(III) complexes and to develop this concept further. Additionally, the concept of the silver-free acid promoted phthalimide (Pht) imidogold precatalyst (LAu(I)-Pht + A$^+$B$^-$ ↔ LAu(I)$^+$B$^-$ + Pht-A) introduced by Hammond et al.[8a] inspired us to develop an analogous system relying on the acid activation of the intramolecular amide-Au(III) bond. Here, we present a set of sulfonamide functionalized NHC-Au(III) complexes that can be readily cyclized into stable cyclometalated species by an inexpensive base treatment and activated for catalysis by using a single equivalent of Brønsted acid.

## RESULTS AND DISCUSSION

We synthesized a series of different NHC-Au complexes by varying the "side arm" length and the aryl group attached to the carbene ring (Scheme 1) by employing a silver-free, mild

**Scheme 1. Synthesized NHC-Au(III) Complexes**




base route developed and reported independently by Gimeno et al.[18] and Nolan et al.,[19] followed by PhICl$_2$ oxidation. The complexes were isolated as white solids, and we were able to confirm the structure of benzoyl-functionalized complex **1** by single crystal X-ray diffraction (Figure 2). The obtained white

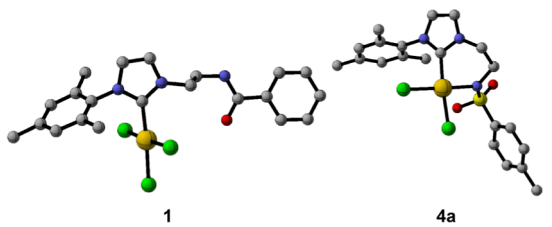



**Figure 2.** Molecular structures of **1** and **4a** in the crystal.

solid Au(III) complexes were dissolved in dichloromethane (DCM) and stirred with K$_2$CO$_3$ to close the amide-metallacycle by eliminating one molecule of HCl, and the new cyclometalated complexes were isolated by flash chromatography as bright yellow solids (**2a-5b**). The more rigid 6-member ring in **4a** allowed the isolation of a single crystal, which was analyzed using X-ray diffraction (Figure 2). Interestingly, the N−Au distance of 2.033(2) Å observed for **4a** (see the Supporting Information) is slightly shorter than the one reported for the Au−N coordination bond of pyridine in an analogous metallacycle complex (2.053(4) Å).[14b] The NMR analysis of **5a** evidenced its higher flexibility as the $^1$H spectrum consisted of multiple broad signals at room temperature, which merged into sharper signals at higher temperatures (see the Supporting Information). All new cyclometalated compounds were bench-stable solids, and the NMR samples in DMSO-$d_6$ stayed unchanged for weeks even after the heating. However, to our dissatisfaction, complex **1** did not cyclize with the K$_2$CO$_3$ treatment and remained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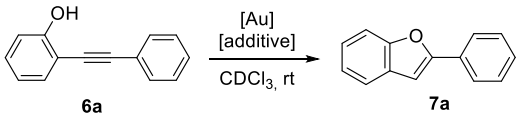
unreactive at elevated temperatures, even in the presence of a stronger base such as sodium hydride.

The catalytic activity of the synthesized gold complexes was tested using 2-(phenylethynyl)phenol **6a** cycloisomerization to 2-phenyl benzofuran **7a** as a probe reaction (Table 1). The

**Table 1. Screening of Catalysts for Benzofuran Synthesis**




**6a** **7a**

| entry | [Au] | additive | [Au] and additive (mol %) | yield (%)[a] after | |
|---|---|---|---|---|---|
| | | | | 0.5 h | 1.0 h |
| 1 | | MsOH | 2 | 0 | |
| 2 | IMesAuCl | MsOH | 2 | 14 | 15 |
| 3 | $IMesAuCl_3$ | MsOH | 2 | 0 | 0 |
| 4 | **3a** | | 2 | 0 | 0 |
| 5 | **3a** | MsOH | 2 | 0 | 0 |
| 6 | **5a** | | 2 | 0 | 0 |
| 7 | **5a** | MsOH | 2 | 99 | |
| 8[b] | **5a** | MsOH | 1 | 49 | 88 |
| 9 | **5a** | MsOH[c] | 1 | 98 | |
| 10 | **4a** | MsOH | 1 | 34 | 64 |
| 11 | **4b** | MsOH | 1 | 36 | 65 |
| 12 | **5b** | MsOH | 1 | 47 | 87 |
| 13 | IMesAuCl | AgOMs | 1 | >99 | |
| 14 | $IMesAuCl_3$ | AgOMs | 2 | 54 | 99 |
| 15 | **5a** | AgOMs | 2 | 5 | 18 |
| 16 | **3a** | AgOMs | 2 | 10 | 19 |

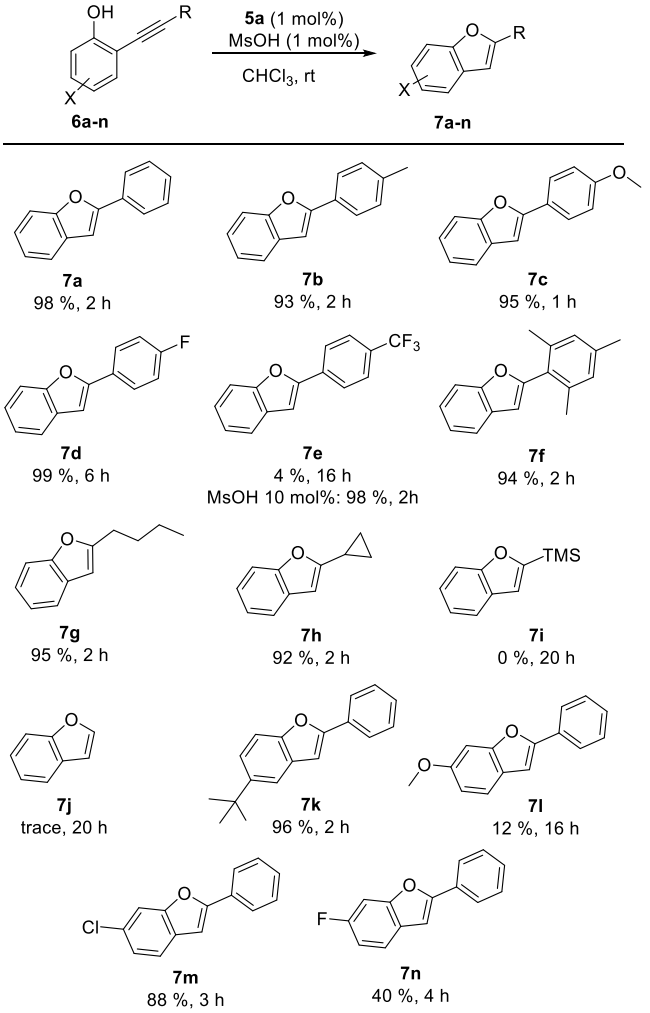
[a]Determined by $^1H$ NMR using 1,3,5-trimethoxybenzene as an internal standard [b]99% after 2 h. [c]2 mol % of MsOH.

interest in benzofurans stems from their well-known antitumoral, antibacterial, antioxidative, and antiviral activities.[20] Their cycloisomerization, as well as other alkyne hydroalkoxylation reactions, has been studied with several transition metal compounds; however, it often relies on the use of a high loading of rare metal catalysts,[21] elevated temperatures,[22] and long reaction times.[23] Few reported examples of this reaction with gold catalysis exist, the first being a work by Belting and Krause in 2006 employing $HAuCl_4$ as a catalyst.[24] Different Au(I) complexes requiring a halide scavenger have been utilized,[25] but to the best of our knowledge, no examples of NHC-Au(III) catalyzed benzofuran synthesis have been reported so far.

Screening of acid additives (Table S1) revealed that the key to promoting catalytic activity is using strong Brønsted acids with counteranions having low affinity toward the gold center. After 1 h of reaction time, some conversion of **6a** to **7a** was observed with $Cl_3CO_2H$ (33% yield), but the best results were obtained with TfOH and $HNTf_2$, with 99 and 95% yields, respectively. Solvent screening (Table S2) revealed chlorinated solvents to be the best environment for this catalytic system, with toluene being a viable alternative despite some solubility issues. Also, an excess of MsOH (entry 9, Table 1) to [Au] is beneficial as the probable rate limiting step in the intramolecular cyclization is protodeauration.

Initially optimized conditions, with MsOH as an acid additive in equal amounts with **5a** and $CHCl_3$ as a solvent, were used for the scope study (Scheme 2). Despite being a weaker acid, it still offered prompt reactivity, likely due to a

**Scheme 2. Benzofuran Synthesis by 2-Alkynylphenol Cycloisomerization with Isolated Yields**




combination of its loose coordination to Au(III) while also being able to strengthen the phenol nucleophilicity as a H bond acceptor.[26]

Excellent yields were achieved with electroneutral ethynyl 2-aryl and alkyl substituents in 2 h (**7a, b, f-h**). A 4-methoxy substituent on the phenyl ring enhanced the reaction rate, and 95% yield was reached in an hour (**7c**). In contrast, electron-withdrawing aryl substituents slowed down the reaction notably: 4-fluorine substituted phenyl product **7d** was obtained in high yield, but the reaction required 7 h, whereas the more electron-withdrawing 4-trifluoromethyl phenyl functionalized 2-ethynylhenol **6e** gave only a negligible yield of 4% after 16 h (**7e**). Yet, this product could be isolated in an excellent yield using a higher loading of acid (10 mol %).

Under the standard conditions, trimethylsilyl functionalized alkyne **6i** stayed unreactive, and no signs of the desired product **7i** were detected. The attempt to obtain a benzofuran using a terminal alkyne was unsuccessful, yielding only a trace of the desired product **7j** in an uncharacterized reaction mixture. In this case, increasing the MsOH loading led to the hydration of the terminal alkyne.

The effect of a substituent at the phenol ring was also explored. A weakly electron-donating *tert*-butyl group at the 4-position of the phenol had no effect, and an excelled yield of **7k** could be isolated. Strong electron-donating groups like



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OMe at the phenol 6-position led to the formation of a complex mixture after 16 h, but when the starting material was consumed, only 12% of the desired product was obtained (**7l**). Electron withdrawing groups at the same position did not have such a dramatic effect but slowed down the reaction notably: chlorine at 6-position (**6m**) led to a good yield of 88% in 3 h (**7m**), whereas the reaction with fluorine substituted phenol (**6n**) stopped completely after 4 h, reaching only a 40% isolated yield (**7n**).

Beyond the benzofuran synthesis, preliminary screening of catalytic activity reveals (Supporting Information) that **5a** + MsOH is able to promote encouragingly, e.g., the lactonization of 4-hexynoic acid.

The oxidation state of gold nuclei is of special interest for the studied catalytic system. It is known that some [(NHC)-Au(III)$X_3$] species can be in an equilibrium with their [(NHC)Au(I)X] + $X_2$ [X= (pseudo)halogen][27] counterparts, and thus, hypothetically, the Au(III) species could act solely as a precatalyst.[28] To follow more closely the species evolution during the course of the catalytic process, we performed the reaction in an NMR tube and monitored it with $^1$H NMR spectroscopy. We were pleased to observe that the reaction is initiated without any induction period that could imply the formation of a new catalytic species in situ (Figure 3) as after it

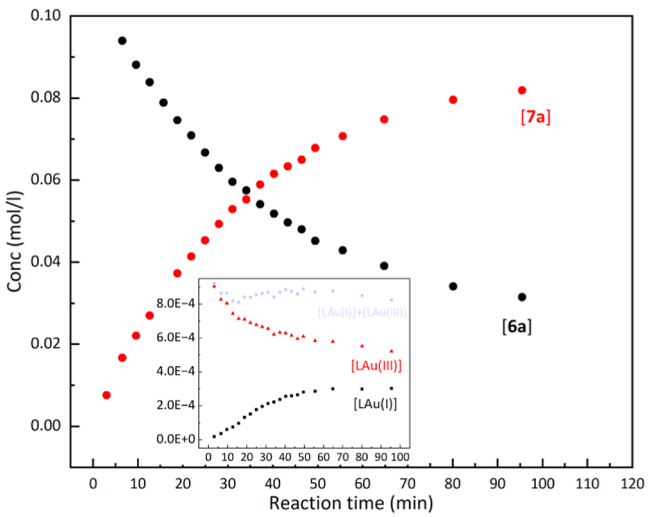


**Figure 3.** Monitoring of the **5a** + MsOH catalyzed conversion of **6a** to **7a**. The inset shows partial degradation of LAu(III) to LAu(I) (Supporting Information).

starts, the reaction proceeds smoothly, with the rate decelerating steadily toward the end as the starting material is progressively consumed. A closer look at the LAu species reveals a partial reduction of LAu(III) to LAu(I) (Figure 3). However, it is rather unlikely that the formed Au(I) degradation species would have a positive effect on the observed catalytic activity as it is probably $Cl^-$ coordinated after the reductive inner sphere elimination of $Cl^-$ and the activated substrate. Labinger, Bercaw, and co-workers have reported this type of mechanistic event for NHCAu(III) complexes, where $I^-$ and Me are eliminated as MeI.[29]

To get theoretical insights into the counteranion equilibrium of the studied complexes, we computed their thermodynamic stabilities with density functional theory (DFT_ [PW6B95D3/def2tzvp/CPCM(DCM)//TPSS/def2svp/CPCM(DCM)]. The summarized results in Figure 4 display the comparison

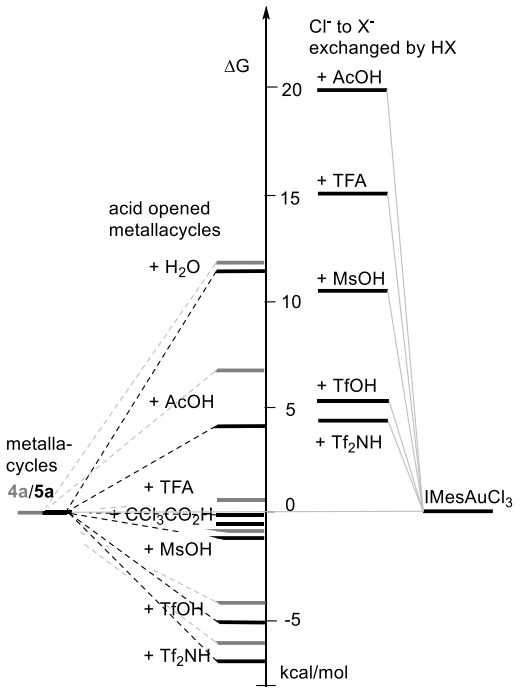


**Figure 4.** DFT calculated equilibrium energetics ($\Delta G$) for metallacycle (**4a**/**5a**) opening with acids vs acid equilibrated counterion exchange between $IMesAuCl_3$ and $IMesAuCl_2X$ (Supporting Information). The $\Delta G$ levels of opened **4a**/**5a** are illustrated with gray and black bars, respectively.

between acid promoted opening cyclometalated complexes **4a** and **5a** and the corresponding energetics of the acid equilibrated counterion exchange of the $IMesAuCl_3$ complex (detailed information in Table S3). The graph reveals the exergonic reactivity of cyclometalated complexes with acids: $CCl_3CO_2H$, MsOH, TfOH, and $Tf_2NH$, while the corresponding equilibriums of $IMesAuCl_3$ are endergonic. For the counteranion exchange/installation, the energy advantage for the cyclometalated complex is ca. 12−15 kcal/mol. The comparison between the cyclometalated complexes reveals that the 7-membered metallacycle of **5a** exhibits a somewhat higher ring distortion energy than **4a**. A more prominent effect arises from the amide hydrogen−counterion hydrogen bonds in the opened complexes, which is noticeable when the counterion is a good H bond acceptor. This is an obvious factor to consider when explaining the larger $\Delta G$ difference between opened amides of **4a** and **5a** with $^-$OAc as a counterion, where the carbonyl oxygen acts as a H bond acceptor, compared to the same species when −OH is the counterion as it does not form H bonds with either complex.

In conclusion, we have demonstrated that NHC-Au(III) complexes equipped with a sulfonamide side arm offer an efficient precatalyst platform, which can be easily converted by $K_2CO_3$ treatment to cyclometalated complexes, easily turned in situ to active catalysts with a variety of Brønsted acids. An equimolar 1 mol % loading of **5a** and MsOH was efficient in catalyzing the synthesis of many benzofurans from 2-alkynylphenols with excellent yields in a few hours at room temperature. Some reduction of the gold center was detected during the reaction, but the initial catalytic Au(III) species remained the dominant active catalyst during the course of the reaction. The successful catalysis based on the square planar geometry of the cyclometalated Au(III) complexes offers an


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interesting approach for alkyne activation, which is more demanding to replicate with Au(I) complexes due to their linear geometry, which will be explored further in future studies. The unveiled catalytic properties suggest that more profound investigations should be carried out to develop the ancillary arm concept further to harvest the full potential of [LAu(III)] complex catalysis, e.g., in asymmetric catalysis.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.organomet.3c00520.

Experimental procedures, computational details, and Cartesian coordinates of DFT optimized structures (XYZ)

XRD structures and copies of $^{1}H/^{13}C$ NMR spectra (PDF)

### Accession Codes

CCDC 2090764−2090765 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest.

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