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Gold(I)-*N*-Heterocyclic Carbene Synthons in Organometallic Synthesis

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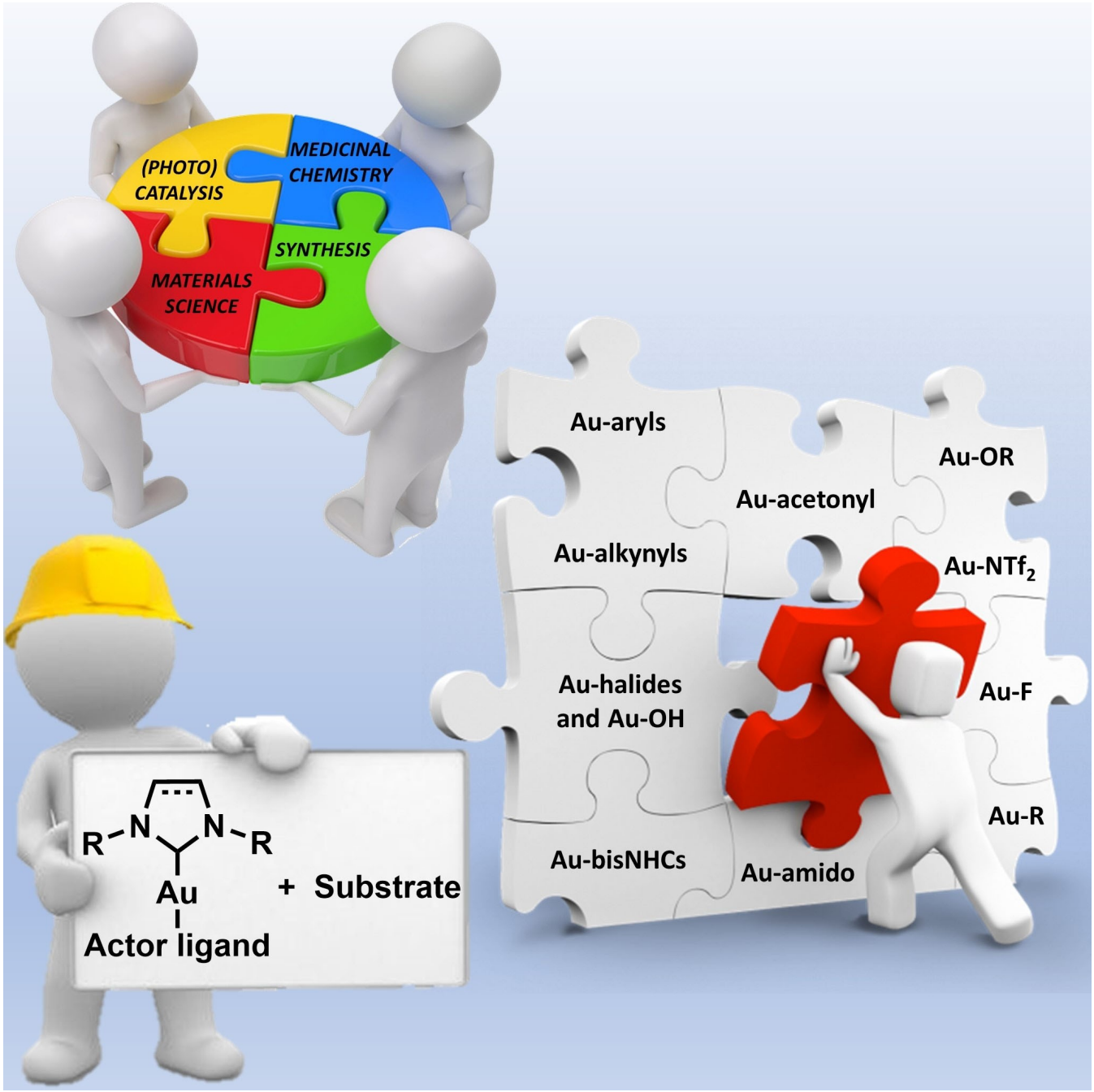

The prominent role of gold-*N*-heterocyclic carbene (NHC) complexes in numerous research areas such as homogeneous (photo)catalysis, medicinal chemistry and materials science has prompted organometallic chemists to design gold-based synthons that permit access to target complexes through simple synthetic steps under mild conditions. In this review, the main gold-NHC synthons employed in organometallic synthesis are discussed. Mechanistic aspects involved in their synthesis and reactivity as well as applications of gold-NHC synthons as efficient pre-catalysts, antitumor agents and/or photo-emissive materials are presented.

1. Introduction

Gold complexes represent an indispensable resource for organometallic chemists of the 21st century. These compounds have permitted the development of new organic reactions, which have proven to be extremely useful for the production of fine chemicals, especially in the pharmaceutical sciences.[1] Moreover, many gold complexes have shown fascinating applications in materials science and medicinal chemistry.[2] The role of ancillary ligands, such as *N*-heterocyclic carbenes (NHCs) and tertiary phosphines, has been of paramount importance in accelerating advances and breakthroughs in these fields. In fact, the choice of the ancillary ligand is crucial in modulating the reactivity and application-range of the complexes of interest.

N-heterocyclic carbenes are some of the most explored ancillary ligands in gold chemistry, since the strength of the gold-NHC bond ensures high stability both in the solid state and in solution, even under physiological conditions.[3] For this reason, *N*-heterocyclic carbenes are also widely used with other transition metals with the aim of developing efficient (photo)catalysts[4] and materials[5] (e.g., OLEDs) as well as new generations of anticancer,[6] antimicrobial[7] and antiviral drugs.[8] Although numerous reviews have summarized the use of gold-NHC complexes in these applications, much less attention has been devoted to the use of gold-NHC complexes as valuable precursors in organometallic syntheses. Many research groups have synthesized gold-NHC complexes which have proven to be particularly reactive towards specific organic and organometallic compounds, providing simple and straightforward synthetic entryways to unprecedented classes of gold complexes with promising biological, catalytic and/or photoemissive properties.

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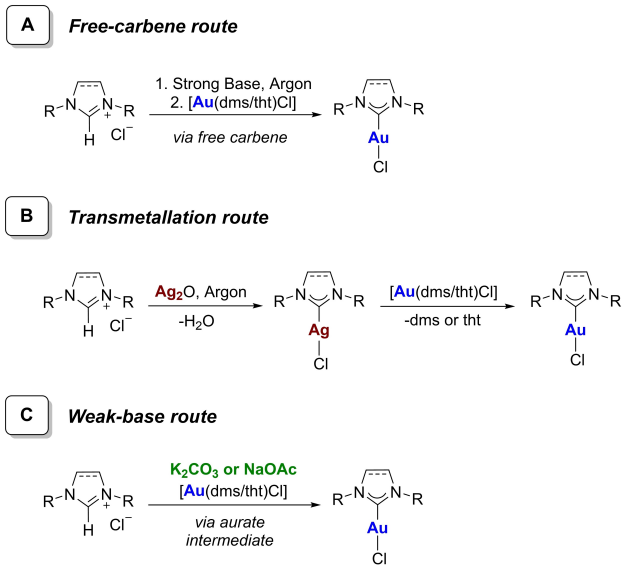
In this review, we will provide an overview of the principle "golden synthons" developed over recent years, with a special focus on mononuclear gold(I) complexes bearing *N*-heterocyclic carbenes. For each class of complexes, their preparation, their reactivity towards substrates and their main applications will be examined.

2. [Au(NHC)X] complexes (X = halide)

NHC-Gold-halides, especially the chloride derivatives, are undoubtedly the most used gold complexes in organometallic synthesis. These compounds can be obtained mainly via three different synthetic strategies: *i)* the free-carbene route; *ii)* the transmetallation route and *iii)* the weak-base route. In the first case, the free carbene is generated *in situ* from the corresponding azolium salt in the presence of a strong base (e.g., KO^{t}Bu, NaH, KHMDS, etc.) and subsequently reacted with [Au(dms/tht)Cl] (dms = dimethylsulfide, tht = tetrahydrothiophene, see Scheme 1A).[9] The transmetallation route consists of synthesizing copper-NHC or silver-NHC precursors of the [M(NHC)X] (M=Cu, Ag) type by reaction between the azolium salt and Cu_2O or Ag_2O, and using these carbene complexes as NHC transfer agents, thus installing NHCs on the metal centre of interest (Scheme 1B).[10] Both of these synthetic routes are disadvantageous from an atom-economy perspective, suffer from incompatibility with functional groups present in some azolium salts, and usually



Scheme 1. Synthetic routes to [Au(NHC)Cl] complexes.

require the use of toxic solvents. During the last decade, it has been shown that such valuable "golden synthons" can be obtained by direct reaction between an azolium salt and [Au(dms/tht)Cl] in the presence of weak and inexpensive bases (e.g., potassium carbonate or sodium acetate) by operating under mild and aerobic conditions with non-anhydrous green solvents (e.g., acetone).[11] This synthetic strategy, known as the *weak-base route*, has also been extensively applied to other metal centres even on a large scale and in continuous flow (Scheme 1C).[12]

The pivotal role of the base, the reaction mechanism, and the wide scope of NHC ligands have been studied in detail by Nolan and co-workers among others, making such gold-NHC complexes accessible to a broad audience, expanding their applications in different areas of research and consolidating their role as the foundations of organogold synthesis. The chloride ligand present on gold can be easily replaced by other halides (*halogen metathesis*, see Scheme 2A)[13] as well as by a wide range of organic and inorganic ligands as will be discussed in the following sections. Emphasis will be placed on how the properties of the final complexes and their applications strongly depend on the nature of the "actor" ligand. Moreover, [Au(NHC)(X)] (X = halide) complexes can be oxidized to gold(III) complexes using halogens or highly reactive organic compounds such as diazonium salts (Scheme 2B).[14] Some of these gold(III)-NHC derivatives have

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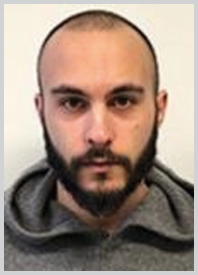
Sébastien G. Guillet obtained his combined master from Sorbonne Université and Ecole Supérieure de Physique et Chimie Industrielle (ESPCI) de la ville de Paris in 2019 after carrying research projects in Jannssen Pharmaceutica and with Prof. L. Fensterbank at the Institut Parisien de Chimie Moléculaire. He is now completing his PhD under the supervision of Prof. Steven P. Nolan at Ghent University where his research is focused on the synthesis and catalytic uses of transition metal NHC complexes.

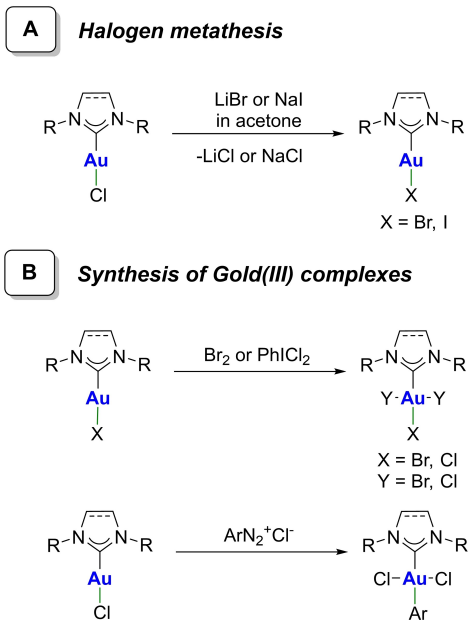


Nikolaos V. Tzouras carried out his diploma thesis research at the university of Athens, on the synthesis of N-Heterocyclic carbene precursors. After obtaining a scholarship for graduate studies in organic synthesis, he carried out his MSc research on sustainable metal-catalyzed C–H activation and multicomponent reactions. Following the completion of a Joint PhD (Ghent University and University of Athens) on innovative concepts in catalysis with Georgios C. Vougioukalakis and Steven P. Nolan as an FWO fellow, he is currently pursuing further research opportunities, focusing on organometallic chemistry and catalysis.

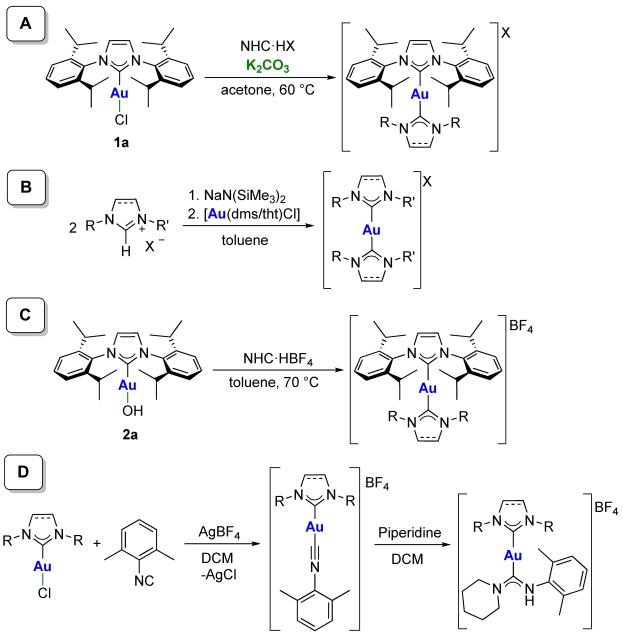
Thomas Scattolin completed his PhD in Chemistry in 2019 under the supervision of Prof. Fabiano Visentin at University of Trieste. In 2019 he was a visiting scientist in the laboratories of Prof. Antonio Togni at the ETH in Zurich. In 2020, he joined the group of Prof. Steven P. Nolan at Ghent University as a postdoc researcher. Since 2022, he is assistant professor (RTDA) in Inorganic Chemistry at the University of Padova. His research activity primarily focuses on the synthesis and reactivity of late transition metal complexes with applications in homogeneous catalysis and medicinal chemistry.

Steven P. Nolan received his PhD from the University of Miami where he worked under the supervision of Prof. Carl Hoff. After a postdoctoral stay with Prof. Tobin J. Marks at North-western University, he joined the University of New Orleans in 1990. In 2006 he joined the Institute of Chemical Research of Catalonia (ICIQ). In early 2009, he joined the School of Chemistry at the University of St Andrews and in 2017 joined the Department of Chemistry of Ghent University as Full Professor. Professor Nolan's research interests revolve around the design and synthesis of catalytic complexes enabling organic transformations.

Eleonora Botter obtained her M.Sc. (2022) in Sustainable Chemistry and Technologies at the Ca' Foscari University of Venice under the supervision of Prof. Fabiano Visentin. In 2022, she joined the laboratory of Prof. Flavio Rizzolio for a postgraduate fellowship in the same University and will apply for a PhD position in Science and Technology of Bio and Nanomaterials with a project entitled "Synthesis and drug-delivery of novel organopalladium complexes of medicinal interest".



Scheme 2. (A) Example of a halogen metathesis reaction and (B) synthesis of gold(III) complexes.



Scheme 3. Synthetic routes to mononuclear bisNHC gold complexes.

displayed interesting catalytic, photoemissive and anticancer properties.[14,15]

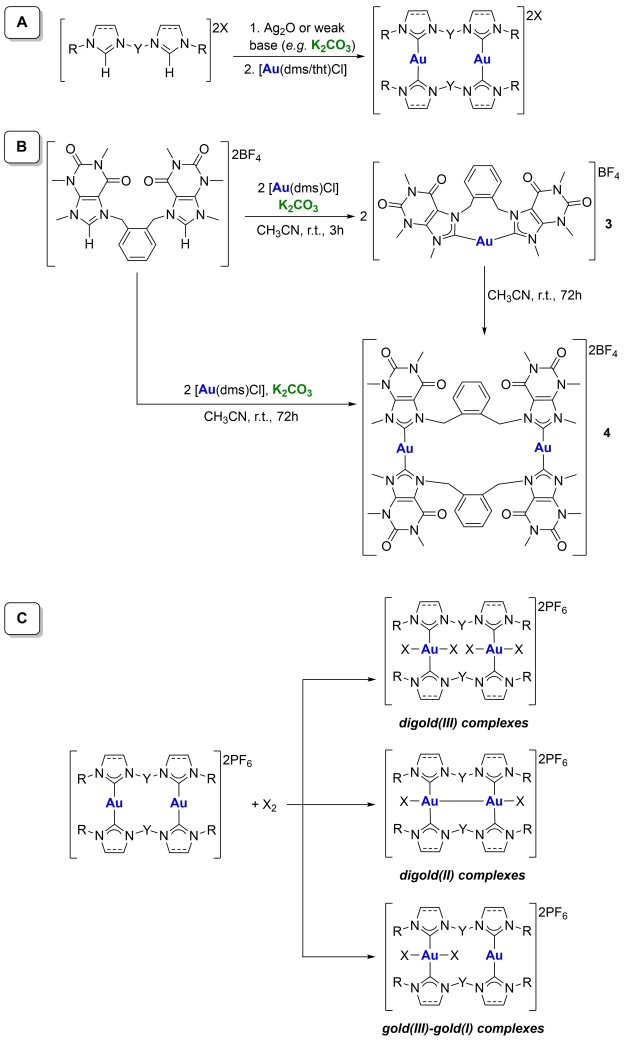
3. Bis(*N*-heterocyclic carbene) gold complexes and nanoclusters

One of the simplest structural modifications that can be performed on [Au(NHC)(X)] complexes reported in the previous section is the replacement of the halide with an additional carbene ligand. The latter can be identical to the NHC initially coordinated on the gold center or of a different nature, thus leading to the formation of homo-bis(carbene) and hetero-bis(carbene) gold complexes, respectively. Such compounds have been observed as side-products in many organic reactions catalyzed by NHC-gold complexes.[16] These are usually considered as *off-cycle* species since the presence of two ligands strongly coordinated to gold hinders the generation of a vacant coordination site and therefore renders the activation of organic substrates more difficult.

Mononuclear gold biscarbene complexes can be easily obtained by reacting a [Au(NHC)(X)] precursor with an azolium salt in the presence of a weak base such as potassium carbonate.[17] The operating conditions strongly depend on the steric and electronic characteristics of the NHC ligands of interest. An example of this synthetic route is illustrated in Scheme 3A.[17a] Alternative synthetic routes involve the reaction of a [Au(NHC)Cl] precursor with a free carbene generated *in situ*[18] or the use of a [Au(NHC)(OH)] precursor in the presence of an azolium salt (Scheme 3B and C).[19] The use of [Au(NHC)(OH)] synthons will be extensively discussed in a following section. Another interesting synthetic option is the reaction between a [Au(NHC)Cl] precursor with an isocyanide in the presence of a silver salt (e.g., $AgBF_4$) followed by attack of a secondary amine on the coordinated isocyanide ligand, leading to the formation of [NHC–Au–NAC]BF_4 (NAC = *N*-acyclic carbene) complexes (Scheme 3D).[20]

By following procedures such as those illustrated previously, research groups have successfully explored the preparation of digold(I) complexes bearing bisNHC ligands (Scheme 4A).[2b] In this context, Tubaro, Biffis and Visentin observed that by adding [Au(dms)Cl] and a caffeine-based bisimidazolium salt in the presence of potassium carbonate, two different gold complexes can be obtained, depending on the reaction time.[21] More specifically, after three hours the formation of a mononuclear cationic complex with the bisNHC ligand chelating the gold centre was observed. However, this species evolved over time to exclusively produce the thermodynamically more stable dinuclear derivative with two bridging bisNHCs (Scheme 4B).

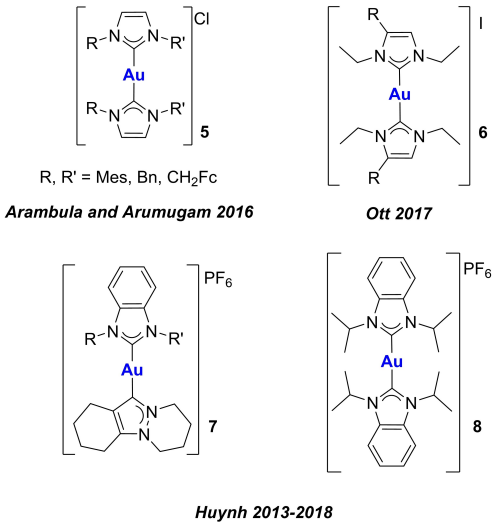
The presence of two strong Au–C bonds on each gold center makes bisNHC gold complexes poorly reactive with a wide range of common organic substrates. However, they can act as efficient starting materials for the synthesis of dinuclear gold(III) complexes using halogens or *N*-bromosuccinimide as oxidizing agents.[22] The operating conditions are usually similar to those employed for the oxidation of [Au(NHC)Cl] complexes. In some cases the formation of digold(II) complexes or mixed gold(III)/gold(I) derivatives has been observed, depending on the nature of the bridge sitting between the NHC moieties and wingtip substituents employed (Scheme 4C).[23] For digold(II) complexes, this unusual oxidation state of gold is stabilized by the presence of a metal-metal bond between the two gold(II) centres. Gold



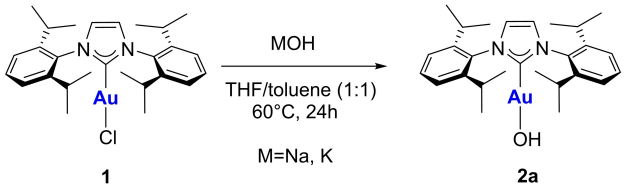
Scheme 4. Synthetic routes to dinuclear bisNHC gold complexes and their oxidation with halogens.

biscarbene complexes have been extensively studied in medicinal chemistry as potent antitumor and antibacterial agents. Most of the complexes investigated present IC_{50} values in the micro- and sub-micromolar range towards several cancer cell lines, with a strong dependence of the cytotoxicity on the type of carbene ligand coordinated to the gold centre.[17b,18a,24] This class of compounds, often exhibit both anticancer and antibacterial properties, features that have been attributed to their mechanism of action. A strong inhibition of thioredoxin reductase (TrxR) was observed in both applications, although this protein has a slightly different structure and composition in the two cases. A few examples of bisNHC gold(I) complexes with interesting biological properties are summarized in Scheme 5.[17b,18a,24]

For a thorough presentation, we believe it should be underlined that a wide range of polynuclear gold complexes stabilized by NHC and bisNHC ligands have emerged in the last decade. These compounds, known as gold nanoclusters, have generally been obtained by reduction of [Au(NHC)(X)] precursors with $NaBH_4$ and present a variable number of gold



Scheme 5. BisNHC gold complexes with promising biological properties.



Scheme 6. Synthesis of [Au(IPr)(OH)] from [Au(IPr)Cl] and M(OH) (M=Na, K, and Cs).

centres and geometry, depending on the procedure employed and the nature of the carbene ligands (see Figure 1).[25] In many cases, it has been possible to insert initially, or in a post-functionalization step, other ancillary ligands such as aryl phosphines, with the aim of modulating the properties of the final nanoclusters. These fascinating systems have attracted the attention of many organometallic chemists as their unique structural characteristics lead in some cases to interesting photoemissive and catalytic properties, different to those of more classical mono- and dinuclear gold-NHC derivatives.

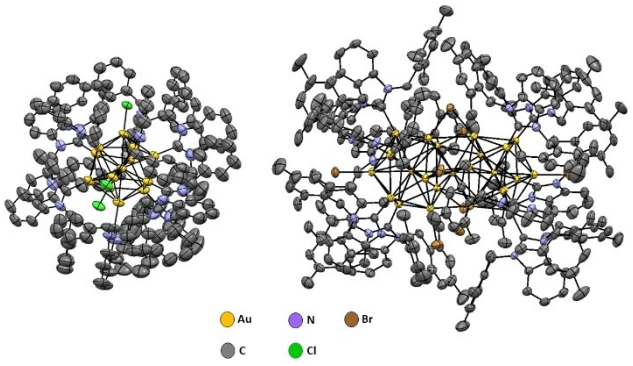
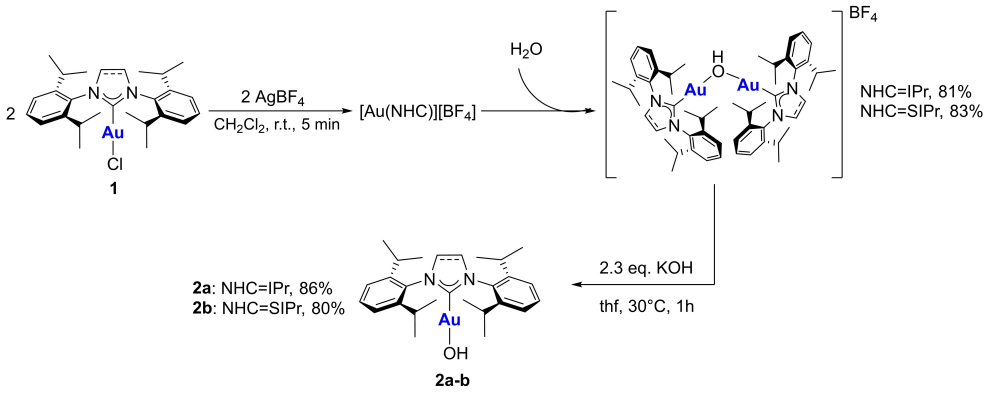


Figure 1. XRD molecular structures of a two examples of gold nanoclusters stabilized by NHC ligands with counterions omitted for clarity (CCDC: 1886732 (left) and 2127779 (right)).[25]



Scheme 7. Synthesis of [Au(IPr)(OH)] using a halide abstractor.

4. [Au(NHC)(OH)] Complexes

The [Au(NHC)(OH)] complexes are an attractive alternative to [Au(NHC)Cl] synthons in organometallic synthesis as the basic properties of the coordinated hydroxide ligand provide this class of compounds unique reactivity with a wide range of organic substrates, as well as the possibility of generating catalytically active species in gold-catalyzed processes. This composition variation represents an effective option for improving the efficiency of creating a cationic gold(I) catalyst combined with a weakly-coordinating anion, by simple addition of acid. These cationic complexes are usually obtained by reacting [Au(NHC)Cl] complexes with suitable silver salts (e.g., $AgBF_4$, $AgPF_6$, etc.).[26] The main advantage of gold-hydroxide complexes is the possibility to be activated by Brønsted acids (e.g., HOTf, $HNTf_2$, HNO_3) instead of silver salts, by virtue of their high Brønsted basicity.[27] Circumventing the need for silver salt activators can now lead to protocols that do not require the exclusion of light and avoid the generation of silver by-products or silver-stabilized intermediates that can interfere with the catalytic reaction.[28]

In 2010, Nolan and co-workers reported the synthesis and reactivity of the first [Au(NHC)(OH)] complex, namely [Au(IPr)(OH)] (**2a**).[29] The latter was prepared from [Au(IPr)Cl] (**1**) by metathesis reactions with different alkali metal hydroxides, exploiting the precipitation of the corresponding metal chlorides (Scheme 6). The reactions were initially conducted with $CsOH \cdot H_2O$ in CH_2Cl_2 at r.t. (88% yield) or later with MOH (M=Na, K) in a 1:1 THF/toluene mixture for 24 h at 60 °C (92% yield). All syntheses can be performed in air using technical grade solvents. Obviously, the selection of sodium or potassium hydroxides are now preferred because of their availability and lower cost.

An option to reduce both temperature and reaction time resides in the use of a halide abstractor such as $AgBF_4$, which results in the formation of the [Au(IPr)][BF_4] intermediate (Scheme 7).[30] The latter, when treated with H_2O, forms the digold species [{Au(NHC)}$_2$(μ-OH)][BF_4], and in the presence of KOH, this dinuclear complex rapidly evolves into the desired [Au(IPr)(OH)] complex (**2a**). With this approach, a one-pot procedure was developed, affording the [Au(IPr)(OH)] complex in 2 h. The procedure is also efficient when the NHC is SIPr.

In 2017, Nolan and Cazin disclosed the possibility of synthesizing [Au(NHC)(OH)] derivatives (**2a–g**) with a selection of saturated and unsaturated NHC ligands (IPr, SIPr, IPr^{Cl}, IPr*, IMes, ICy, IAd) under aerobic conditions and in the presence of KO^tAm as the base (route c, Table 1).[28] The large scale synthesis of [Au(SIPr)(OH)] (**2b**) (1.75 g) was successfully performed in toluene at room temperature for 2 h (90% yield). Notably, due to its low solubility in toluene, complete conversion of [Au(IPr*)Cl] (**2d**) to its hydroxide congener, was obtained using a 1:1 toluene/THF mixture. Gold hydroxide complexes bearing IMes, ICy and IAd could not be isolated in pure form (Routes a and c).

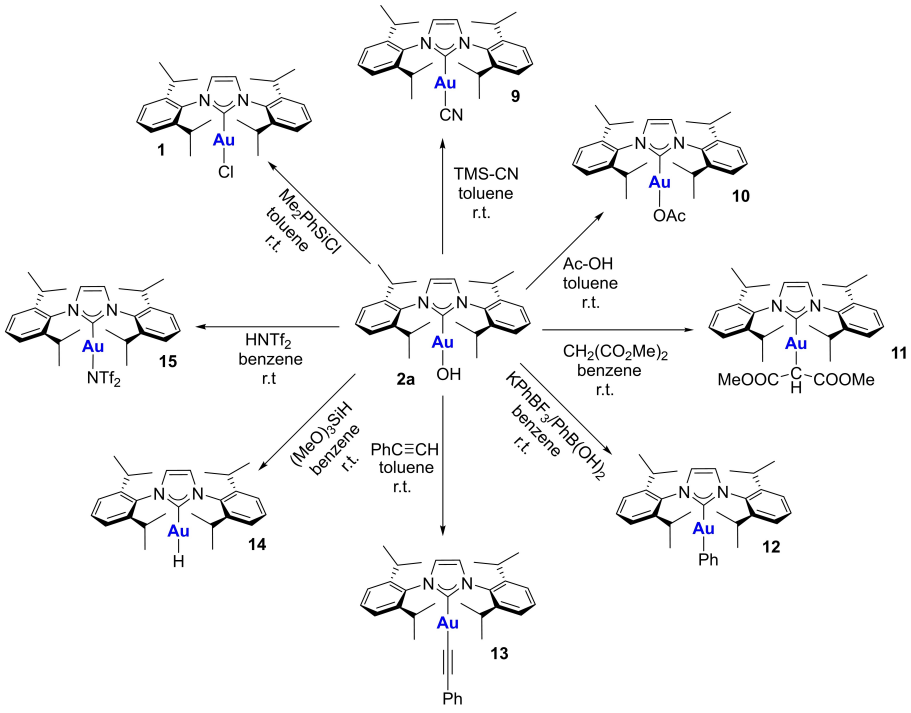
For thorough analysis, a comparison between three different procedures leading to [Au(NHC)(OH)] complexes is provided in Table 1.[28,31,32]

The [Au(NHC)(OH)] complexes possess unique reactivity towards a wide scope of inorganic and organic substrates (Scheme 8).[29] For example, the reaction between [Au(IPr)(OH)] and HCl (or chlorodimethylphenylsilane) selectively produces [Au(IPr)Cl] in toluene at room temperature. Under similar conditions, the reaction between [Au(IPr)(OH)] and trimethylsilyl cyanide, acetic acid or dimethylmalonate afforded [Au(IPr)(CN)] (**9**), [Au(IPr)(OAc)] (**10**) and [Au(IPr)(CH(CO_2Me)$_2$)] (**11**), respectively.

Table 1. Synthesis of [Au(NHC)(OH)].[28]

[Au(NHC)Cl] —routes a, b, c→ [Au(NHC)(OH)]

Entry	NHC	Route a	Route b	Route c
1	IPr (**2a**)	87	–	92
2	SIPr (**2b**)	72	–	71
3	IPr^{Cl} (**2c**)	76	–	79
4	IPr* (**2d**)	75	–	86[z]
5	IMes (**2e**)	0	98	0
6	ICy (**2f**)	0	93	0
7	IAd (**2g**)	0	80	0

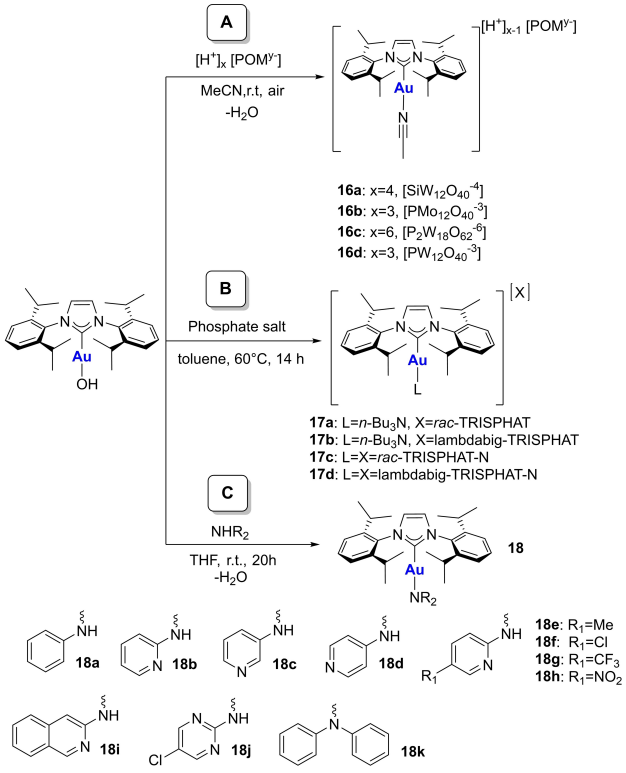


Scheme 8. Use of [Au(IPr)(OH)] as synthon (part A).

Procedures: **route a**: NaOH (6 equiv.), *t*-AmOH (0.2 equiv.), THF, in air, r.t.; **route b**: CsOH (10 equiv.), benzene, argon, r.t.; **route c**: (1) KO*t*-Am (1.5 equiv.), toluene; (2) H_2O, in air, r.t.; [z]Toluene/THF (1 : 1).

Gold-aryl (**12**) complexes can be obtained by treating [Au(IPr)(OH)] with aryl boronic acids (e.g., phenylboronic acid) or potassium phenyltrifluoroborate. Under harsher conditions (60–80 °C, 14–24 h) it is possible to introduce fluorinated benzene rings, using pentafluorobenzene or tetrafluorobenzene as organic substrates (Scheme 8). Unfortunately, in the case of 1,3,5-trifluorobenzene no product was observed. The [Au(IPr)OH] can also be used for the preparation of [Au(IPr)H] (**14**) and [Au(IPr)(NTf_2)] (**15**), in reactions performed at room temperature with trimethoxysilane and bis(trifluoromethylsulfonyl)imide, respectively. The conditions used for the preparation of [Au(IPr)(NTf_2)] are also suitable for the C – H activation of terminal alkynes such as phenylacetylene, with the production of the corresponding gold-alkynyl complex (**13**).

The [Au(NHC)(OH)] complexes can also be deployed for the production of gold-POMs (POM = polyoxometalates) (Scheme 9A, **16a**–**d**). Gold-POMs prepared from inorganic gold salts, are often unstable and tend to form gold nanoparticles.[33] However, the gold polyoxometalates obtained from [Au(NHC)(OH)] precursors are sufficiently robust to be successfully tested as heterogeneous and homogeneous catalysts in organic reactions such as the rearrangement of 2-methylundec-1-en-3-yn-5-yl acetate (heterogenous), the cycloisomerization of *N*-allyl-4-methyl-N-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (heterogenous) and diphenylacetylene hydration (homogeneous).[34]



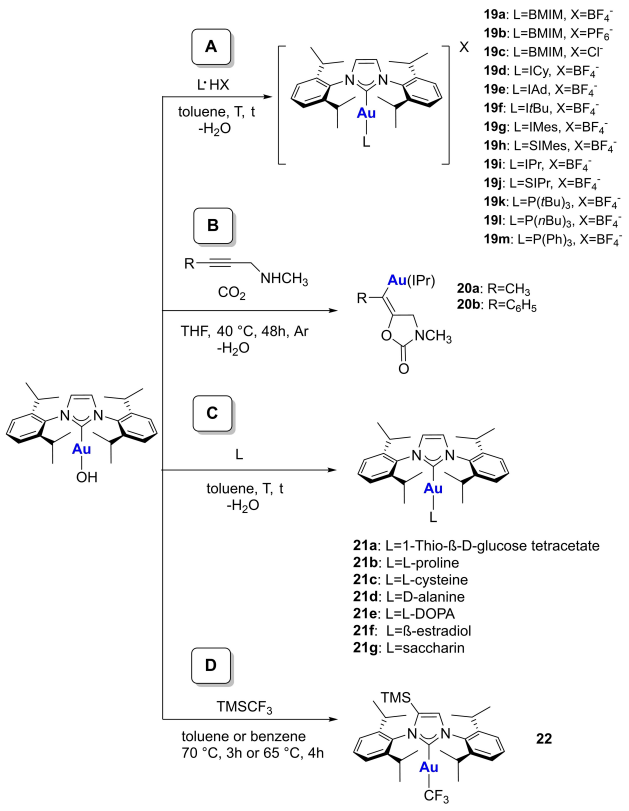
Scheme 9. Use of [Au(IPr)(OH)] as synthon (part B).

Interestingly, [Au(NHC)(OH)] complexes can be used as efficient synthons to yield chiral gold complexes, with the chiral information carried by the counterion. To this end, two different phosphate counterions were used: TRISPHAT

(tris(tetrachlorobenzenediolato)phosphate(V)) and its chloropyridine congener (TRISPHAT–N).[35] The chiral gold complexes **17a–d** were obtained by mixing [Au(IPr)(OH)] with 1 equiv. of phosphate salt in toluene at 60 °C, overnight (Scheme 9B). The driving force of the process is the extrusion of water, with the subsequent coordination of the amine to the $[Au(IPr)]^+$ moiety.

With the aim of further investigating the potential of [Au(NHC)(OH)] synthons, Nolan and colleagues have successfully reported the N–H activation of primary and secondary amines with the formation of fluorescent NHC–Au-amido complexes **18a–k** (Scheme 9C).[36] This category of compounds will be discussed in more detail shortly.

With a similar approach, $[Au(NHC)(L)]^+$ complexes (L=NHC, PR_3) can be obtained from [Au(NHC)(OH)] by its reaction with the imidazolium salt or phosphonium salt of interest, in toluene, with temperatures and times optimized for each specific ligand (Scheme 10, A).[19]



Scheme 10. Use of [Au(IPr)(OH)] as synthon (part C).

Ikariya and Kayaki showed that [Au(IPr)OH] can react with a propargyl amine and carbon dioxide, affording an Au(I)-alkenyl complex containing a cyclic urethane unit (Scheme 10B, **20a** and **b**)[37] while examining the carboxylative cyclization of propargyl amines and carbon dioxide to yield 2-oxazolidones. The proposed catalytic cycle is presented in Scheme 11.

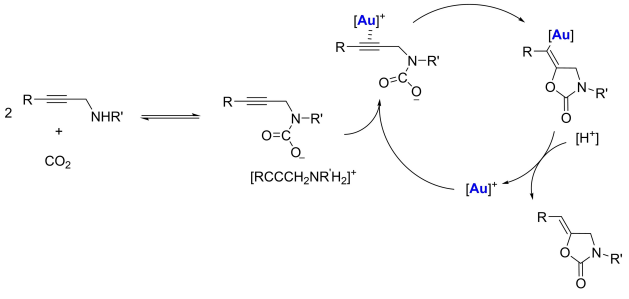
[Au(IPr)(OH)] and one equivalent of HBF_4 produce a mixture of $[Au(IPr)][BF_4]$ and $[\{Au(IPr)\}_2(\mu\text{-OH})][BF_4]$.[26] The dimeric complex can be selectively obtained by using 0.5 equiv. of aqueous HBF_4. On the other hand, the formation of the monomeric species $[Au(IPr)][BF_4]$ is favoured when a large excess of $HBF_4 \cdot OEt_2$ is used. The dimeric complex $[\{Au(IPr)\}_2(\mu\text{-OH})][BF_4]$ and mononuclear [Au(IPr)(OH)] were studied as catalysts for benzonitrile and diphenylacetylene hydration.[26] Good to excellent performances were also obtained in others catalytic reactions such as in the synthesis of enones from propargylic acetates, skeletal rearrangement and alkoxycyclization of enynes, 3,3′-rearrangement of allylic acetates, intramolecular hydroamination of alkenes and a Beckmann-type rearrangement.[26]

In 2011, Nolan and Riches reported the synthesis and characterization of Au(I) complexes bearing different ligands derived from amino acids, carbohydrates and hormones, using [Au(IPr)(OH)] as synthon (complexes **21a–g** in scheme 10C).[38]

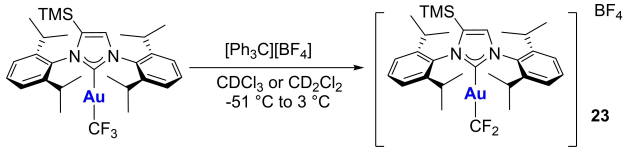
The synthon and the obtained complexes were tested as antiproliferative agents on different cancer cell lines. [Au(IPr)(OH)] and the thioglucose complex **21a** were the most active towards LNCaP (prostate carcinoma) and MDA MB231 (triple-negative breast cancer) cancer cells, with IC_{50} in the low micromolar range. Most of the synthesized complexes exhibited a remarkable antiproliferative activity towards B42CL16 (breast carcinoma) and P21PZ (prostate carcinoma) cell lines, with IC_{50} in the sub-micromolar range. Unfortunately, similar results were obtained on P21TZ and SV-HUC-1 normal cells, suggesting poor selectivity for the tested compounds.

In a recent work, the reaction between [Au(IPr)(OH)] and $TMSCF_3$ at 70 °C in toluene or benzene was studied and led to the formation of the unusual derivative $[Au(TMS\text{-}IPr)(CF_3)]$ (**22** in Scheme 10D).[39] This complex was used to study the formation of difluorocarbene derivatives. More specifically, $^{19}F\{^1H\}$ NMR analysis of the reaction between $[Au(TMS\text{-}IPr)(CF_3)]$ and $[Ph_3C]BF_4$ under inert conditions at 3 °C indicated the formation of $[Au(TMS\text{-}IPr)(CF_2)][BF_4]$ (**23**), which is the first example of a gold difluorocarbene complex reported (Scheme 12).

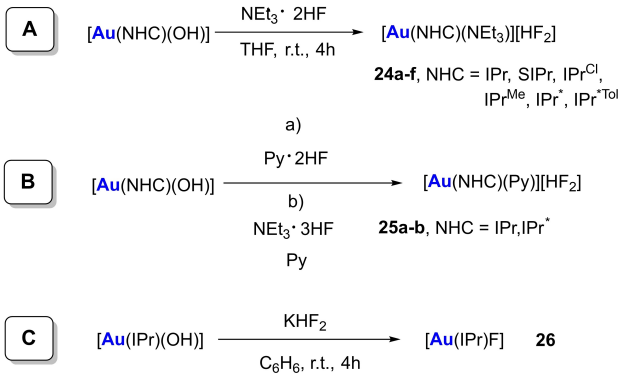
When [Au(NHC)(OH)] complexes react with triethylamine in the presence of HF, a wide range of $[Au(NHC)(NEt_3)][HF_2]$ complexes can be obtained (Scheme 13A, **24a–f**).[40] Similar complexes (**25a–b**) were obtained when pyridine dihydrofluoride was used instead of (or in addition to) triethylamine, following the conditions reported in Scheme 13(B). All gold



Scheme 11. Catalytic cycle of carboxylative cyclization of propargyl amines and carbon dioxide.



Scheme 12. First example of a gold(I)-NHC difluorocarbene complex.



Scheme 13. Synthesis of [Au(NHC)(NEt_3)][HF_2], [Au(NHC)(Py)][HF_2] and [Au(IPr)(F)] complexes.

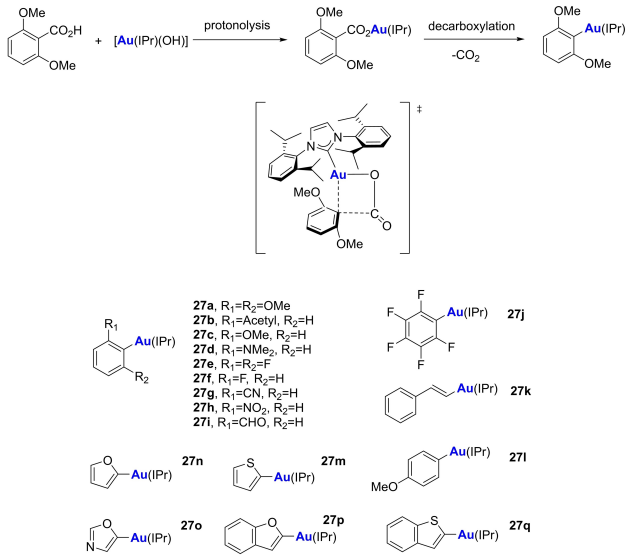
bifluoride complexes are air-stable in the solid state. In the same contribution, the synthesis of the gold monofluoride complex [Au(IPr)F] (**26**) from [Au(IPr)(OH)] and KHF_2 was reported (Scheme 13C).

Complexes **24a–e** were tested as catalysts in alkyne hydrofluorination. Those complexes, bearing the bulkier ligands (IPr* **24e**, IPr*Tol **24f**), proved the most active. The reaction proceeds with good to excellent yields, with high stereoselectivity, also being compatible with highly functionalized unsymmetrical alkynes and alkynyl sulfides.

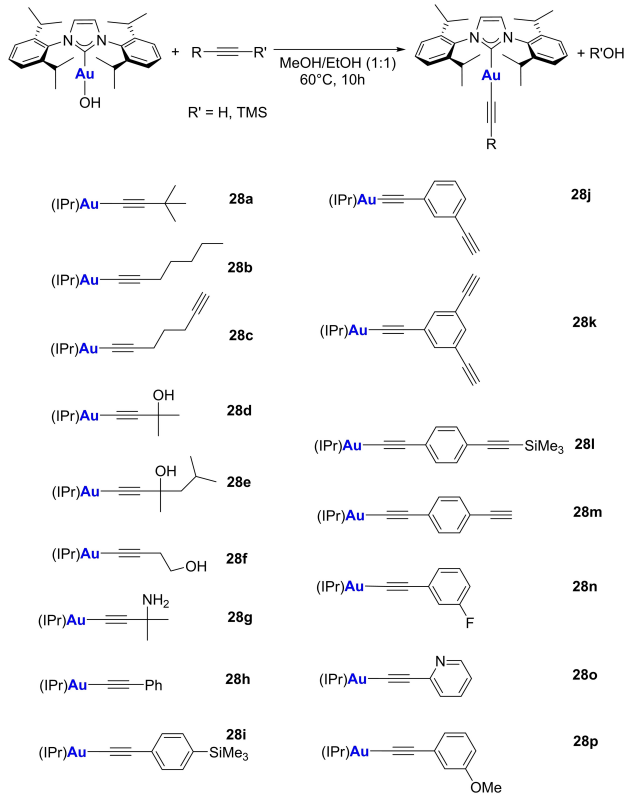
An additional application of [Au(NHC)(OH)] complexes is the decarboxylation of aromatic carboxylic acids.[41] The hypothesised mechanism for that process suggests the formation of a gold(I)-carboxylato intermediate (see Scheme 14). Afterwards, a four-membered transition state with loss of CO_2 should provide an avenue for gold-aryl bond formation. The reaction was performed with different carboxylic acids in 1,4-dioxane or toluene at 110 °C (Scheme 14).

In 2010, Nolan and co-workers reported a versatile one-step synthesis of σ-bounded gold acetylide complexes from terminal alkynes and trimethylsilyl protected analogues, using [Au(IPr)(OH)] as a synthon (Scheme 15, **28a–p**).[42] All reactions proceed in organic solvents (e.g., MeOH/EtOH mixture, THF, toluene, dichloromethane, acetonitrile) and the only by-product is trimethylsilanol or water. Gratifyingly, isolated yields are higher compared to those reported with other golden synthons. Photoluminescence properties of some of the synthesized complexes were examined. Notably, complex **28m** displayed the highest absorption and emission, with a quantum yield of 17% measured in THF.

Finally, Bochmann and Romanov reported the preparation of the [Au(CAAC)(OH)] complex (CAAC = cyclic alkyl amino carbenes) depicted in Figure 2 (**29**).[43] This complex



Scheme 14. Decarboxylation of carboxylic acids and proposed mechanism.



Scheme 15. Acetylide complexes obtained from the synthon [Au(IPr)OH].

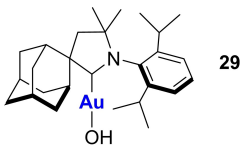


Figure 2. CAAC gold complex as synthon.

exhibits the same reactivity as the [Au(NHC)(OH)] derivatives, especially when the substrates illustrated in Scheme 8 are considered.

5. [Au(NHC)(OR)] (OR = acetate, alkoxide, aryloxide, triflate) and [Au(NHC)(acetonyl)] Complexes

In 2013, Huynh and co-workers prepared [Au(*i*Pr$_2$-bimy)(acetate)] (**30**, Scheme 16A) from [Au(*i*Pr$_2$-bimy)Cl] and AgOAc.[44] This gold species was used as a synthon for a wide range of *hetero*-bis-NHC gold complexes, exploiting the basic character of the acetate ligand for metallation of the imidazolium salts (scheme 16B). The reaction of **30** with a dicationic salt ditz·(H$^+$BF$_4^-$)$_2$ led to *hetero*-bis-NHC complex **31f** (scheme 16C).

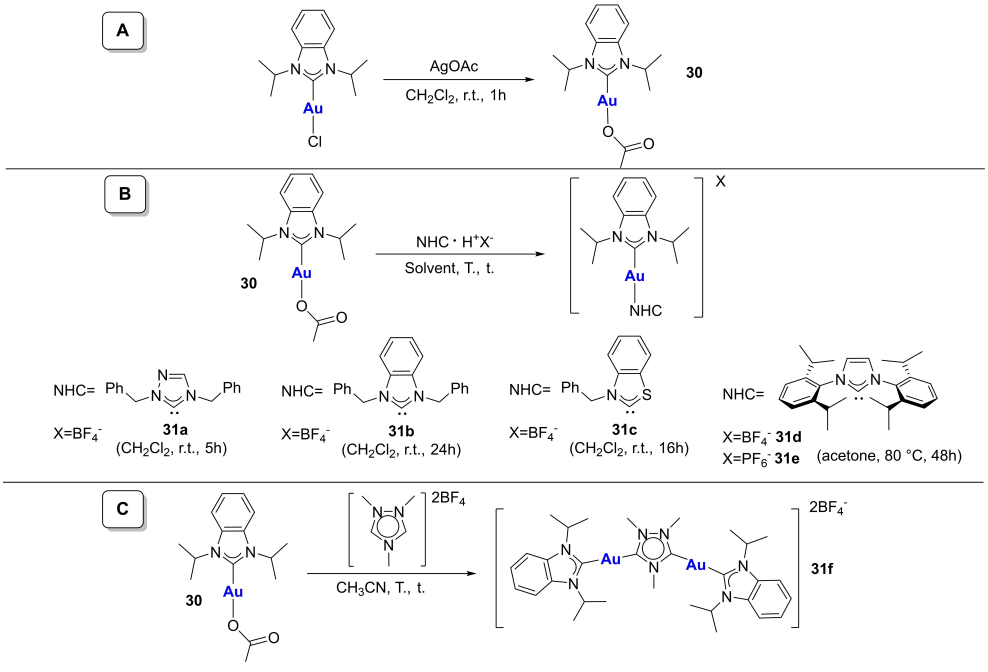
During the synthesis of complexes **31b–f**, the authors noticed that prolonging the reaction time generally favoured an irreversible ligand redistribution process that afforded *homo*-bis-NHC complexes.

Two years later, the same group synthesized another NHC-gold-acetate complex (**32a**) from its gold-chloride precursor and used it as a synthon for the preparation of the *homo*-bis-NHC gold complex **32b** (Scheme 17A)[45] Chiral complexes **32c** and **32d** were synthesized with a similar protocol by the Gung research group, which studied their IR spectra in detail, in order to evaluate the CO stretching of the acetate ligands (Scheme 17B).[46] Complex **32e** was synthesized and tested in vivo on Zebrafish Embryos by Farooq and co-workers (Scheme 17C).[47] The complex is scarcely toxic in a concentration of 10 μM, whereas at 50 μM showed an high toxicity with 100% mortality. Zebrafish Embryos treated with this complex showed head hypoplasia and notochord degeneration in a dose dependent manner. Moreover, a 40% reduction of total glutathione was observed in embryos threated with 30 μM of complex **32e**. The latter was also evaluated as antimicrobial agent on different Gram-positive and Gram-negative bacteria.[48]

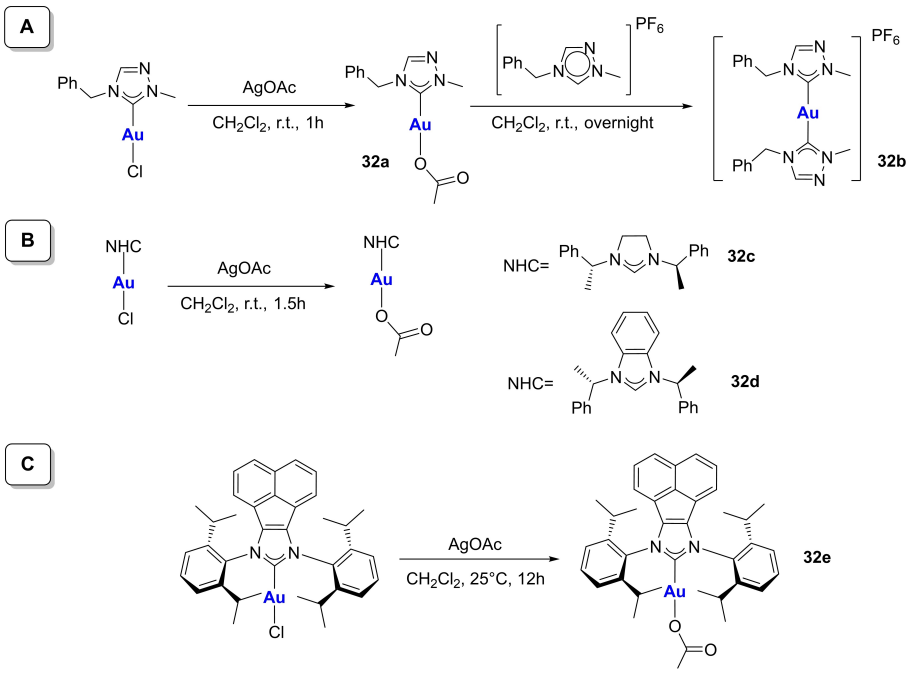
[Au(NHC)(acetonyl)] complexes are another important family of golden synthons. Nolan and colleagues reported the preparation of **33a** obtained by mixing IPr·HCl, [Au(SMe$_2$)Cl] and K$_2$CO$_3$ (6 equiv.) in acetone at 60 °C for 48 h (80% yield) (Scheme 18A).[49] When KOH is used as a base instead of K$_2$CO$_3$, the gold-acetonyl complex was obtained in a 47% isolated yield. Conversely, the use of NEt$_3$ does not allow the reaction to proceed beyond the [Au(IPr)Cl] complex. The latter can be converted into [Au(IPr)(acetonyl)] using 6 equiv. of K$_2$CO$_3$ in acetone at 60 °C for 24 h with a 84% yield (Scheme 18B). The large excess of base promotes the deprotonation of acetone thus generating its enolate, that reacts with the gold-chloride complex. This mechanism is supported by the identification of 4-hydroxy-4-methyl-pentanone (*homo*-aldol condensation product of acetone).

With this synthetic procedure a plethora of [Au(NHC)(acetonyl)] complexes was obtained in high yields (**33b–g** in scheme 18).[49] The gold-acetonyl complex **33a** can also be obtained from [Au(IPr)(OH)] and acetone at room temperature in 4 h, leading to a 90% yield (Scheme 18C), exploiting the basic character of the coordinated hydroxide ligand.

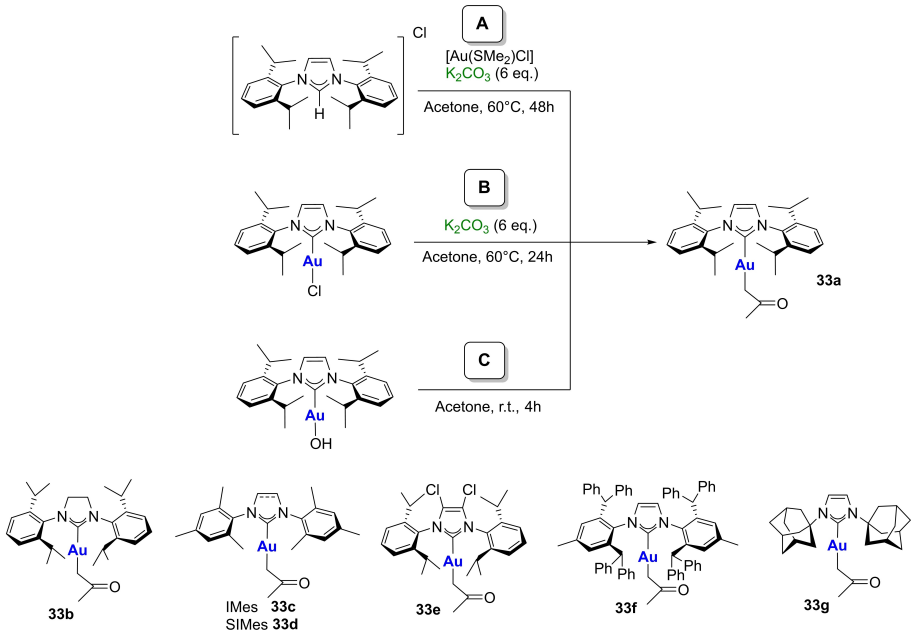
All reactions reported in Scheme 18 can be carried out in air and make use of technical grade solvents.



Scheme 16. (A) Synthesis of [Au(*i*Pr$_2$-bimy)(acetate)], (B) Synthesis of hetero bis-NHC-complexes **31a–e**, (C) Synthesis of the hetero bis-NHC digold complex **31f**.



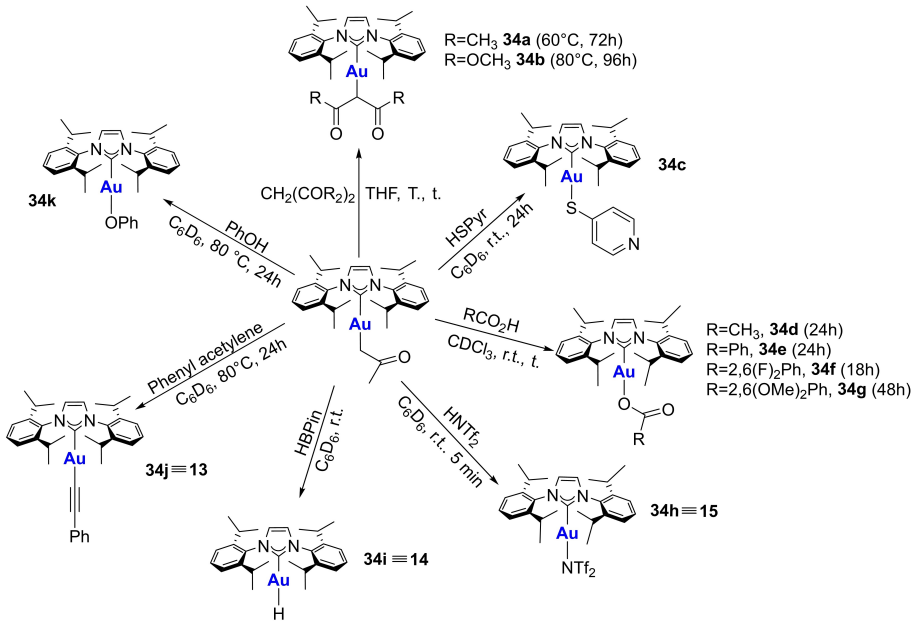
Scheme 17. (A) Synthesis of **32a** and its *homo*-bis-NHC gold derivatives **32b**, (B) synthesis of gold-acetate complexes **32c–d**, (C) Synthesis of BIAN-NHC (BIAN = bis(imino)acenaphthene) complex **32e**.



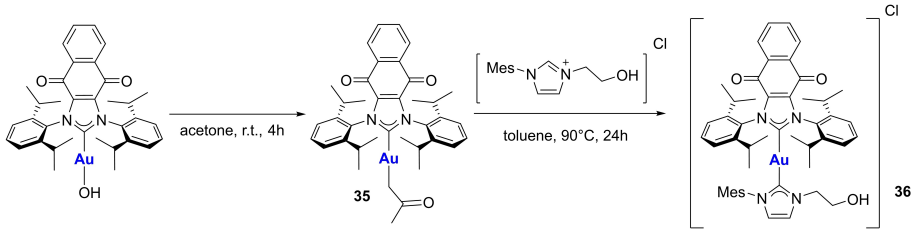
Scheme 18. Synthetic routes to [Au(IPr)(acetonyl)] complexes.

The reactivity of complex **33a** is summarised in Scheme 19.[49] Reaction with acetylacetone and dimethoxy malonate led to diketonato complexes **34a–b**. As recently reported by Nolan and Cazin, complex **34a** can also be prepared from [Au(IPr)Cl] and acetylacetone in the presence of 3 equiv. of K_2CO_3 in EtOH at r.t. for 16 h (96% yield).[50] This complex was also tested as catalyst in metal-catalyzed addition of carboxylic acids to alkynes and in alkynoic acid cyclization.

Returning to Scheme 19, the reaction between [Au(IPr)(acetonyl)] and 4-mercaptopyridine produced the gold-thiolato **34c**, whereas the carboxylato complexes **34d–g** were obtained using various carboxylic acids. [Au(IPr)(NTf_2)] (**34h**), [Au(IPr)H] (**34i**) and [Au(IPr)Cl] were obtained using bis(trifluoromethylsulfonyl)imide, pinacolborane and



Scheme 19. Uses of the [Au(IPr)(acetonyl)] synthon.



Scheme 20. Synthesis of complex **35** and its *hetero*-bis-NHC complex **36**.

*t*BuPh$_2$SiCl, respectively. When [Au(IPr)(acetonyl)] reacts with phenylacetylene and phenol, the gold-alkynyl and -phenolato complexes (**34j** and **34k**) were obtained, respectively. Notably, the results summarized in Scheme 19 can be extended to other NHC ligands (e.g. IMes).[49]

As for the applications of gold-acetonyls, **33a** was successfully employed as catalyst in alkyne hydration and in the transformation of propargylic acetates into substituted allenes and indenes.[49] [Au(IPr)(acetonyl)] (**33a**) and [Au(IPr)(acetate)] (**34d**) were also investigated as potential inhibitors of α-glucosidase, thymidine phosphorylase, β-glucuronidase and xanthine oxidase with good results, especially for complex **34d**.[51] Moreover, they were evaluated as antileishmanial agents, with higher activity than the standard drug, pentamidine. Finally, complexes **33a** and **34d** were tested towards PC-3 (prostate carcinoma), HeLa (Human papillomavirus-related endocervical adenocarcinoma, with immense gratitude to Henrietta Lacks), MCF-7 (breast carcinoma) cancer cells, showing a lower but still good cytotoxicity with respect to doxorubicin.

Another gold-acetonyl complex (**35**) was synthesized by Cui, Sessler and Arambula and used as precursor for the preparation of the *hetero*-bis-NHC gold complex **36** (Scheme 20).[52] Complex **35** was studied for immunogenic cell death (ICD), a unique cell death mechanism, in which rejuvenation of tumour-specific immune system occurs after treatment with certain therapeutic modalities. The complex was tested towards different cancer cell lines: A549 (lung adenocarcinoma), HCT116 (colon carcinoma) and CT26 (mouse colon adenocarcinoma). In all cases, complex **35** exhibited superior activity compared to auranofin (positive control). A significant increase in reactive oxygen species (ROS) was observed with respect to auranofin treatment.[52]

ICD was proven because of the observation of three main biochemical hallmarks: *i)* relocation of the ER-resident chaperon protein calreticulin (CRT) to the outer cell membrane of early apoptotic cells, *ii)* autophagy-dependent active secretion of adenosine triphosphate (ATP) and *iii)* extracellular secretion of high mobility group box 1 (HMGB1) protein because of cell membrane permeabilization during late-stage apoptosis.

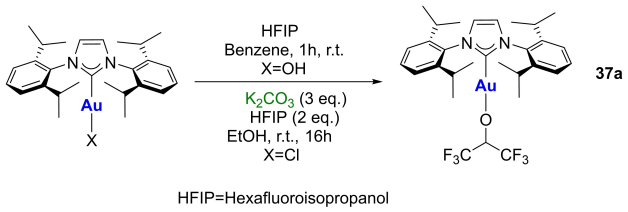
Notably, complex **35** was also tested in vivo on mice models, resulting in inhibiting, or delaying the tumour growth.[52]

With the aim of exploring the outstanding properties of HFIP (hexafluoroisopropanol) in gold catalysis, Tzouras, Nolan

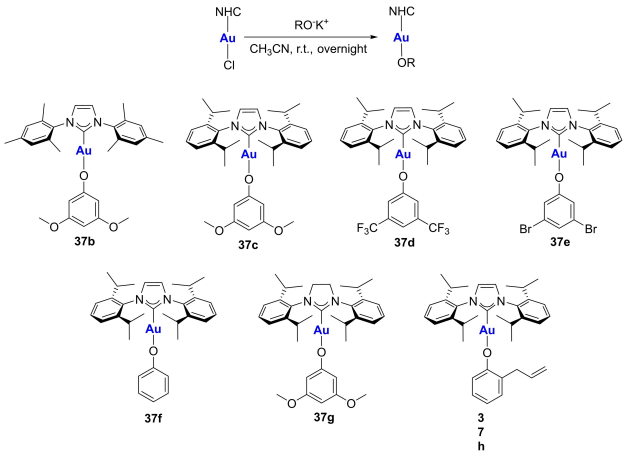
and Vougioukalakis have recently reported on the synthesis of the gold-alkoxide complex **37a** from the classical [Au(IPr)(OH)] or [Au(IPr)Cl] synthons (Scheme 21).[53] This gold-alkoxide species is a key intermediate in catalytic propargylamide cycloisomerization with Brøntsted-basic gold catalysts in the absence of any activator, other than the solvent.

A similar straightforward procedure was developed by Hashmi and co-workers for the preparation of gold-phenolates. In this instance, [Au(NHC)Cl] synthons were converted into the final products using potassium phenolate salts (Scheme 22).[54] Complexes **37b** and **37c** were tested as catalysts for phenylacetylene hydration with moderate yields.

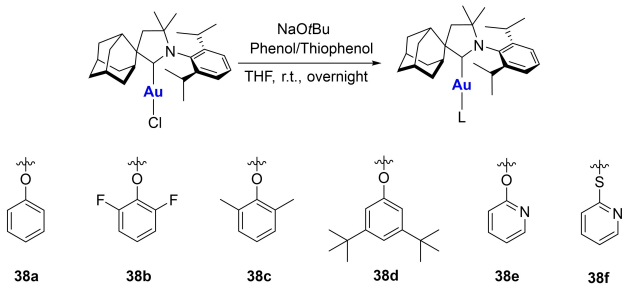
A strong base such as sodium *tert*-butoxide was used by Bochmann for the preparation of a series of CAAC-gold-phenolato/thiophenolato complexes **38a–f** (Scheme 23).[55] The photoemission of those complexes is dominated by a delayed process with long lifetimes (hundreds of ns) and quantum yields of up to 57%. Because of the effect of *ortho*-substituents, the emissions of complexes **38b** and **38c** are completely quenched.[55]



Scheme 21. Synthesis of gold-alkoxide complex **37a**.



Scheme 22. Synthesis of NHC-gold-phenolate complexes.



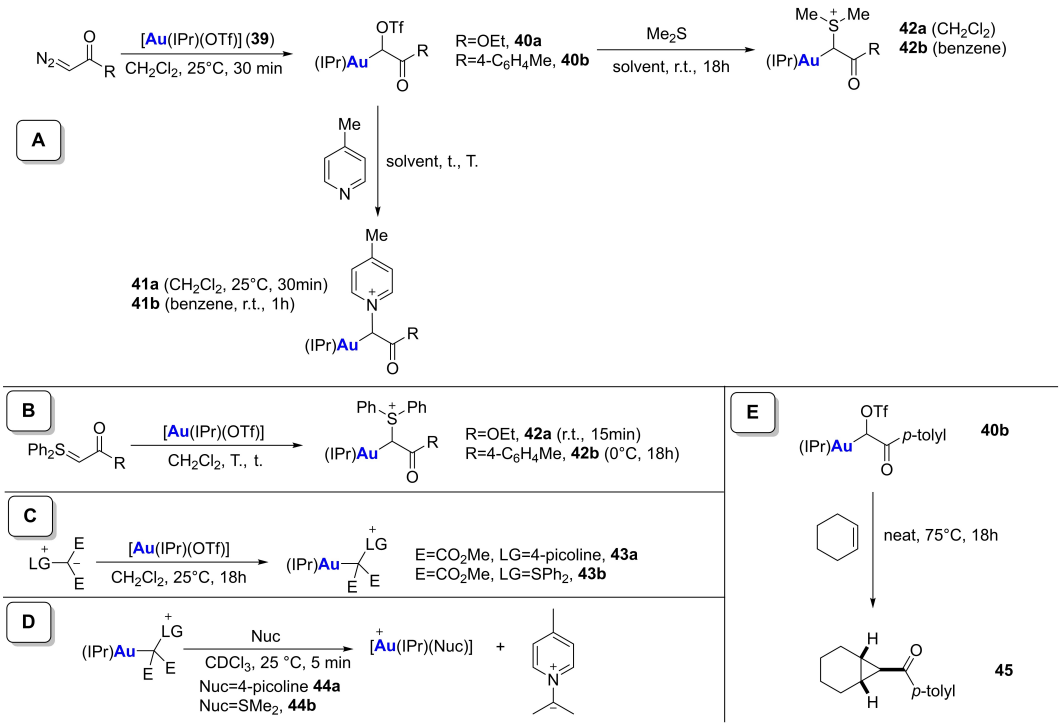
Scheme 23. Synthesis of CAAC-gold-(thio)phenolato complexes **38a–f**.

An interesting family of golden synthons is represented by NHC-gold-triflate complexes. Here, [Au(IPr)(OTf)] (**39**) was prepared by Sadighi and co-workers by reacting [Au(IPr)Cl] with AgOTf in CH_2Cl_2 for 30 min at r.t. in the dark.[56] This gold-triflate complex, a frequently employed catalyst, was successfully used as a synthon as illustrated in Scheme 24.[57] In particular, the reaction with α-diazo carbonyl compounds led to α-oxo carbenoid complexes **40a–40b** (Scheme 24A). The latter can react with 4-picoline and dimethylsulfide, affording complexes **41a–41b** and complexes **42a–42b**, respectively (Scheme 24A).[57] Reaction between Ph_2SCHCO_2Et/$Ph_2SCHCO(4\text{-}MeC_6H_4)$ and [Au(IPr)(OTf)] led to complexes **42a–42b** in good yields (Scheme 24B).[57] The synthesis of α,α′-dioxo carbenoid complexes can also be performed by reacting the gold-triflate synthon and 4-picoliniumbis(methoxycarbonyl)methylide/diphenylsulfoxonium bis-(methoxycarbonyl)methylide leading to complexes **43a–43b** (Scheme 24C).[57] The reaction between **43a** with an excess of 4-picoline resulted in immediate displacement of 4-picolinium bis(methoxycarbonyl)methylide to form the gold picoline complex [(Au(IPr)(4-MeC_5H_4N)]OTf (**44a**) (Scheme 24D). Similarly, treatment of **43b** with an excess of dimethyl sulfide led to immediate formation of [(Au(IPr)(SMe_2)]OTf (**44b**). Finally, a reaction between complex **40b** and cyclohexane was investigated in order to evaluate the potential of this gold complex to engage alkene cyclopropanation, leading to bicyclo[4.1.0]-heptane **45** (Scheme 24E).[57]

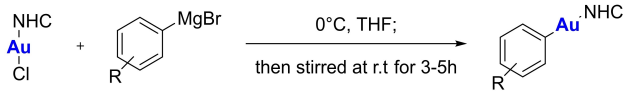
6. [Au(NHC)(aryl)] Complexes

An interesting class of gold(I)-NHC synthons is that of *N*-heterocyclic carbene gold(I)-aryl complexes, often invoked as intermediates in many gold-catalyzed reactions.[58] Despite the remarkable photophysical properties of some of these gold complexes, their use as synthons has been explored only recently, probably due to the challenging methods used for their preparation. Indeed, the classical synthetic approach to NHC-gold(I)-aryls consists in the reaction between [Au(NHC)Cl] and a Grignard reagent (Scheme 25).[59] The latter is air-sensitive, thermolabile and incompatible with some functional groups. Moreover, flash column chromatography of the crude mixture and subsequent recrystallization from THF/hexane are usually required.

The modern synthetic routes to [Au(NHC)(aryl)] complexes can fall in two main categories: *i)* base-assisted transmetalation between an aryl boronic acid (or ester) and a NHC-gold(I) precursor; *ii)* decarboxylation of benzoic acids. The transmetalation route was first developed by Gray and co-workers in 2006.[60a] This procedure was originally proposed as a new entryway into [Au(PR_3)(Ar)] complexes but it was also found suitable for some *N*-heterocyclic carbene congeners. The desired complexes can be obtained by reacting the gold precursor [Au(L)X] (L=PR_3, NHC; X=Cl, Br)



Scheme 24. Synthesis of the α-carbenoid gold complexes (A,B,C,D) and gold to alkene carbene transfer (E).



Scheme 25. Synthesis of *N*-heterocyclic carbene gold(I)-aryl complexes using Grignard reagents.

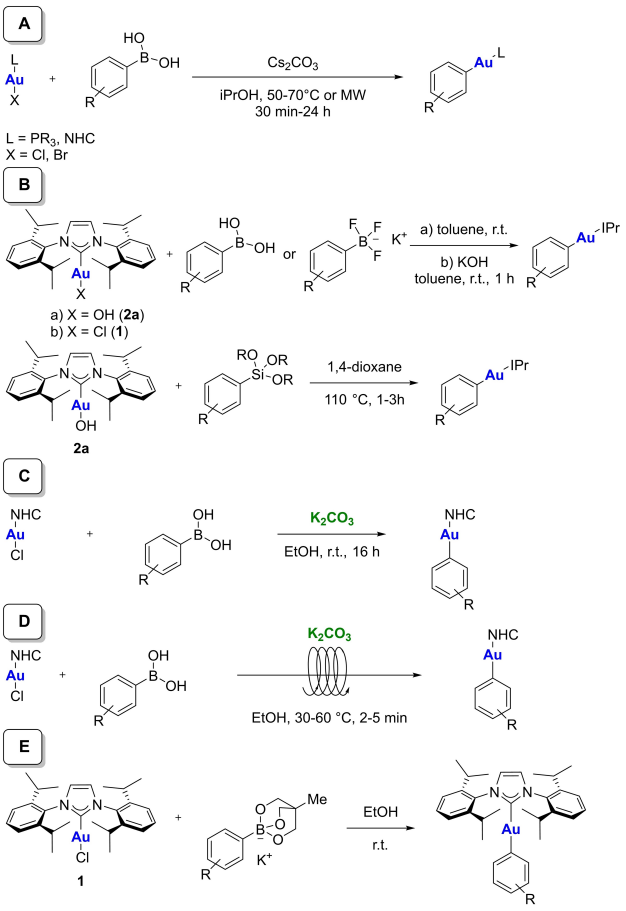
with an excess of aryl boronic acid in the presence of cesium carbonate (Scheme 26A). The final products can be isolated in moderate to high reaction yields with a wide scope of aryl boronic acids.[60]

This synthetic route was improved in 2010 by Nolan and co-workers using [Au(IPr)(OH)] (**2 a**). The latter reacts smoothly and at room temperature with the aryl boronic acid or trifluoroboronate of interest, affording the NHC-gold(I)-aryl complexes in quantitative yields.[29,61] Later, the Nolan group obtained the same complexes using organosilanes as transmetalating agents (Scheme 26B).[62]

Recently, the Nolan group explored the reaction between [Au(IPr)Cl] (**1**) and a small excess of an aryl boronic acid using a weak base such as K_2CO_3 (Scheme 26C).[63] Interestingly, all these reactions occur at room temperature under aerobic conditions in technical grade ethanol. Use of a EtOAc/H_2O mixture obviates reaction monitoring as a transparent biphasic solution form upon reaction completion and facilitates the separation of the final product. This approach was used to successfully perform a 6-gram-scale synthesis of [Au(IPr)($C_6H_5OCH_3$)] (**27 l**). Moreover, the synthetic routes proved to be compatible with different functional groups, since they are effective with aryl boronic acids bearing both electron-withdrawing and electron-donating groups. Similarly, the reaction is also compatible with different NHC ligands. This simple *weak-base driven* procedure has allowed the development of a simple continuous flow process for the synthesis of this valuable family of gold complexes. This important result was achieved as an extension of a continuous flow protocol previously developed by Stevens, Cazin and Nolan for the preparation of [M(NHC)Cl] (M=Cu, Au) and palladium-cinnamyl complexes.[64] According to this synthetic protocol, an acetone solution of the azolium salt and metal precursor of interest flows through a microreactor filled with K_2CO_3, affording the desired products in high yield and purity. Taking advantage of the same setup, the continuous flow reaction between [Au(IPr)Cl] (**1**) and a selection of aryl boronic acids was successfully performed at 30–50 °C, in remarkably short reaction times (2 min) using EtOH as solvent and THF (or 2-Me–THF) as co-solvent (Scheme 26D). The short residence times also proved to be useful to avoid side-reactions such as the protonolysis of the boronic acid (*protodeboronation*). This simple continuous flow procedure proved to be compatible with a wide range of aryl-boronic acids and NHCs.[65]

With a similar procedure, Pilarski and colleagues were able to obtain *N*-heterocyclic gold(I)-aryl complexes using pre-synthesized triol-boronates of the type K[ArB(triol)] and [Au(IPr)Cl] (**1**) as starting materials (Scheme 26E).[66] The reaction proceeds at room temperature, in green solvents (2-MeTHF) and gave a wide range of products in high yield, displaying notable functional group tolerance.

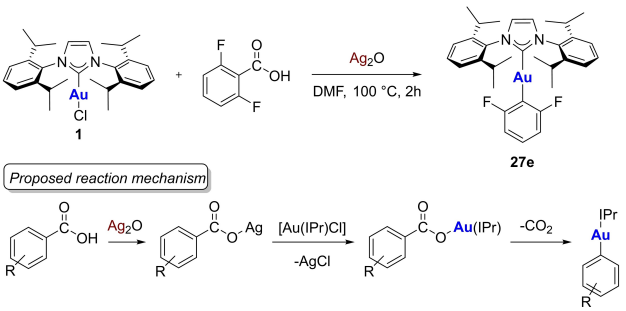
An alternative synthetic route to *N*-heterocyclic carbene gold(I)-aryl complexes is via the decarboxylation of benzoic



Scheme 26. Synthesis of *N*-heterocyclic carbene gold(I)-aryl complexes via transmetalation between aryl boronic acids and an NHC-gold(I) precursors.

acids. In 2011, Larrosa explored this method starting from the [Au(IPr)Cl] (**1**) precursor and 2,6-difluorobenzoic acid in the presence of Ag_2O (Scheme 27).[67] Studies on the reaction mechanism showed that the first step is the formation of a silver(I) complex, which then undergo ligand exchange with the gold-NHC precursor, thus generating a gold(I)-carboxylato complex. Finally, a decarboxylation step leads to the desired gold-aryl complex.

Taking advantage of the strongly basic properties of [Au(IPr)(OH)] (**2a**), Nolan and Cazin managed to achieve this

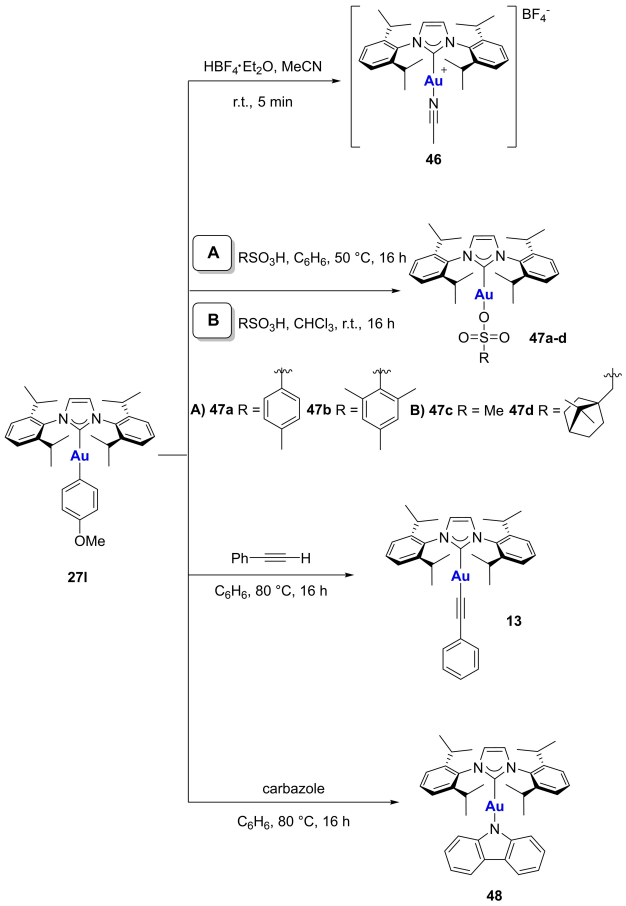


Scheme 27. Synthesis of *N*-heterocyclic carbene gold(I)-aryl complexes via decarboxylation of benzoic acids.

reaction without the need of any other additive (see Scheme 14).[41] The reaction between [Au(IPr)(OH)] (**2a**) and different aromatic carboxylic acids at 110 °C in toluene led to the desired *N*-heterocyclic carbene gold(I)-aryl complexes in high yields.

Gold(I)-aryl complexes can be used as efficient synthons for the preparation of a plethora of valuable gold derivatives. In this context, Nolan and co-workers probed the reactivity of the commercially available [Au(IPr)($C_6H_5OCH_3$)] (**27l**) in order to obtain the corresponding nitrile, sulfonate, alkynyl and carbazolyl complexes (Scheme 28).[63] In particular, the reaction between [Au(IPr)($C_6H_5OCH_3$)] (**27l**) and acetonitrile in the presence of $HBF_4{\cdot}Et_2O$ (1.1 equiv.) led to the formation of the nitrile compound **46** at room temperature. The use of aromatic sulfonic acids (e.g., *p*-toluenesulfonic and mesitylenesulfonic acid) in benzene, led to gold-sulfonates **47a–b** after 24 h at 50 °C. The same reaction is compatible with aliphatic sulfonic acids such as methanesulfonic and (+)-camphorsulfonic acid, leading to compounds **47c–d** using chloroform as solvent at room temperature.

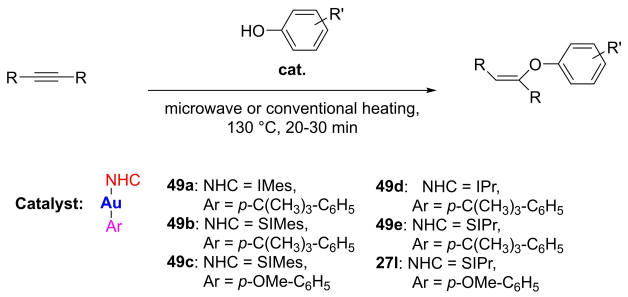
The C–H activation of a terminal alkyne such as phenylacetylene was successfully carried out by reacting [Au(IPr)($C_6H_5OCH_3$)] (**28l**) with phenylacetylene in benzene at 80 °C for 16 h, thus obtaining complex **13**. Using the same



Scheme 28. Use of [Au(IPr)(*p*-OMe–C_6H_5)] as synthon.

conditions, it was possible to achieve the N–H activation of carbazole, obtaining the gold-carbazolyl complex **48**.

A number of gold(I)-aryl compounds can be used in homogeneous catalysis. For example, complexes **49a–e** and **27l** were tested by the Stockland group as pre-catalysts in the hydrophenoxylation of unactivated internal alkynes.[60f] The results demonstrated that only complexes bearing SIPr and IPr lead to the desired compounds in high yields without decomposition of the organometallic species (Scheme 29).



Scheme 29. Use of [Au(NHC)(Ar)] compounds as pre-catalysts in the hydrophenoxylation of unactivated internal alkynes.

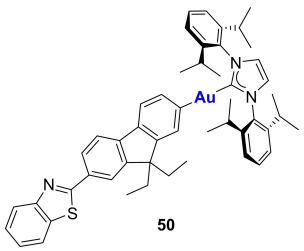


Figure 3. Luminescent [Au(NHC)(Ar)] complex **50** synthesised by Gray and co-workers.

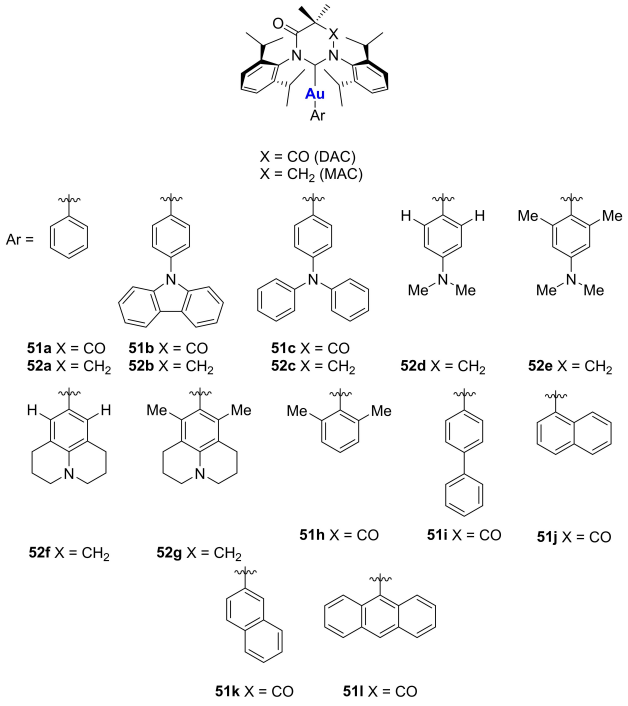


Figure 4. Luminescent [Au(carbene)(Ar)] complexes described by Thompson and co-workers.

Furthermore, some [Au(NHC)(aryl)] compounds present interesting photophysical properties. For example, Gray and co-workers obtained complex **50** (Figure 3), which exhibited both fluorescent and phosphorescent properties and, due to the higher contribution of the blue fluorescence, showed a resulting dual emission that appeared violet in colour.[68]

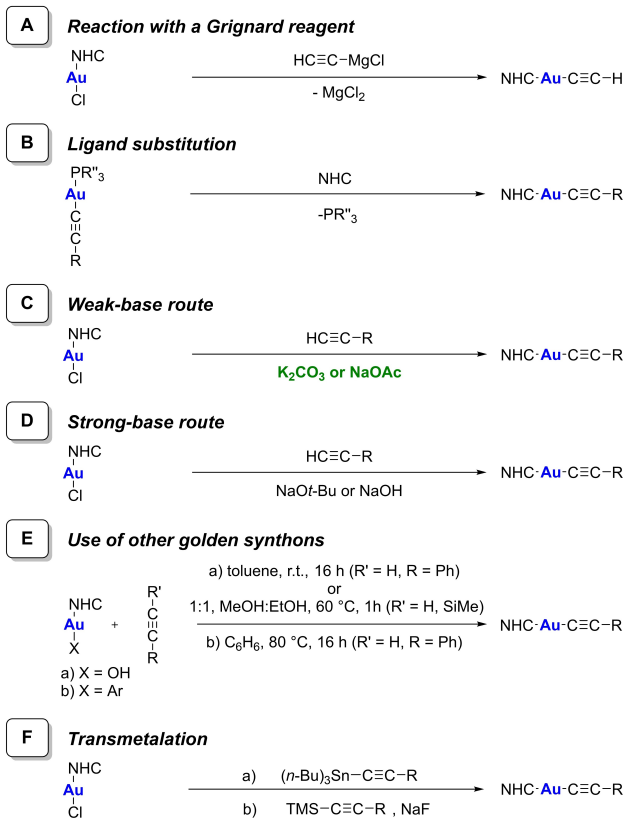
More recently, Thompson and colleagues have obtained different [Au(carbene)(aryl)] complexes by adding an aryl boronic acid or a pinacol ester to [Au(carbene)Cl] precursors in toluene/benzene at room temperature in the presence of KOH.[69] Due to a combination of an electrophilic diamidocarbene (DAC) or monoamido-aminocarbene (MAC) and an aryl ligand with an electron-donating substituent, these complexes (**51a–c** and **52a–g**, Figure 4) showed promising luminescence via ICT (*Inter-ligand Charge Transfer*). Unlike linear d^{10} complexes with a MLCT (*Metal-to-Ligand Charge Transfer*) emissive state, nonradiative decay associated with Renner-Teller effect is avoided. Moreover, in complexes **52e–g**, in which the nonradiative decay involving the rotation around the Au–C_{aryl} and C–N bond of the arylamine is prevented due to steric restriction, the luminescence efficiency is even higher.

The same research group described the preparation of complexes **51h–l** (Figure 4) with an electrophilic monoamido-aminocarbene (MAC) and different aryl ligands. These compounds showed phosphorescent emission, especially when doped into polystyrene thin films (1 wt.%) at room temperature.[70]

7. [Au(NHC)(alkynyl)] Complexes

Gold(I)-alkynyl complexes bearing *N*-heterocyclic carbene ligands have received considerable attention in recent years, especially due to their interesting photophysical properties. These complexes often display strong luminescence that is deeply dependent on the presence of aurophilic interactions.[2b] The first synthetic route employed for the preparation of these compounds is the reaction between a [Au(NHC)Cl] complex and a Grignard reagent (Scheme 30A).[71] Afterwards, several other methods have been used to obtain the desired gold(I)-alkynyl complexes, such as the phosphine substitution by a NHC ligand (Scheme 30B) and the addition of a terminal alkyne to a [Au(NHC)Cl] species in the presence of weak (Scheme 30C)[11b,72] or strong bases (Scheme 30D).[73] In addition, other gold(I) synthons such as [Au(NHC)(OH)][29,42] and [Au(NHC)(Ar)][63] have been successfully used to obtain the desired alkynyl derivative by simply adding the corresponding terminal alkyne (Scheme 30E).

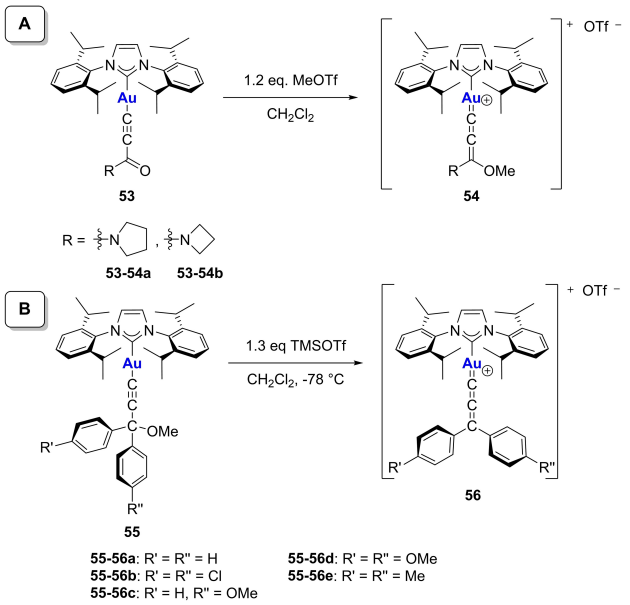
[Au(NHC)(alkynyl)] complexes can also be synthesised through transmetalation between a [Au(NHC)Cl] complex and an organotin compound. The reaction mechanism has been investigated by Canovese and colleagues, who noted a strong influence of the solvent on the reaction rate.[74] In



Scheme 30. Synthetic routes to NHC-gold(I)-alkynyl complexes.

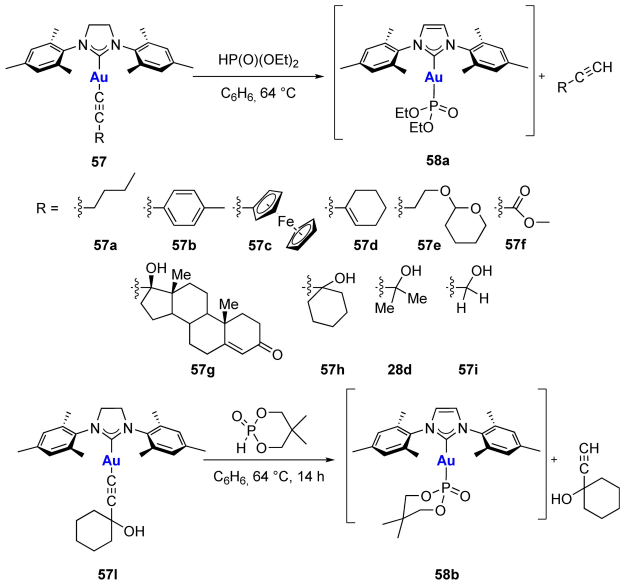
particular, the reaction proceeds more slowly in $CHCl_3$ than in CH_3CN, probably because the latter can better solvate both the gold precursor and the alkynyl-stannane. In 2018, Mohr and co-worker exploited the transmetallation with Sn(IV) or Si(IV) compounds, namely nBu$_3$SnC≡CH or the cheaper TMS–C≡CH, to obtain ethynyl gold-NHC complexes (Scheme 30F).[75] This result is noteworthy as most of the above-mentioned methods are not suitable to access compounds with unsubstituted alkynyl moieties. Both reactions are also compatible with different *N*-heterocyclic carbene ligands.

[Au(NHC)(alkynyl)] complexes can be used as efficient synthons for the preparation of various gold compounds. For example, the reaction of gold(I)-acetylides (**53a–b**) with a small excess (1.2 equiv.) of MeOTf leads to the formation of cationic gold-allenylidene complexes (**54a–b**, Scheme 31A).[76] Similar products can be obtained in high yields through the reaction of a γ-methoxy gold acetylide precursor (**55a–c**) with TMSOTf (trimethylsilyl trifluoromethanesulfonate) in CH_2Cl_2 at −78 °C (**56a–c**, Scheme 31B).[77] The obtained complexes generally show low thermal stability, which is strongly dependent on the delocalization of a positive charge both on the C1 and C3 allenylidene carbon atoms. Both the aryl substituent on the alkynyl group and the NHC(Au) fragment participate in the stabilization of that positive charge.



Scheme 31. Reaction between NHC-gold(I) alkynyl compounds and ROTf (R=Me, TMS) to obtain allenylidene derivatives.

Moreover, the reaction of gold(I)-alkynyl complexes **57a–l** and **28d** with a phosphite in benzene at 64 °C leads to the corresponding [Au(NHC)(P(O)(OR))] (**58a–b**) complexes and the extrusion of a terminal alkyne (Scheme 32).[78] The reaction is compatible with a wide range of alkynyl substituents (even with those bearing a propargyl alcohol group), with a significant dependence of the reaction rate on the electronic features of the organic fragment. Therefore, the reaction rate is faster in the presence of EDG groups and slower with EWG groups.



Scheme 32. Synthesis of gold(I)-phosphonates from gold(I)-alkynyls.

[Au(NHC)(alkynyl)] complexes can also be used as precursors to obtain gold-triazolyls via [3 + 2] azide–alkyne cycloaddition. This reaction, which is considered one of the most powerful examples of *click-chemistry*, can be achieved even when the alkyne moiety is coordinated to a metal centre through a simple addition of a terminal azide in the presence of a copper-based catalyst (Scheme 33).[79] The synthetic route is compatible with different substituents on both the alkynyl and azide moieties, with the exclusive formation of the 1,4 regioisomer. Interestingly, similar products can also be obtained using [Au(NHC)(azide)] complexes and a terminal alkyne.[80]

As stated above, gold(I)-alkynyls have been extensively studied for their photochemical and luminescent properties. In most cases, they exhibit phosphorescence due to the presence of intra-ligand π-π* excited states perturbed by the heavy gold centre.[81] Interestingly, some [Au(NHC)(alkynyl)] complexes such as **60a** and **60b** (Figure 5), studied by Seki and Ito, exhibit mechano-chromism (the change on the emission colour after mechanical stimulation).[82] Complex **60a** shows a hypsochromic shift from green to blue after grinding, while complex **60b** shows a bathochromic shift

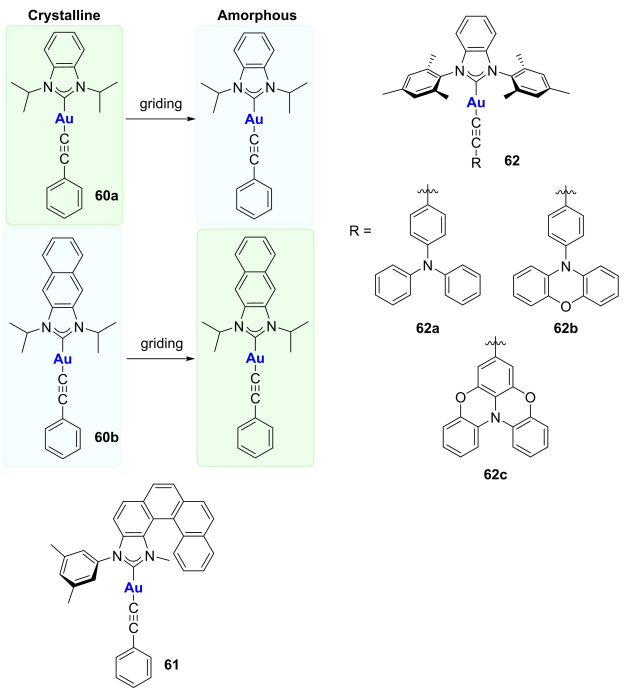
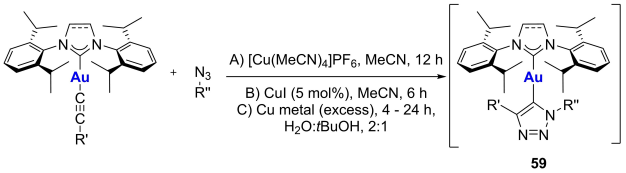
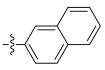
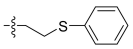
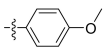
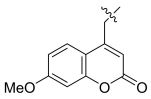
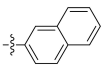
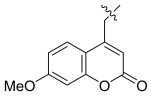
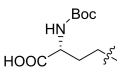
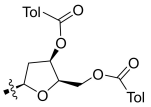


Figure 5. Example of luminescent *N*-heterocyclic gold(I)-alkynyls.



	NHC	R'	R''	Method
59a	SIPr			A
59b	SIPr	*t*Bu		A
59c	IPr	*t*Bu		B,C
59d	IPr	*t*Bu	$CH_2(CH_2)_6CH_3$	B,C
59e	IPr	*t*Bu		B,C
59f	IPr	*t*Bu		C
59g	IPr	*t*Bu		B,C
59h	IPr			B,C
59i	IPr	*t*Bu		B,C
59j	IPr	*t*Bu		C

Scheme 33. *N*-heterocyclic gold(I)-alkynyl complexes to gold-triazolyls via copper-catalysed cycloaddition.

from blue to green. In both cases, the X-ray diffraction analysis of the compound crystals and powders pointed out a crystal-to-amorphous phase transition upon grinding. For **60a**, further analysis suggested that the mechano-chromism is based on the loss of the intermolecular interactions after the mechanical stimuli. On the contrary, for complex **60b** the red-shift in the emission colour is due to the increased degree of π-π stacking interactions around the NHC moieties in the amorphous form.

In 2021, Crassous and co-workers synthesised and studied the luminescent properties of a helically chiral [5]helicene-NHC gold(I) complex bearing an acetylide ligand (**61**, Figure 5), which is obtained as enantiopure after chiral HPLC.[83] This compound shows both phosphorescence and fluorescence, with high overall quantum yields and high ratio between phosphorescence and fluorescence. Moreover, this gold complex possesses high ECD (Electronic Circular Dichroism) activity, which is strongly correlated with the presence of the helicene ligand, and a clearly detectable CPL (Circularly Polarized Luminescence) activity.

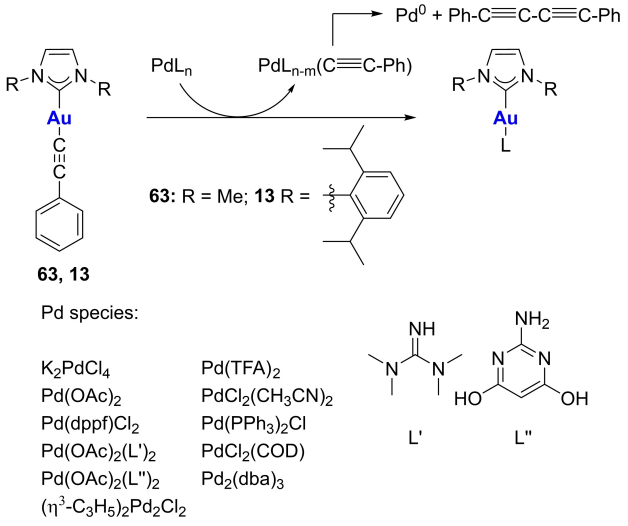
Some gold(I) alkynyl complexes have been investigated also as TADF (Thermally Activated Delayed Fluorescence) emitters. As an example, complexes **62a–c** (Figure 5), bearing an amino-containing alkynyl ligand, are characterized by strong TADF emissions due to the presence of a ligand-to-ligand charge transfer (LLCT) excited state.[84] These compounds can be used for the preparation of solution-processed OLEDs with high performance compared to other gold diodes.

In 2020, Tang, Zheng and Kwok functionalized tetraphenylethylene with different groups, among which an alkynyl

one that was coordinated to an NHC-gold(I) moiety to obtain a AIEgen (Aggregation-Induced Emission luminogen).[85] Unfortunately, the alkynyl complex possesses negligible luminescence and cytotoxicity in vitro, even though it displays blue photoluminescence in a 80:20 H_2O:THF mixture.

One year later, Nolan and Perrier used the reaction of the previously reported polymer poly(PYMP)[86] with the golden synthon [Au(IPr)(OH)] to obtain a hyper-branched gold-functionalized polymer which exhibited phosphorescent properties with high quantum yields.[87]

Beside their application in materials science, some [Au(NHC)(alkynyl)] complexes have been tested for their potential biological activity. For example, Zou and colleagues have recently demonstrated that gold-alkynyl compounds **63** and **13** can undergo bio-orthogonal transmetalation in the presence of their Pd(II) congeners, forming active gold(I) species (Scheme 34).[88] The [Au(NHC)(L)] complexes obtained from this transmetalation process display catalytic activity associated with the lability of the new Au–L bond. This type



Scheme 34. Bio-orthogonal reaction between NHC-gold(I) alkynyls and Pd(II) derivatives.

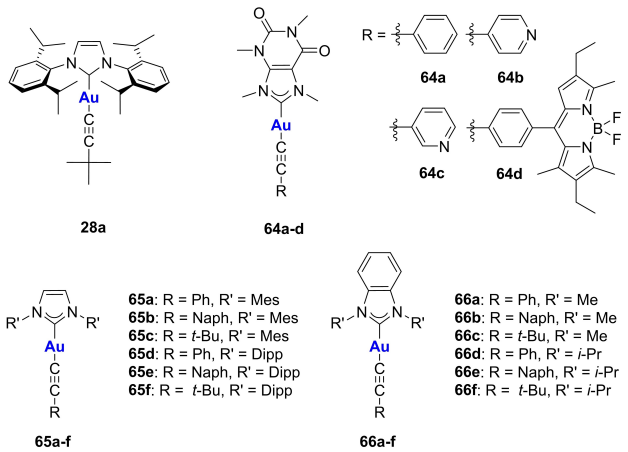


Figure 6. Example of *N*-heterocyclic gold(I)-alkynyls tested for their anti-tumor activity.

of compound, however, is susceptible to poisoning in the presence of physiological nucleophiles.

With this transmetalation approach, it was possible to achieve the in situ activation of the gold complexes, confirmed by the formation of fluorescent coumarin in PBS media supplemented with GSH, in living cells and in zebrafish models. Moreover, the Pd(II) compounds are able to enhance the reactivity of the gold complexes towards thiol-containing enzymes (as thioredoxin reductase, TrxR) and their cytotoxicity in cancer cells.

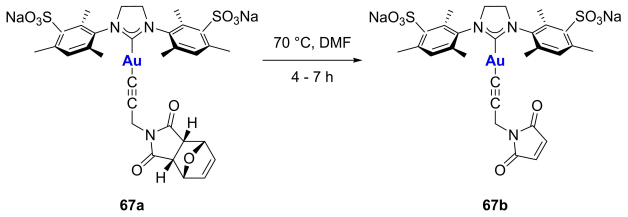
In 2017, Casini and colleagues synthesised complex **28a** (Figure 6), which has an overall good stability in DMSO/H_2O mixture but undergoes displacement of the alkynyl ligand in the presence of *D,L*-homocysteine, taken as model nucleophile.[89] Interestingly, compound **28a** displayed cytotoxicity in vitro, with IC_{50} in the micromolar range, against different human cancer cell lines (colorectal carcinoma HCT116 p53 wild type and HCT116 p53 null, breast adenocarcinoma MCF-7, malignant melanoma A375) but low ex vivo toxicity towards healthy rat kidney tissues.

In 2020, Bonsignore and Casini studied the biological activity of four different gold(I)-alkynyl complexes bearing 9-methylcaffeine-8-ylidene as NHC ligand (**64a–d**, Figure 6).[90] These compounds show an acceptable stability in aqueous solution and the reactivity studies towards *N*-acetylcysteine (NAC), chosen as model nucleophile, confirm the high stability of **64c**, while **64a** undergoes a displacement of the alkynyl ligand by NAC within 24 h. The FRET (Fluorescence Resonance Energy Transfer) DNA melting assays revealed no stabilising properties of the complexes towards DNA G-quadruplex. However, compounds **64a–c** are slightly active and selectively cytotoxic against MCF-7 breast cancer cells.

Similarly, Kühn and Casini obtained a series of gold(I) complexes combining different NHC and alkynyl ligands (**65a–f** and **66a–f**, Figure 6).[91] All complexes are stable in DMSO/H_2O, 80:20, but undergo alkynyl ligand displacement in the presence of ethanethiol, selected as model nucleophile. The reaction occurs in the presence of water and is highly influenced by the NHC scaffold, the *N*-substituent in the NHC ligand and the R substituent in the alkynyl fragment. The overall stability in PBS is low and strongly dependent on the alkynyl ligand substituent. Even in this case, no significant DNA G-quadruplex stabilisation properties was observed (with the only exception of compound **66c**) and the activity towards different cancer cell lines (SKOV-3, ovarian adenocarcinoma; MCF-7, breast carcinoma; A375, skin malignant melanoma) is low.

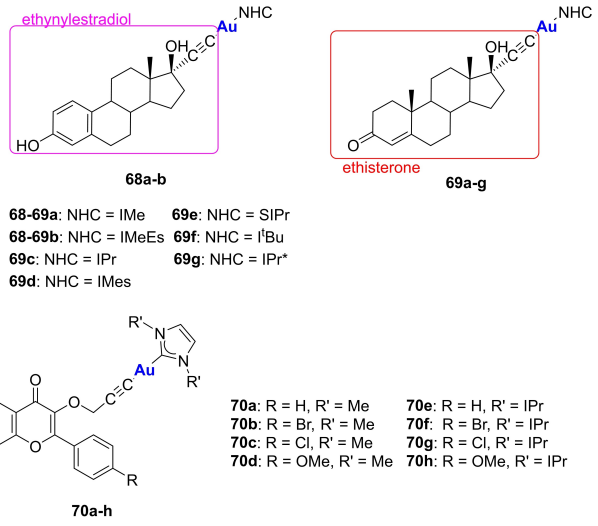
An interesting strategy to improve the biological activity of metal complexes is the coordination of biomolecules or their synthetic derivatives. Following this idea, Besenius and co-workers managed to obtain a gold(I)-alkynyl protected compound (**67a**), which can be easily transformed into its maleimide derivative (**67b**) through a retro Diels–Alder reaction (Scheme 35).[92] The latter can potentially react with other biomolecules in situ through Diels-Alder reactions.

Other interesting examples of gold(I) complexes bearing a bioactive alkynyl fragment are reported in Figure 7. These



67a 67b

Scheme 35. Deprotection of compound **67a** through retro Diels-Alder reaction.



68a-b 69a-g

68-69a: NHC = IMe
68-69b: NHC = IMeEs
69c: NHC = IPr
69d: NHC = IMes
69e: NHC = SIPr
69f: NHC = I^{t}Bu
69g: NHC = IPr*

70a: R = H, R' = Me
70b: R = Br, R' = Me
70c: R = Cl, R' = Me
70d: R = OMe, R' = Me
70e: R = H, R' = IPr
70f: R = Br, R' = IPr
70g: R = Cl, R' = IPr
70h: R = OMe, R' = IPr

70a-h

Figure 7. *N*-heterocyclic gold(I) complexes coordinating biomolecules containing an alkynyl moiety.

complexes (**68a–b** and **69a–b**) were synthesised by Miguel and Montagner, and bear ethynylestradiol and ethisterone, both estrogens.[93] The antimicrobial activity of all complexes was tested in vitro against a Gram-positive and a Gram-negative strain, showing poor activity compared to the chloride congeners. Nevertheless, in vivo test on *G. melonella* insect model pointed out an increase in larvae survival when they are treated with the higher non-toxic concentration of complex (150 μM) and subsequently infected with *E. coli*.

More recently, taking advantage of the *weak-base route*, Nolan and colleagues also obtained new NHC-gold(I) derivatives containing ethisterone as the alkynyl moiety (**69c–g**, Figure 7).[94] These complexes displayed good cytotoxicity against different cancer cell lines (A-549, lung carcinoma; HT-29, colon adenocarcinoma; MDA-MB-231, breast carcinoma). Studies on the uptake mechanism confirmed the role of the steroid moiety in the enhancement of the cellular accumulation.

In 2022, Cerrada and Rodríguez-Yoldi synthesised NHC-gold(I) compounds bearing a propargyl ether functionalized with a flavone moiety (**70a–h**, Figure 7).[95] These complexes are stable under physiological conditions and showed low anticancer activity towards the Caco-2 (human colorectal adenocarcinoma) cell line, coherent with the low capability of inhibiting both human and bacterial TrxR (thioredoxin reductase). Nevertheless, compounds **70b** and **70f** displayed antibacterial activity towards both Gram-positive and Gram-negative strains, as well as significant alteration of the dihydrofolate reductase (DHFR) activity. This information suggests a mechanism of action that is different from the one based on the reduction of TrxR, that is typical for gold complexes.

The structural characteristics of [Au(NHC)(alkynyl)] complexes have prompted the study of self-assembly processes involving the family of golden synthons. For example, complexes **71a–b** (Figure 8), synthesised by Che and Lu, aggregate into nanowires in a 1:9 THF:H_2O mixture.[73b] Moreover, Yam and co-workers described some hydrophobic π-conjugated gold(I)-alkynyl complexes with NHC ligands bearing long alkyl chains as substituents at the N positions (**72a–c**, **73a–c**, Figure 8).[96] These compounds, which also display moderate luminescent properties, aggregate in spherical particles with a diameter of 0.3–1 μm in a 1:1 THF/H_2O mixture. Two notable exceptions are complexes **72a** and **73a**, which exhibit sheet-like nanostructures in the same conditions. This result is ascribable to the higher length of the alkyl chains, that makes them assemble through hydrophobic-hydrophobic interactions in a preferred direction.

Recently, Rodríguez and Gómez-Lor managed to synthesised NHC-gold(I) complexes bearing 4-ethynyl-7-(4-nonylphenyl)benzo[*c*][1,2,5]thiadiazole (**74a–c**, Figure 8).[97] This molecule contains both a 2,1,3-benzothiadiazole moiety, which can confer luminescent properties, and a phenylnonyl moiety, which can induce the self-assembly. The target gold complexes exhibit high fluorescence quantum yield and lifetimes in dichloromethane, with the only exception of compound **74c**, which suffers from non-radiative decay due to aurophilic interactions. The luminescent properties in the solid state are worse than in solution, but they can be strongly enhanced though dispersion in a polymer matrix,

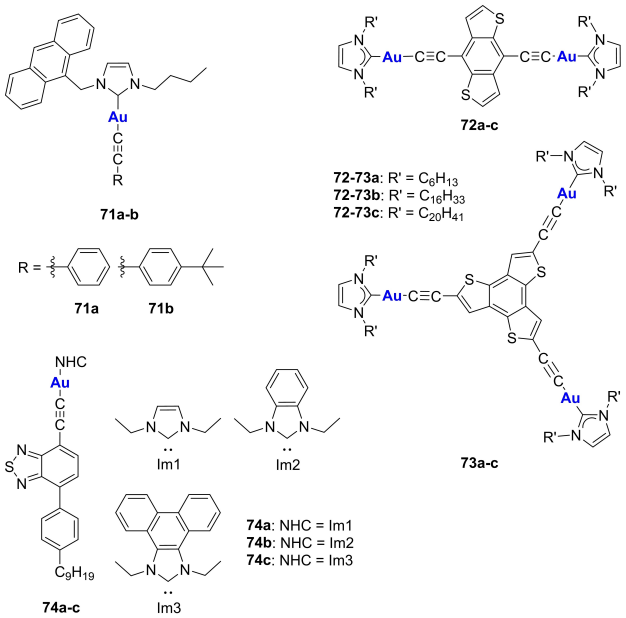


Figure 8. *N*-heterocyclic gold(I) alkynyl complexes with self-assembly and supramolecular properties.

making these compounds promising candidates to produce luminescent materials.

Finally, particular attention has been paid to dinuclear gold(I)-alkynyl complexes bearing bridging dicarbene ligands. This class of compounds can be obtained in a number of ways (see Scheme 36), namely via *i)* the reaction between a $NHC^nAu_2X_2$ (NHC^n = *N*-heterocyclic bidentate carbene, X=Cl, Br) and a terminal alkyne in the presence of K_2CO_3;[98a] *ii)* the reaction of a $NHC^nAu_2Cl_2$ precursor with Tl(acac) (acac = acetylacetonate), followed by the addition of a terminal alkyne;[98a] *iii)* the carbene-transfer reaction from a silver carbene complex to a gold(I)-alkynyl polymeric species;[98a] *iv)* the reaction between a bis(imidazolium) salt with a gold(I)-alkynyl polymeric species in the presence of Cs_2CO_3;[98b] *v)* by grinding a $NHC^nAu_2Br_2$ precursor with KOH and an excess of phenylacetylene.[98c] The latter involved the formation of the corresponding hydroxo-species, which can react with the alkynyl substrate, and is applicable to complexes with $n > 1$.

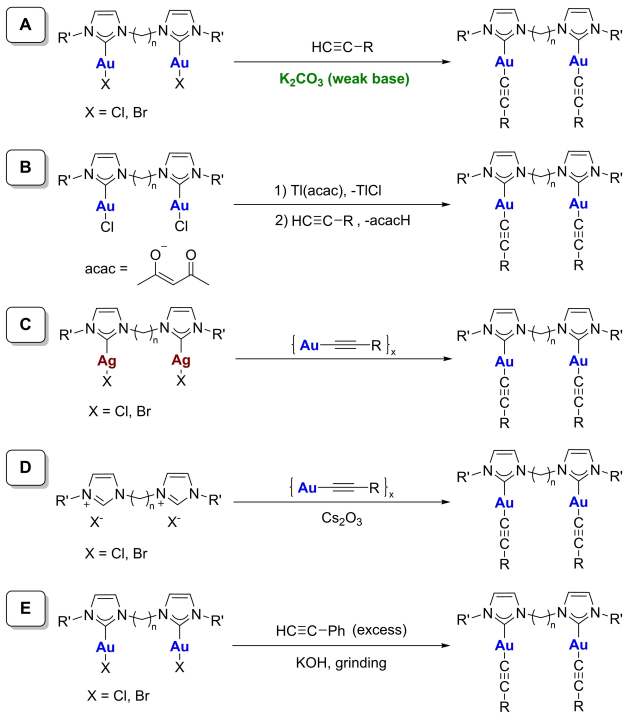
These complexes display often interesting luminescent properties, with structured emission due to gold-perturbed intra-ligand $^3[\pi\text{-}\pi^*]$ (C≡C–R) excited states.

8. [Au(NHC)(alkyl, olefin, alkyne, benzyl, vinyl and allyl)] Complexes

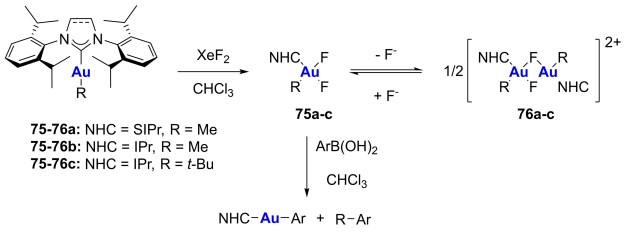
Another class of NHC-gold(I) synthons bears an alkyl fragment. [Au(NHC)(alkyl)] complexes can be obtained from the corresponding chloride precursors by ligand exchange with *n*-BuLi.[99] The oxidation of this kind of compounds with XeF_2 in $CHCl_3$ led to the formation of the Au(III) derivatives **75 a–c** and **76 a–c**, which can subsequently react with arylboronic acids to form a [Au(NHC)(aryl)] complex and an Ar–R coupling product (Scheme 37).

Moreover, gold(I)-alkyl compounds can undergo β- or α-hydride elimination in the presence of Ph_3CX (X = Al(OC-$(CF_3)_3)_4$, BF_4) in CH_2Cl_2, leading to the corresponding η^2-olefin or biscarbene product.[100] [Au(NHC)(η^2-olefin)] or [Au-(NHC)(η^2-alkyne)] complexes can also be easily obtained by adding a dehalogenating agent such as $AgBF_4$ to a [Au-(NHC)Cl] precursor in the presence of the desired alkene/alkyne. In the gold(I)-η^2-alkyne compounds, the ion pair structure shows the anion on the carbene side, while in alkene compounds both *NHC-side* and *olefin-side* orientations have been observed.[101] In particular, NHC-gold(I)-η^2-alkyne complexes are well-known in gold catalysis as key intermediates in the activation of alkynes.[101c]

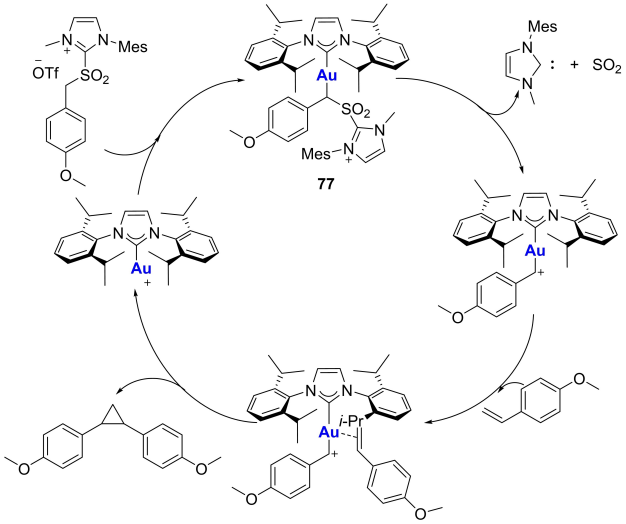
A peculiar category of gold-alkyl compounds is that of gold-benzyl derivatives. In this arena, Chen and Ringger have developed a benzyl precursor (**77**), obtained from the corresponding azolium salt and [Au(IPr)(CH_3CN)]BF_4 in the presence of *n*-butyl lithium, which can be successfully employed in the cyclopropanation of *p*-methoxy styrene.[102] The reaction involves the formation of a carbocationic species, which is the operating catalyst (Scheme 38).



Scheme 36. Synthetic routes to dinuclear gold-alkynyl complexes.



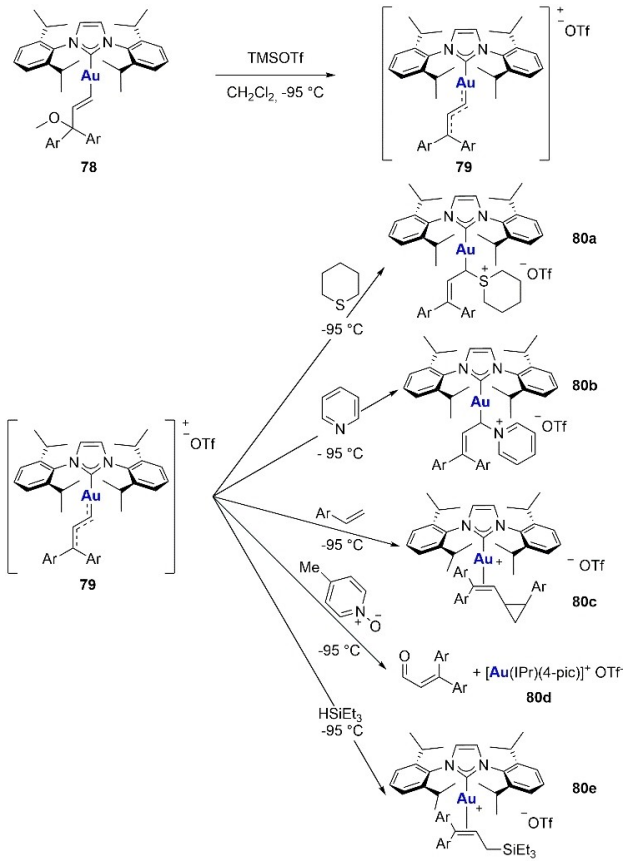
Scheme 37. Oxidation of NHC-gold(I)- alkyl complexes with XeF_2.



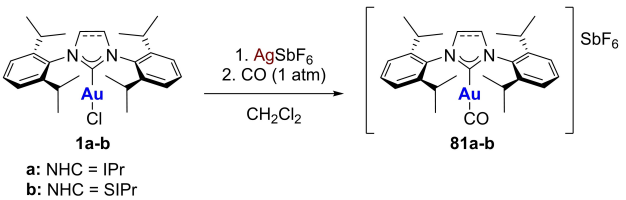
Scheme 38. Catalytic cyclopropanation of *p*-methoxy styrene in the presence of the gold-benzyl precursor **77**.

As for [Au(NHC)(vinyl)] complexes, γ-metoxy-(γ,γ-diaryl)vinyl derivatives (**78**), obtained from a boronic ester and [Au(IPr)Cl] with the assistance of Cs_2CO_3, can be used as synthons to produce allyl carbene derivatives (**79**) in the presence of a slight excess of TMSOTf in CH_2Cl_2 at −95 °C (Scheme 39).[103] The obtained complexes are stable only at low temperatures but can efficiently react with neutral or anionic nucleophiles at the C1 position, thus forming complexes such as **80 a**–**f** (Scheme 39).

One of the most used C-donor ligands is carbon monoxide. NHC-gold(I) complexes containing this ligand have been synthesised by Rasika Dias and Kroll by dehalogenating [Au(NHC)Cl] with $AgSbF_6$ and subsequently adding CO in CH_2Cl_2 (**81 a**–**b**, Scheme 40).[104] The obtained complexes display shorter C–O bond length and higher νCO value than the free carbon monoxide, suggesting that the carbonyl ligand behaves more as a σ-donor than a π-acceptor.



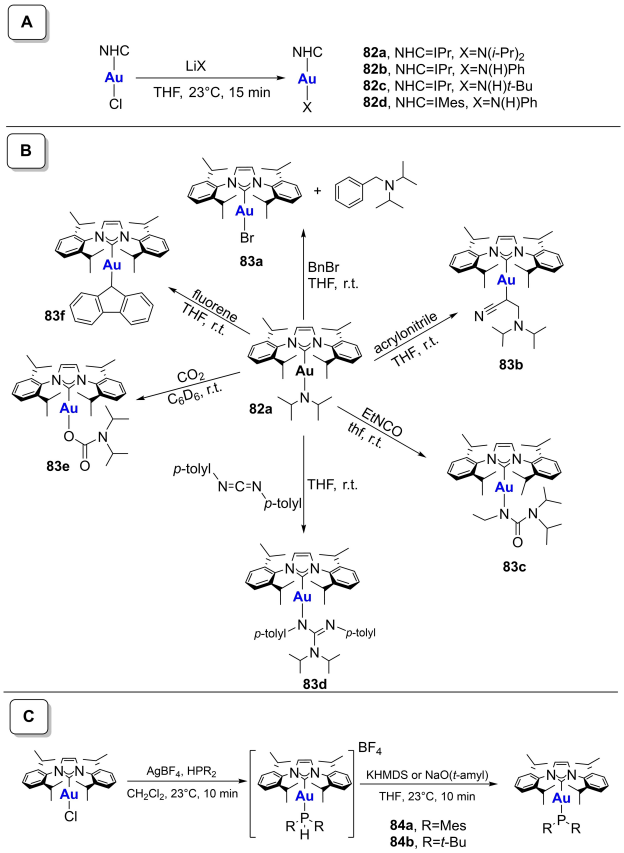
Scheme 39. Use of NHC-gold(I)-vinyl and -allyl carbene complexes as synthons.



Scheme 40. Synthesis of [Au(NHC)(CO)] complexes.

9. [Au(NHC)(amido)] Complexes

Carbene-metal-amides (CMAs) are important intermediates in different catalytic reactions such as Buchwald-Hartwig amination[105] and olefin hydroamination.[106] Interestingly, these carbene complexes can also be used as starting materials for a wide range of gold-NHC derivatives. In this respect, Toste and Bergman, reported in 2012 the first examples of [Au(NHC)(amido)] complexes used as synthons.[107] The latter were obtained by reaction of a [Au(NHC)Cl] precursor and a lithium amide (Scheme 41A). Afterwards, the reactivity of complex **82 a** towards different organic substrates was successfully explored (Scheme 41B). The reaction with benzyl bromide led to immediate alkylation of the amido ligand and the formation of [Au(IPr)Br] (**83 a**). When acrylonitrile was used as substrate, an insertion reaction, leading to an alkyl complex was observed (**83 b**). Other insertion processes were observed in the presence of ethyl isocyanate (**83 c**), *p*-tolyl carbodiimide (**83 d**) and carbon dioxide (**83 e**). Finally, the basicity of the amido ligand was sufficient to deprotonate fluorene, leading to the corresponding gold-alkyl complex (**83 f**).



Scheme 41. (A) Synthesis of [Au(NHC)(NR_2)] complexes **82 a**–**d**; (B) [Au-(IPr)(N*i*Pr_2) as synthon; (C) Synthesis of [Au(NHC)(PR_2)] complexes **84 a**–**b**.

In the same contribution, the authors tried to synthesize gold(I)-phosphide complexes from [Au(NHC)Cl] and a phosphine, leading to the phosphine salt as intermediate, that can be deprotonated with a base to form the final gold-phosphide complexes (Scheme 41C). Unfortunately, complex **84 b** was not isolated because of its instability.

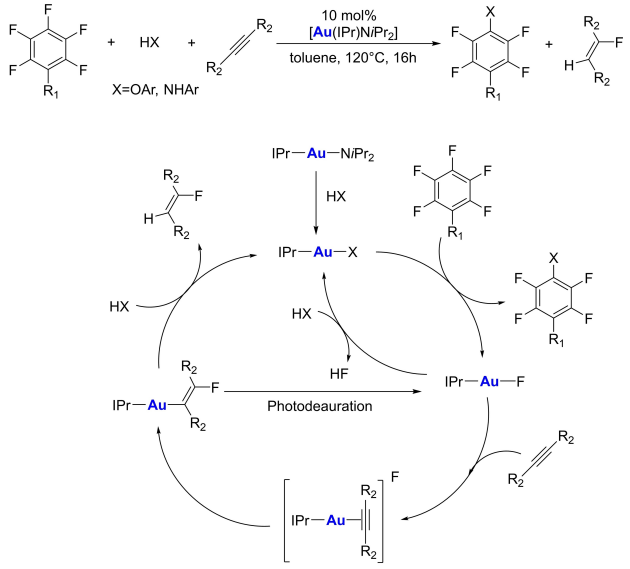
Complex [Au(IPr)(N*i*Pr$_2$)] was also tested as catalyst for HF addition to alkynes, leading to fluoro-alkenes.[108] The method avoids the need to directly handle HF or related compounds and represents an important alternative for recycling fluorinated compounds. The catalyst was tested with different nucleophiles, fluoroarenes and alkynes. High to modest yields were obtained and the reaction produced exclusively (*E*)-alkenes. The catalytic experiments suggest a complex catalytic cycle involving both cS$_N$Ar and hydrofluorination mechanisms within a single reaction network (Scheme 42).

Carbene-metal-amido complexes bearing cyclic alkyl amino carbene (CAAC) ligands have recently emerged as a new class of highly efficient light-emitting materials.[109] In many cases, their luminescence is ascribed to thermally activated delayed fluorescence (TADF) due to ligand-to-ligand charge transfer (LLCT) involving electron donation from the electron-rich amido ligand to a LUMO, based on the carbene p orbital, which acts as π-acceptor. Because of the small energy separation between the lowest singlet and triplet excited states, the intersystem crossing from the long-lived triplet to the faster radiating singlet state is facilitated.[110]

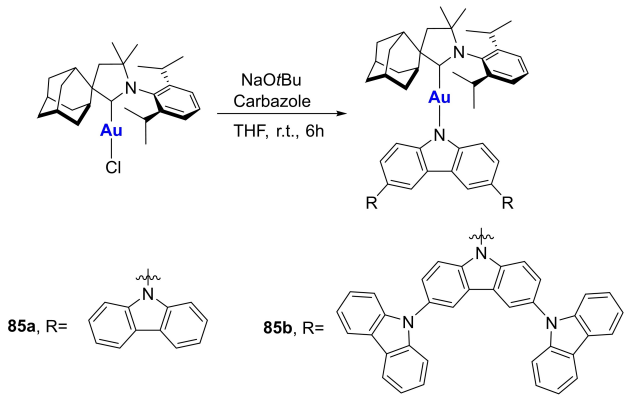
In 2019 Romanov, Yang, Linnolahti, Credgington and Bochmann synthesized two [Au(CAAC)(amido)] complexes (**85 a**–**b**) bearing first and second generations carbazole dendrimers as amido ligands (Scheme 43).[111] These complexes are stable for long periods in air and in aprotic organic solvents. Both complexes displayed high Photoluminescence Quantum Yields (PLQY) in toluene and in 20 % weight doped polyvinylcarbazole (PVK) films. The solution photoluminescence decays were <1 μs in both cases. The complexes were tested as emitters in OLED devices showing good performances such as low turn-on voltages (3.2 V) and high maximum luminance, especially for complex **85 a**.

A similar procedure was adopted for the synthesis of complex **86** (Scheme 44).[109] This complex showed high energy intra-ligand transitions associate to both ligands and a low HOMO-LUMO energy gap. For these reasons, the complex showed red emission properties with a sub-microsecond excited state lifetime.

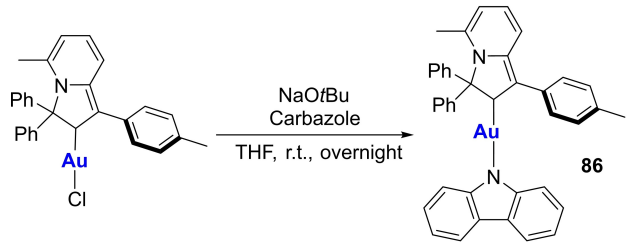
Other [Au(NHC)(amido)] complexes were synthesized by Li, Cui and Chen, using 5 % NaOH aq. as base (Scheme 45).[112] Only for complex **87 d** tetrabutylammonium bromide was added and CH_2Cl_2 was used as solvent. The XRD analysis revealed a sp^2 hybridization of the coordinating C and N atoms, with the Au–N bond in the plane of the carbazolyl ligand. As demonstrated in the past, this molecular configuration is ideal for both intense charge-transfer transition and proper separation of frontier orbitals leading to rapid



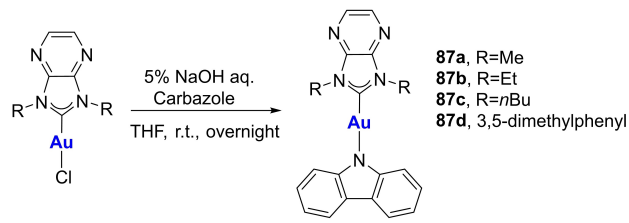
Scheme 42. Gold-catalyzed alkyne hydrofluorination reaction and plausible catalytic cycle.



Scheme 43. Synthesis of gold complexes **85 a**–**b** bearing carbazolyl dendrimers.



Scheme 44. Synthesis of complex **86**.



Scheme 45. Synthesis of complexes **87 a**–**d**.

radiative transitions and high TADF emission efficiency.[112] For complexes **87 c–d** high emission efficiencies were measured in doped PMMA films ($\phi = 0.89–0.91$ at r.t.). All complexes exhibit highly efficient TADF emission with short delayed fluorescence lifetimes (< 1 μs) in doped films which are appealing for OLED fabrications.

Dinuclear gold-amido complexes showed promising luminescence properties.[113] In this respect, Thompson and coworkers synthesized the homo-bimetallic gold complex **88** starting from the corresponding gold-Cl synthon (Scheme 46). Theoretical modelling indicated that the emissive inter-ligand charge transfer (ICT) excited state involves both NHC ligands. The complex displayed blue luminescence with a high photoluminescent quantum yield ($\phi = 0.80$).

Mononuclear carbene-metal-amides were synthesized and characterized by the same group (Scheme 47).[110] Three couples of complexes were synthesized varying the metal (Au, Ag, Cu) and NHC ligand. In all cases the complexes showed high photoluminescent quantum yields and, in general, extinction coefficient for the charge transfer bands were higher in the case of gold complexes.

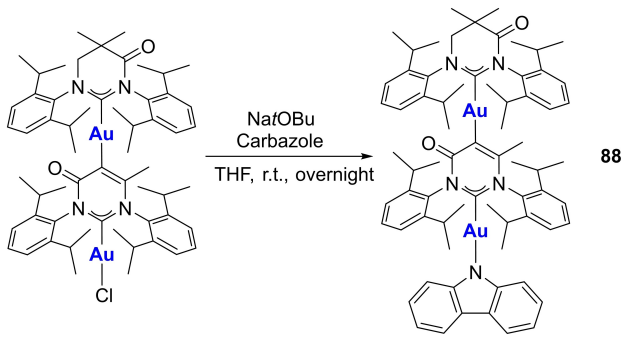
With a similar procedure, complexes **90 a–b** were obtained by Linnolahti, Bochmann and Romanov using two [Au(CAAC)Cl] synthons (Scheme 48).[114] Complex **90 b** showed superior photostability compared to **90 a** if irradiated with UV light at 290 nm in different media. Compared to other metals (Cu, Ag), gold derivatives proved more photostable. Notably, complex **90 b** showed 100 % quantum yield in toluene.

In the case of complexes **91 a–f**, reported in 2022 by Cui and Li, the dihedral angle between the carbene and the carbazolyl ligands strongly depends by the aromatic group bound to the carbazolyl moiety (Scheme 49).[115] Owing to the twisted conformation, these gold-NHC complexes exhibited high PLQYs and sub-microsecond lifetimes. As usual, the complexes were examined for solution-processed OLEDs but the maximum external quantum efficiency (EQE) was below expectations.

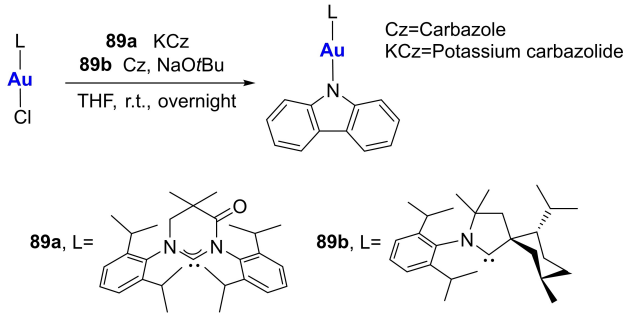
The strong base route was also exploited by Romanov, Linnolahti, Credgington and Bochmann for the synthesis of CMA complexes bearing wide range of amido ligands (**92 a–h** in scheme 50).[116] Those complexes are non-planar and conformationally flexible. Strong π-π* transitions were noted in THF solution, ascribed to an intra-ligand transition of the CAAC. An interesting property is the mechanochromic response of complex **92 a** due to the possibility to crystallize it in two different forms: monoclinic (475 nm emission) and orthorhombic (540 nm and 475 nm emission).

Complexes **92 i–n** were synthesized with the aim of evaluating the influence of aza-substitution in carbazole ring on photoluminescence.[117] The substitution allows the systematic variation of both charge transfer (CT) and locally excited (^{3}LE) states. Using the same CAAC ligand, Romanov, Linnolahti, Credgington and Bochmann prepared complexes **92 o–r**, which exhibited green emission and a TADF behaviour.[55]

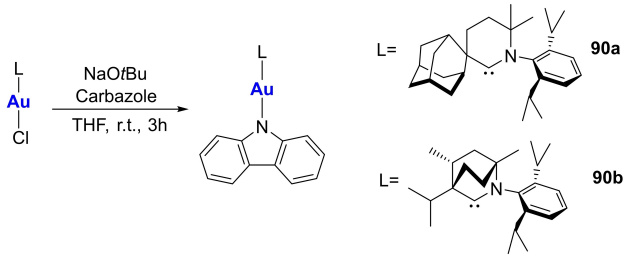
In the last three years, Nolan and Cazin have demonstrated the possibility of synthesizing Carbene-Gold-Amido complexes using a weak base such as K_2CO_3 under mild



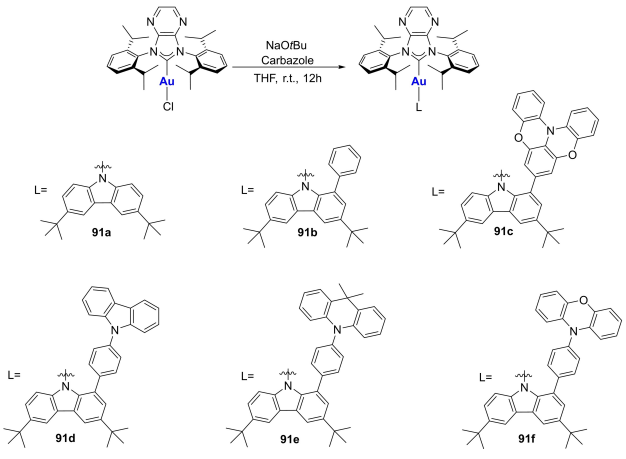
Scheme 46. Synthesis of complex **88**.



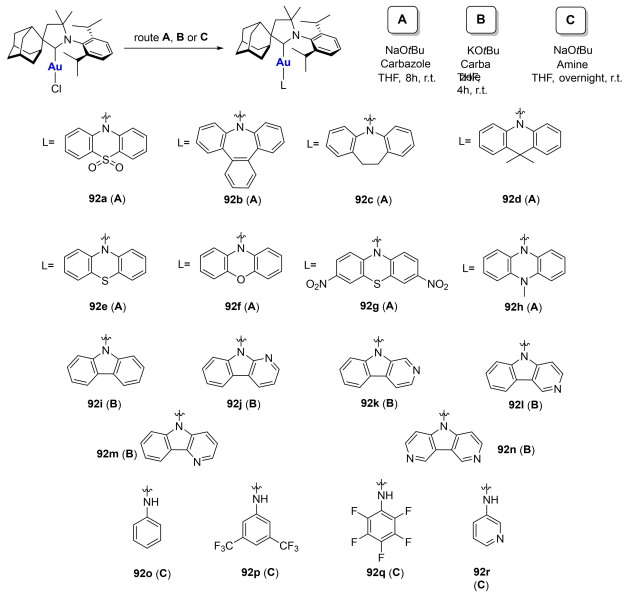
Scheme 47. Synthesis of complexes **89 a–b**.



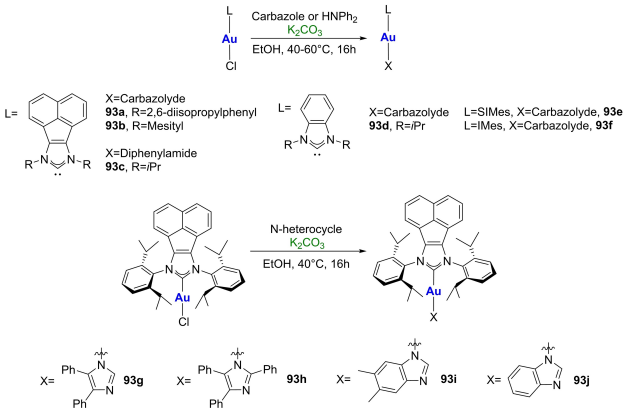
Scheme 48. Synthesis of luminescent complexes **90 a–b**.



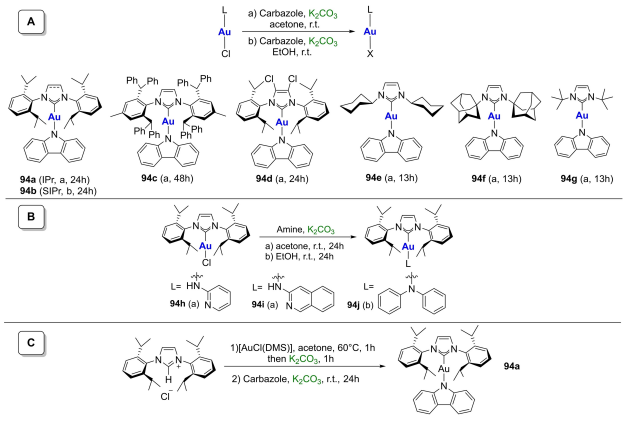
Scheme 49. Synthesis of NHC-gold luminescent complexes bearing different carbazolyl ligands.



Scheme 50. Synthesis of complexes **92a–r**.



Scheme 51. Synthetic procedure using K_2CO_3 as base.



Scheme 52. A: synthesis of carbazolyl complexes; B: synthesis of gold complexes bearing other amido moieties; C: One-pot synthesis of **94a**.

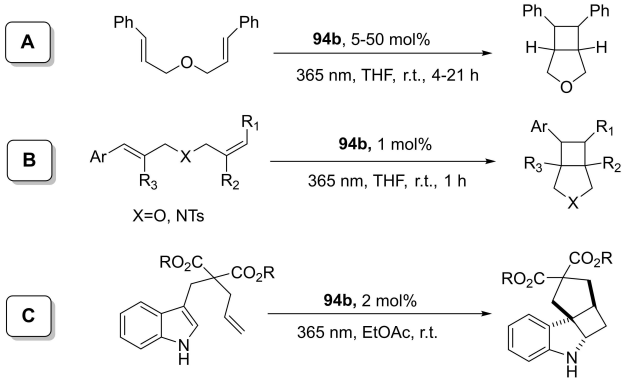
conditions.[118a] As an example, in the case of BIAN-NHC derivatives, the reactions were performed in EtOH at 40–60 °C for 16 h under aerobic conditions (Scheme 51).[118] These [Au(BIAN-NHC)(amido)] complexes, alongside other Au-based CMAs, were successfully tested as catalysts in hydrocarboxylation of diphenylacetylene and in alkynoic acid cyclization to lactones.

This *weak-base driven* procedure is tolerant by a wide range of NHC and amido ligands as presented in Scheme 52A–B.[118b] In the case of carbazole, when a bulkier NHC ligand is present, the reaction requires more than 24 h (e.g., complex **94c**). A one-pot synthesis of complex **94a** was performed with high yields (Scheme 52C). Importantly, this synthetic procedure was also applicable in the cases of Ag- and Cu-based CMAs.

Complexes **94a–b** were studied for their photophysical properties and complex **94b** possessed the highest photostability and high energy phosphorescence in the blue-green range with a long lifetime in solution. For these reasons, complex **94b** was chosen as photocatalyst in the [2 + 2] cycloaddition of (E,E')-dicinnamylether via triplet energy transfer (Scheme 53A).[118b] Gratifyingly, full conversion of the substrates was observed at room temperature. The same complex was explored as photocatalyst in the [2 + 2] cycloaddition of diallyl ethers and *N*-tosylamides with good to excellent yields (Scheme 53B).[118c] The reaction proceeds faster compared to classical iridium photocatalysis.

Moreover, in the challenging [2 + 2] cycloaddition of indoles, good to excellent yields were obtained with complex **94b**. The performances of this catalyst far exceed classical ruthenium-based and iridium-based photocatalysts (Scheme 53C).[118d]

With the aim of improving the access to carbene-metal-amides, Nolan, Cazin and Stevens developed a continuous flow process for the synthesis of these valuable species.[119] With a microreactor filled with potassium carbonate, complexes **94a–e** were synthesized starting from the [Au(NHC)Cl] precursor and carbazole under extremely mild conditions (60 °C, 2 min of residence time and ethanol as solvent). As an extension of this continuous flow protocol, the [Au-



Scheme 53. [2 + 2] cycloaddition catalysed by complex **94b**.

(IPr)(Harmine)] complex (**95**) was synthesized in excellent yields (Scheme 54).[119]

Interestingly, the same continuous flow setup is suitable for the synthesis of NHC-gold-thiolato complexes,[119] with extremely reduced reaction times compared to the standard batch protocol.[11b]

The possibility of choosing between two synthetic approaches (strong base route and weak base route) depending on the NHC ligand of interest was exploited by Thompson and co-workers for the preparation of complexes **96a–n** (Scheme 55).[120] They explored the impact of π-extending the carbene and amido ligands on the photophysical properties of CMA complexes. They noticed that π-extending the carbene and amide moieties together lead to some of the highest radiative rates observed for a triplet-controlled emission process. Curiously, the type of NHC in [Au(NHC)(Cz)] complexes did not affect significantly the photophysical properties of the gold derivatives. Conversely, π-extending the amide ligand significantly influence some photophysical properties such as decay rates.

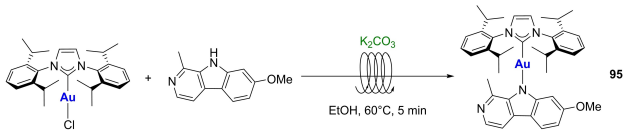
In 2022, Nolan and Rizzolio reported a series of gold-carboline and gold-harmine complexes **95**, **97a–d** as well as the dinuclear gold complex **97e** (Scheme 56).[121] The complexes were synthesized via an improved, green procedure (filtration from EtOH/H_2O) and screened for their antiproliferative properties against tumor and non tumor cell lines. Generally, the antiproliferative activity was similar to cisplatin on A2780 (ovarian cancer), OVCAR5 (ovarian cancer, high grade serous HGSOC) and LOVO (colon cancer). Only complex **97a** was inactive on MRC-5 normal cells, thus suggesting a selective anticancer activity. Interestingly, complex **97a** was active against HGSOC patient-derived 3D tumoroids with an $IC_{50} = 2.2 \pm 0.8$ μM (Carboplatin > 200 μM).

The promising anticancer activity of [Au(NHC)(amides)], with a preferential cytotoxicity on cancer cells, was confirmed by Nolan and colleagues in another contribution.[122] In that case, gold complexes bearing a wide range NHC and nitrogen-based heterocyclic ligands were successfully synthesized with a unified procedure and tested in vitro towards ovarian cancer cell lines and MRC-5 normal cells (Scheme 57).

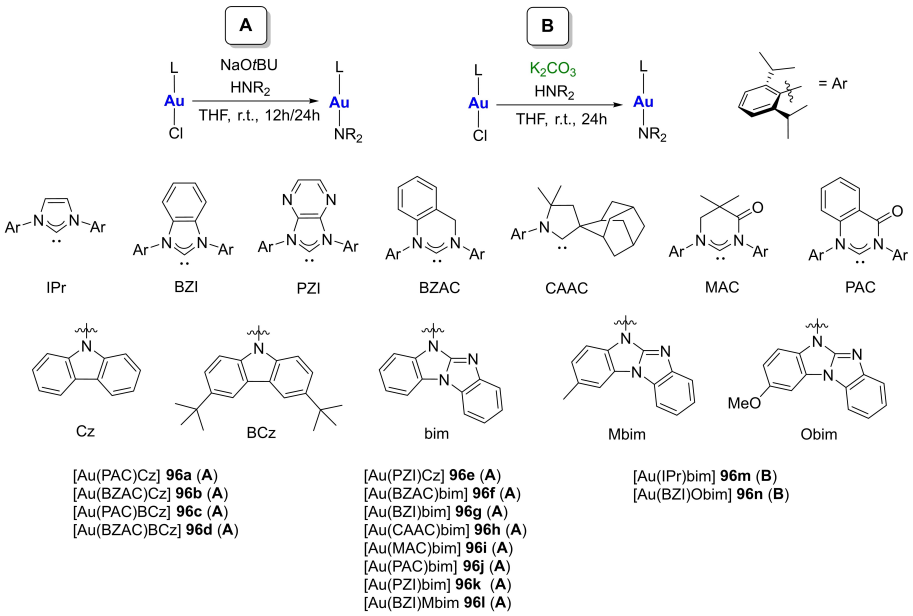
10. [Au(NHC)(NTf_2)] Complexes

[Au(NHC)(NTf_2)] complexes (NTf_2 = bis(trifluoromethanesulfonimide)) are widely used in organometallic chemistry as synthons as well as efficient homogeneous catalysts. These valuable species are usually prepared by mixing a [Au(NHC)Cl] precursor with $AgNTf_2$.[123] Alternative protocols involve the use of [Au(NHC)(OH)] or (Au(NHC)(acetonyl)] complexes and $HNTf_2$ as starting materials.[49,123] For example, Nolan and co-workers have synthesized [Au(NHC)(NTf_2)] (NHC=IPr, SIPr, IPr^{Cl}, IPr*) and [Au(ITent)(NTf_2)] (Tent = Tentacular) complexes by reacting their [Au(NHC)(OH)] precursors and $HNTf_2$ in toluene or benzene at room temperature for a few hours (Scheme 58A and B).[32,36] Notably, [Au(ITent)(NTf_2)] complexes were successfully tested as catalysts in alkyne hydration, nitrile hydration and homoallylic ketone synthesis (Scheme 58C).

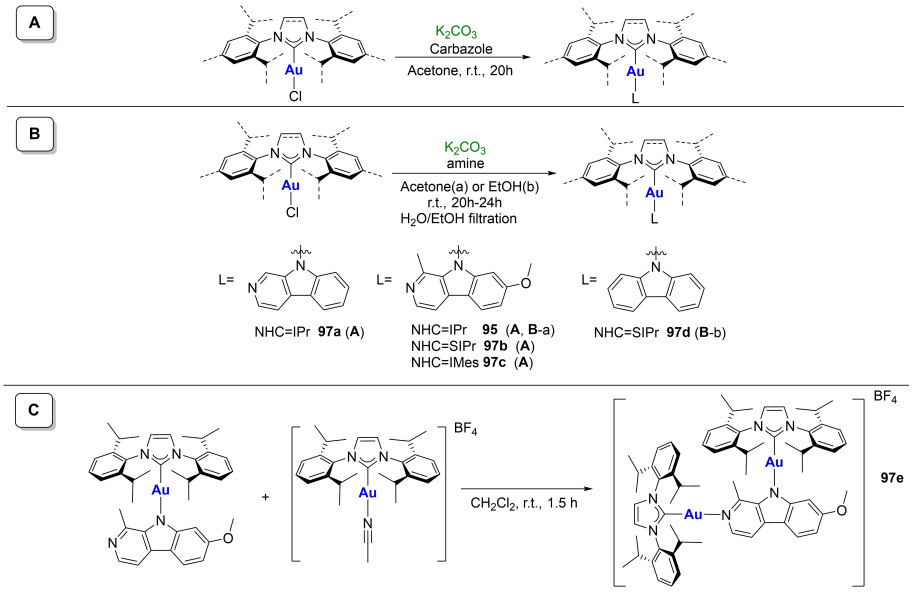
In 2017, the reaction between [Au(IPr)(NTf_2)] and a selection of phosphines was reported. The reactions pro-



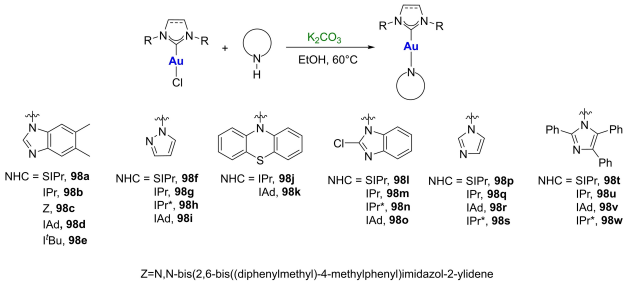
Scheme 54. Continuous flow synthesis of complex **95**.



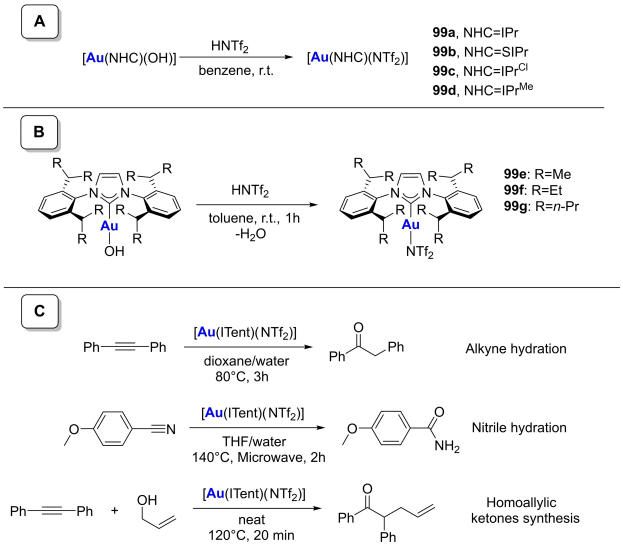
Scheme 55. Synthesis of luminescent complexes bearing different carbene and carbazolyl ligands.



Scheme 56. Synthetic routes for NHC-gold-carboline complexes and synthesis of the dimeric complex **97e**.



Scheme 57. Synthesis of gold-NHC complexes bearing different nitrogen-based heterocyclic ligands as promising antitumor agents.

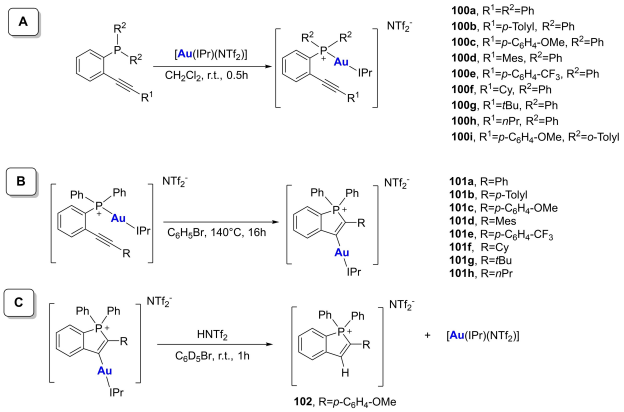


Scheme 58. Synthesis and catalytic applications of some [Au(NHC)(NTf_2)] complexes.

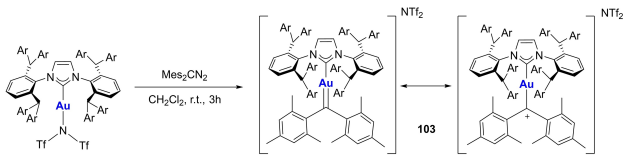
ceeded towards the formation of NHC-gold-phosphino complexes **100a–i** (Scheme 59A).[124] The latter evolve at 140 °C in 16 h into the corresponding phosphinidolium salts that were isolated in good yields (Scheme 59B). The reaction between complexes **101a–h** and $HNTf_2$ led the fast protodemetalation and to the formation of the [Au(IPr)(NTf_2)] complex (Scheme 59C). One of the key factors of the abovementioned processes is the use of a phosphine bearing an *o*-alkynyl group.

Straub and co-workers have synthesized a non-heteroatom-stabilized gold-carbene complex with predominant carbenium character using [Au(NHC)(NTf_2)] as synthon in combination with dimesityldiazomethane (Scheme 60).[125]

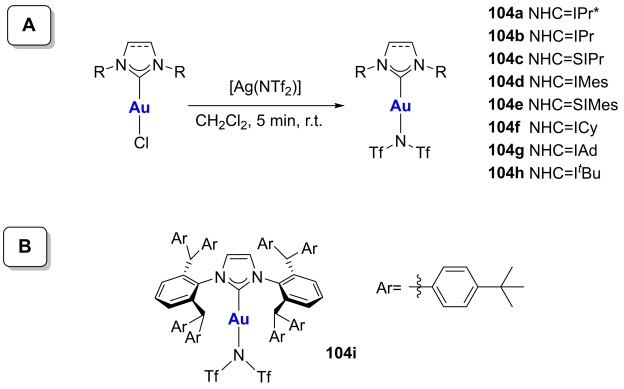
With a silver-based protocol, Nolan and Cazin studied the catalytic activity of [Au(NHC)(NTf_2)] complexes **104a–i** reported in Scheme 61.[123] The first catalytic reaction was the formation of 4-alkoxy-2(5H)-furanones from a variety of propargylic alcohols, in which the most active complex was



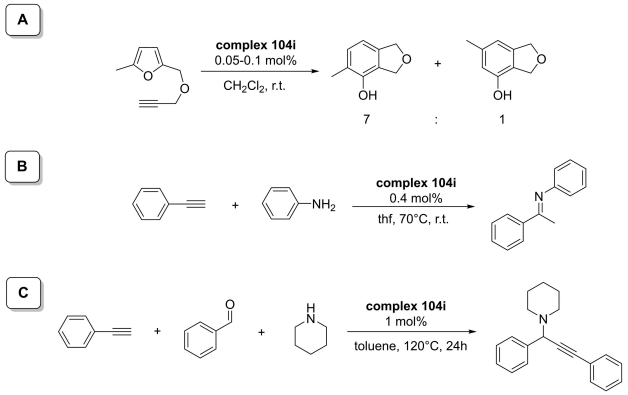
Scheme 59. (A) Synthesis of gold-phosphino complexes **100a-l**, (B) Cyclization reaction, (C) Protodemetalation.



Scheme 60. Synthesis of a non-heteroatom-stabilized gold-carbene complex.



Scheme 61. Synthesis of [Au(NHC)(NTf_2)] complexes from the chloride synthon.



Scheme 62. (A) Gold-catalyzed phenol synthesis, (B) Gold-catalyzed amination of phenylacetylene, (C) Gold-catalyzed three-component catalytic reaction.

[Au(IAd)(NTf_2)] (85% conversion).[126] In the rearrangement of propargylic acetates into conjugated enones or substituted indenes the most active complexes were [Au(I^tBu)(NTf_2)] and [Au(IPr)(NTf_2)].[126]

Straub and colleagues investigated complex **104i** as a robust and highly active catalyst in the Hashmi phenol synthesis (Scheme 62A), amination of phenylacetylene (Scheme 62B) and in the three-component coupling reaction of benzaldehyde, piperidine and phenylacetylene (Scheme 62C).[127] In the case of reactions reported in Schemes 62A–B, complex **104i** was produced in situ from [Au(NHC)Cl] and $AgNTf_2$.

Complex **104b** was investigated in other catalytic reactions such as the selective coupling of the carbene moieties from diazo compounds (Scheme 63A–B).[128,129] With the conditions reported in Scheme 63C, which represents a formal [3 + 2] cycloaddition, only one isomer was obtained.

In 2021, Sarkar and colleagues reported the synthesis of [Au(MIC)(NTf_2)] complex **105** (Scheme 64), which was tested as catalyst in the hydroamination of phenylacetylene.[130]

In 2014, the reactivity of [Au(IMes)(NTf_2)] in transmetalation reaction with a tungsten carbene complex was studied by Fürstner and colleagues (Scheme 65A).[131] The reaction led to a *gem*-bimetallic complex (**106a**) that is stable at r.t. in CH_2Cl_2 solution for hours. When a chromium carbene complex is used as reagent, the reaction primarily leads to the analoguous bimetallic complex **106b**, that rapidly evolves into complex **106c** by CO loss (Scheme 65B).[131] Notably, the final complex is stabilized by charge delocalization over the metals, the carbene centre and the *ipso* carbon of the arene.

11. Gold-NHC Complexes Bearing Other Nitrogen-Based Ligands

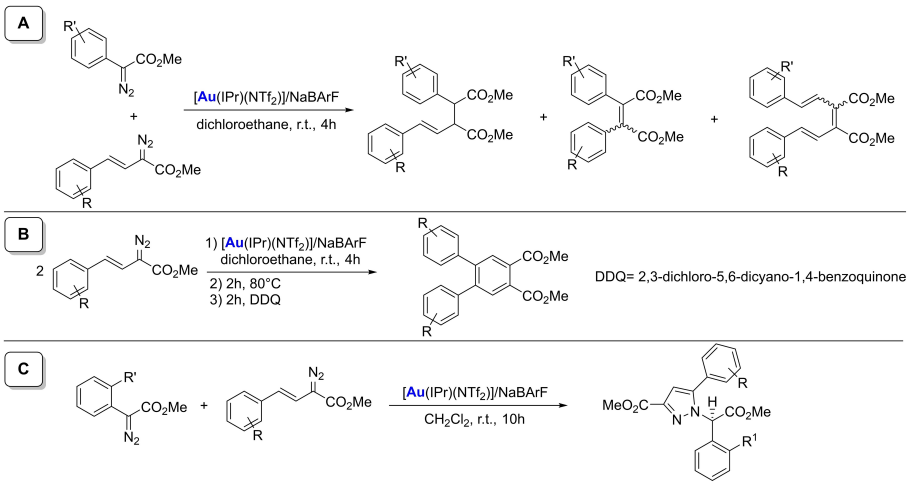
In addition to gold-amido and gold-NTf_2 complexes, some golden synthons bearing other nitrogen-based ligands have been developed over the years. Hrobárik, Bochmann and Rocchigiani have synthesized [Au(NHC/CAAC)(NCMe)][SbF_6] complexes (Scheme 66A) and examined their reactivity towards different metal hydride complexes.[132] The reaction with [$W(Cp)_2H_2$] and [$Zr(Cp)_2H_2$] led to different H-bridging adducts which are reported in Schemes 66B–C.[133,134]

Others gold-nitrile complexes were synthesized by Pérez, Prieto and Echavarren from gold-chloride and gold-NTf_2 synthons as reported in Scheme 67.[135]

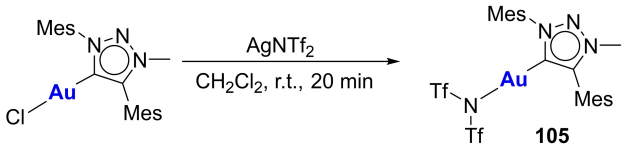
Gold-nitrile complexes can be used as catalysts in many organic processes such as intramolecular [4 + 3] cycloadditions with good yields and enantiomeric excesses (Scheme 68).[136]

In 2021, Jin and Ito developed a homobimetallic NHC–Au-pyrazine complex belonging to the category of amphidynamic crystals.[137] The latter are molecules that generate sufficient volume near axially linked molecular rotators that allow for large angular displacements also in the solid phase. These crystals are studied for the development of smart materials and molecular machines. The synthesis was performed threating [Au(IPr)Cl] with deuterate pyrazine and [$Ag(SbF_6)$] (Scheme 69). In this case, bulky carbenes are the encapsulating stators and pyrazine the rotator (having π-accepting ability), and gold as a centre of the axle. The rotor exhibited a quantum yield of 0.12 and emission lifetimes on the microsecond scale.

Hattori and colleagues later reported a series of luminescent gold complexes that contain a pyridyl radical ligand.[138] The target complexes were obtained from a gold-chloride precursor and showed a strong adsorption band around 420 nm and the strongest one around 370 nm (Scheme 70). Complex **111a** showed the highest fluorescence quantum yield (36%).



Scheme 63. (A) Carbene coupling from diazo compounds; (B) Homocouplig of vinyldiazoacetate; (C) Reaction conditions to obtain only one isomer using the [Au(IPr)(NTf$_2$)]/NaBAr$_4$ catalyst.



Scheme 64. Synthesis of a mesoionic carbene-Gold-NTf$_2$ complex.

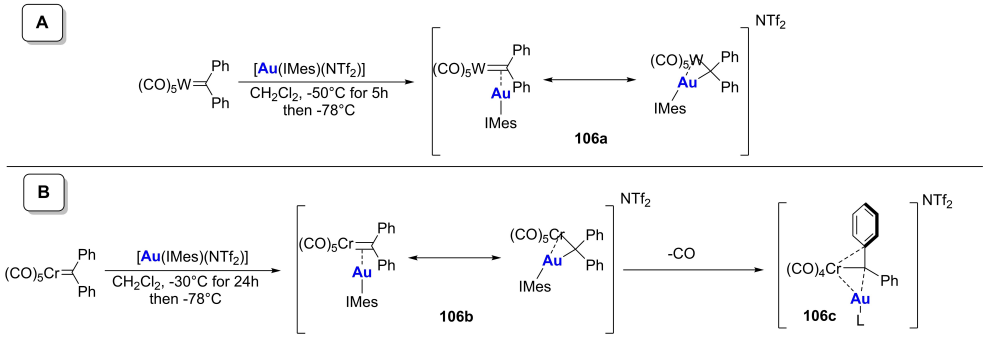
In the same year, some gold(I/III)-pyridyl complexes were synthesized and their reactivity is summarized in Scheme 71.[139]

More in detail, dinuclear complexes **112a–b** were obtained from [Au(NHC)Cl] precursors in the presence of $AgSbF_6$. Addition of $PhIX_2$ afforded their mononuclear derivatives **112c–d**. Moreover, when biphenylene and diazonium salts are added in the reaction mixture, complexes **112e** and **112f** were obtained, respectively.

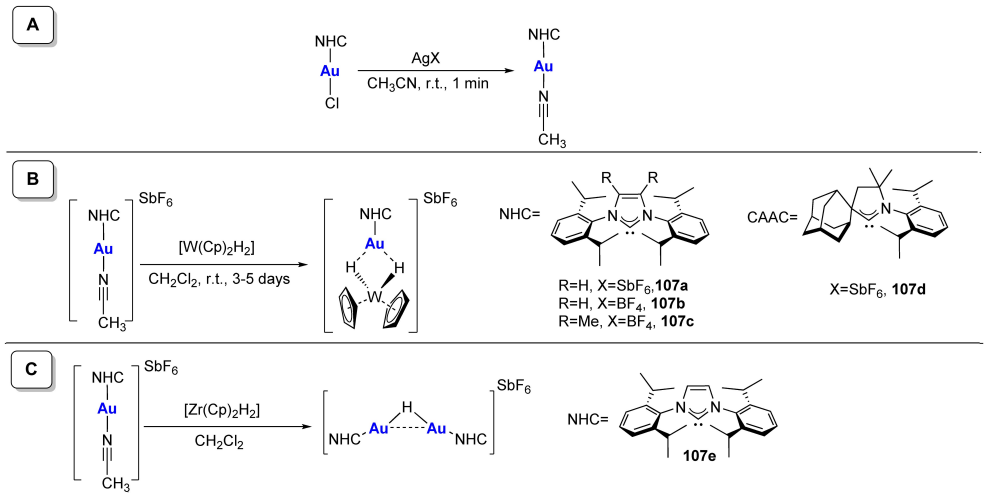
Complex **112f** was also tested as catalyst in the arylation-lactonization of alkenoic acids. This reaction was performed in the presence of $AgSbF_6$, 4-pentenoic acid, 4-iodoanisole and K_3PO_4 leading to γ-benzyl-γ-butyrolactone in 73% yield.

With a similar procedure, a wide scope of [Au(NHC)(bis(aryl)acenaphthenequinonediimine)] complexes was synthesized following the conditions reported in Scheme 72A. These gold derivatives were tested as catalysts in the addition of a nucleophilic carbon to an 1,6-enyne (Scheme 72B).[140] This latter process should proceed via a three steps mechanism: *i)* coordination and activation by gold(I) of the alkyne moiety; *ii)* rearrangement of the alkene function to a distorted anticyclopropyl gold(I) carbene; *ii)* attack of the indole to the carbene gold(I) or the cyclopropyl ring.

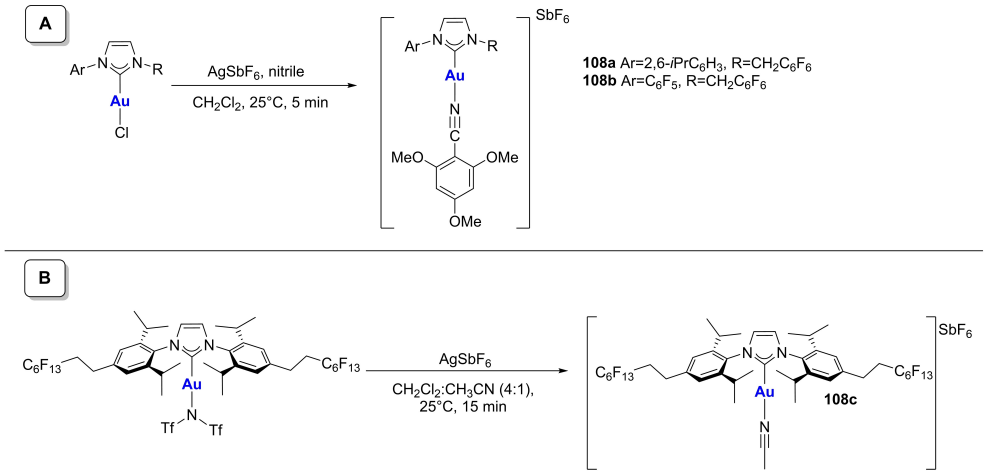
Finally, some [Au(NHC)(organoazido)] complexes were recently synthesized by Dias and Cundari (Scheme 73A).[141] Although these gold derivatives are surprisingly stable at room temperature (both in the solid state and in solution) and can be exhaustively characterized, they undergo nitrogen extrusion at 50 °C, leading to gold complexes reported in Scheme 73B.



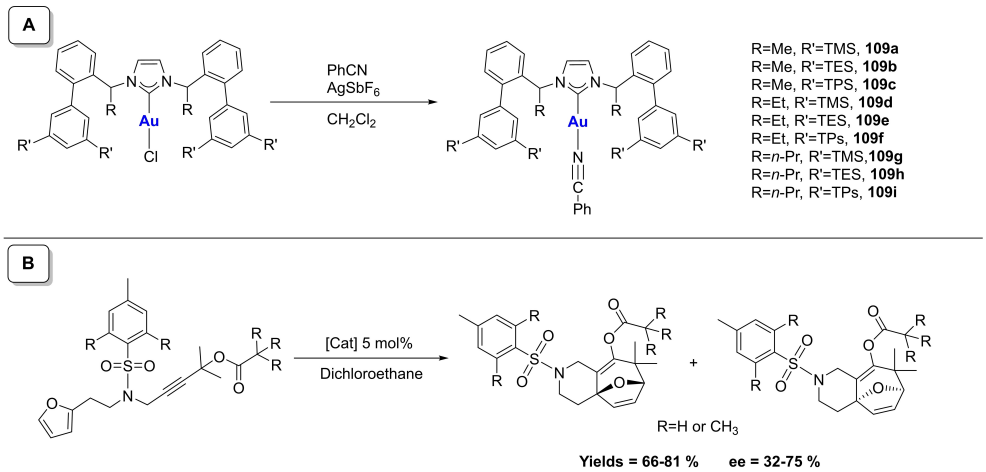
Scheme 65. (A) Reactivity of [Au(IMes)(NTf$_2$)] and a tungsten carbene complex; (B) Reactivity of [Au(IMes)(NTf$_2$)] and a chromium carbene complex.



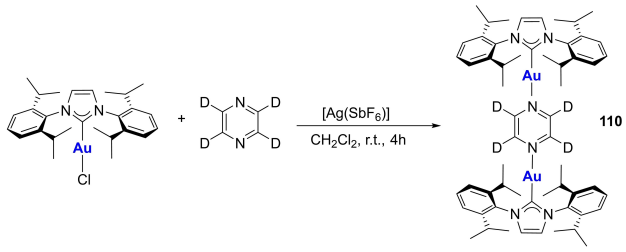
Scheme 66. (A) Synthesis of gold-acetonitrile complexes; (B) and (C) Reactions with metal hydrides.



Scheme 67. Synthesis of fluorinated nitrile complexes.



Scheme 68. (A) Synthesis of gold nitrile complexes **109 a-i**; (B) Gold-catalyzed intramolecular [4 + 3] cycloadditions.



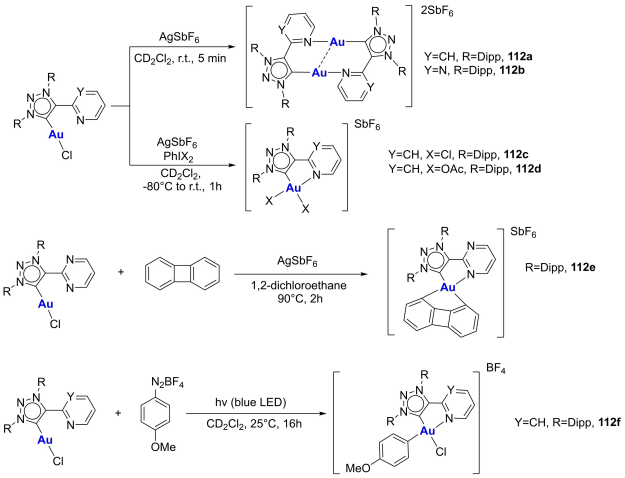
Scheme 69. Synthesis of complex **110**.

12. Gold-NHC complexes bearing fluorinated ligands

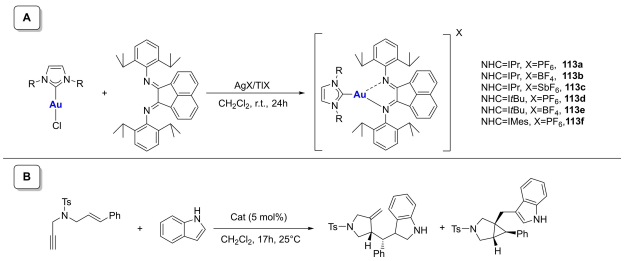
Fluorine is one of the most earth abundant elements. Its small size, high electronegativity and high oxidation potential place it in a unique position. It is present in many man-made pharmaceutical compounds, where it brings advantages such as permeability and metabolic stability. When connected to a transition metal, it drastically changes its properties.[2a] In the case of gold, complexes of the AuF_n family are usually unstable and have only ever been observed in the gas phase through indirect techniques.[142]

To obtain an isolable gold fluoride complex, the metal centre needs to be stabilized with a highly donating ligand. The first example of such a complex was reported in 2005, using SIPr as ancillary ligand and triethylamine tris(hydrofluoride) as fluoride source (Scheme 74).[143] A few other NHCs were used later to exemplify the family of [Au(NHC)F] complexes.[144] These gold derivatives are stable in the solid state but rapidly decompose in solution in DCM.

Gold(I) complexes are not the only examples containing Au–F bonds. As mentioned in a previous section, in 2010, Toste and colleagues reported the synthesis of Au(III) fluorinated complexes using XeF_2 (Scheme 37). The desired complexes are only isolable in their fluorine dissociated dimeric form.[99] Alternatively, the Riedel group later showed the possibility to prepare [Au(SIMes)F_3] from AuF_3 and the corresponding free carbene (complexes **115** and **116a–b**, Scheme 75).[145] This trifluorogold complex proved to be a very valuable intermediate towards other [Au(SIMes)(L)F_2] complexes, due to the weaker Au–F bond in the *trans* position to the NHC.[146]



Scheme 71. Synthesis of MIC–Au(I/III)-pyridyl complexes and their reactivity.

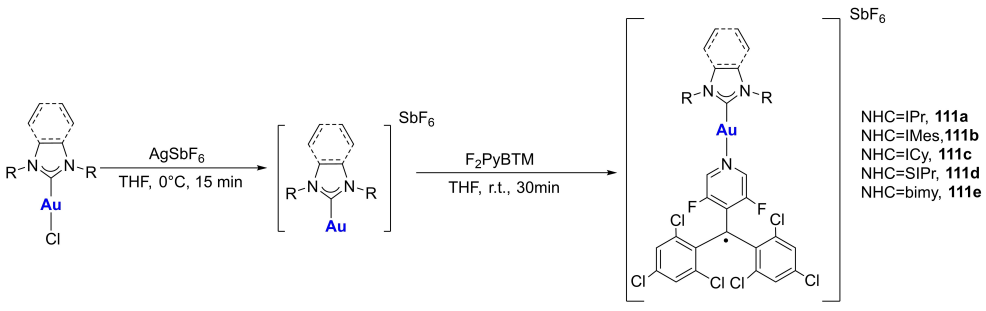


Scheme 72. A) Synthesis of BIAN complexes; B) Catalytic application of complexes **113a–113f**.

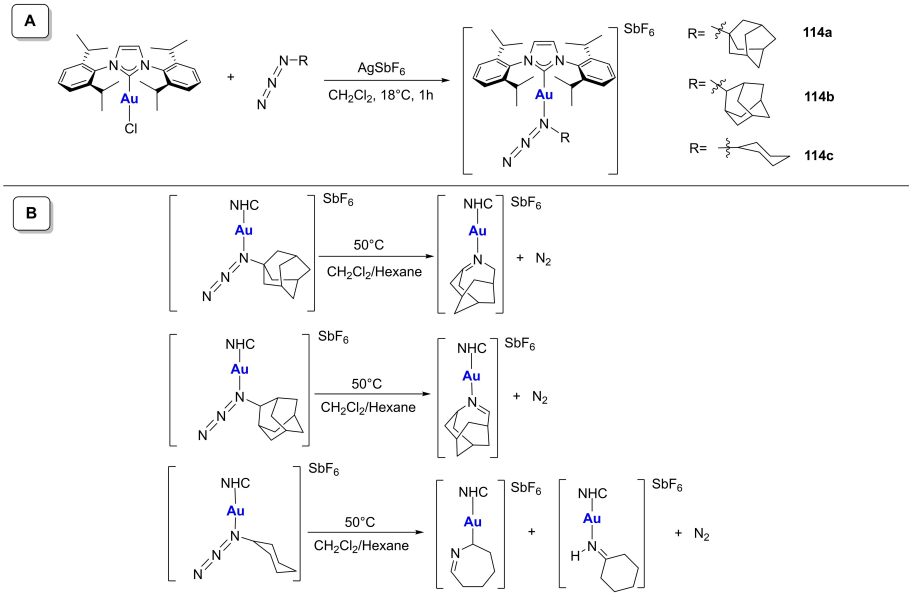
Elaborating on the work of Sadighi,[143] Nolan and co-workers reported the effect of solvent on the resulting complexes. They realized that moving from benzene to THF led to the selective production of a cationic gold bifluoride (Scheme 76).[40] These new complexes can be interconverted back and forth with [Au(NHC)F].

All these various examples of gold fluorides have proven useful for further developments. Shortly after the report of the first [Au(NHC)F], Sadighi showed that alkynes could be inserted into the Au–F bond to yield fluorovinyl gold complexes **117** (Scheme 77).[147]

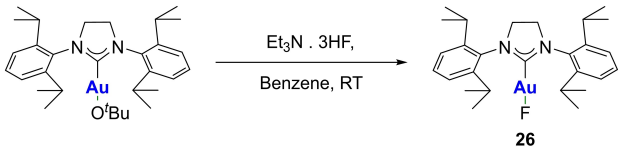
Gold fluoride complexes have also been proposed to be a key intermediate in hydrodefluorination of perfluoroarenes,



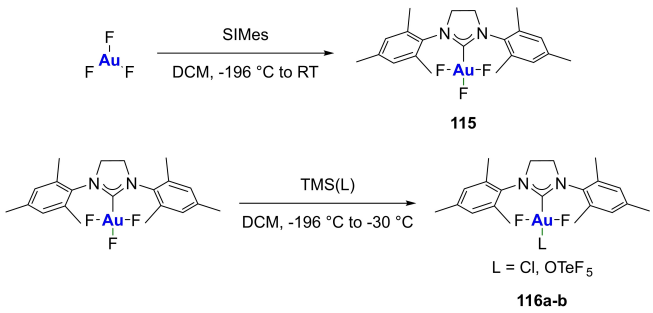
Scheme 70. Synthesis of luminescent radical gold-pyridyl complexes.



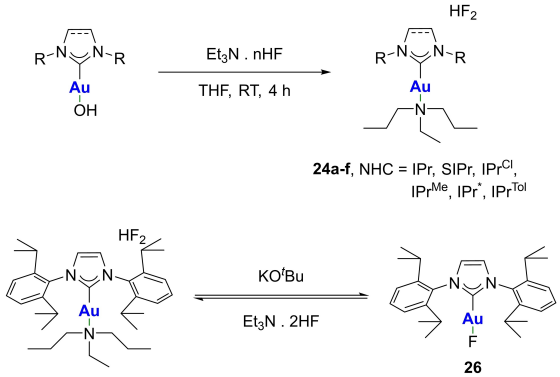
Scheme 73. (A) Synthesis of gold-organoazido complexes; (B) Reactivity towards nitrogen extrusion reaction.



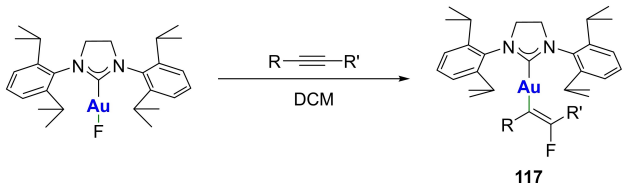
Scheme 74. First example of NHC stabilized gold fluoride complex.



Scheme 75. Synthesis of [Au(SIMes)F_3] and derivatisation to other [Au(SIMes)(L)F_2] complexes.



Scheme 76. Synthesis of gold bifluoride complexes in THF and their interchange with gold fluoride complexes.

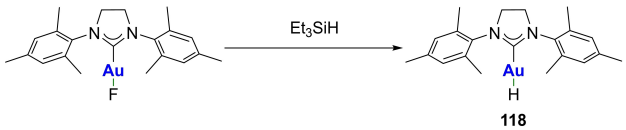


Scheme 77. Alkyne insertion into Au–F bonds.

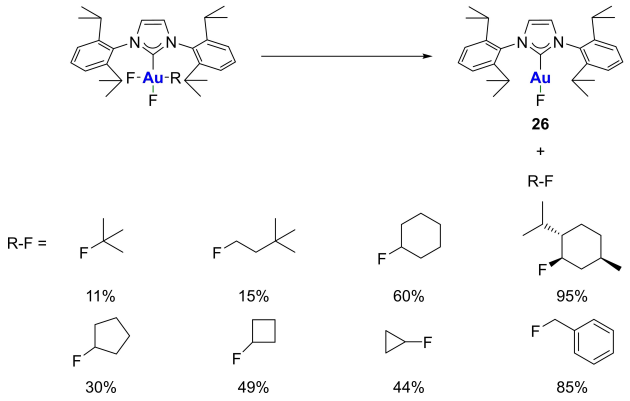
where a silane mediated hydrogen fluoride exchange allows the regeneration of the initial gold hydride (compound **118**, Scheme 78).[148]

On the gold(III) side, Toste and co-workers studied the reductive elimination reaction involving the [Au(NHC)(alkyl)F_2] complexes to mediate both fluorination reactions (Scheme 79)[149] and cross-coupling with boronic acids (Scheme 80).[99] The fluorine atoms were revealed to be critical in this reaction, that does not proceed with other halides.

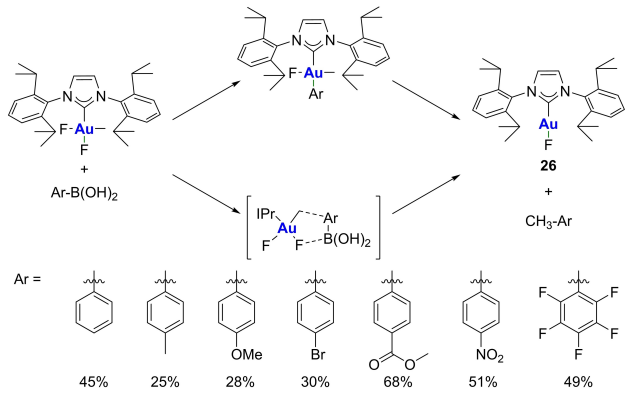
The Nolan group has designed a versatile procedure using their cationic bifluoride gold complexes in the catalytic hydrofluorination of alkynes (Scheme 81), while digold hydroxide species bearing a bifluoride counterion were identified as catalytically relevant intermediates when hydrofluoric acid is used as the HF source.[40,58] Notably, neutral gold(I) bifluorides containing an Au–F–HF bonding arrange-



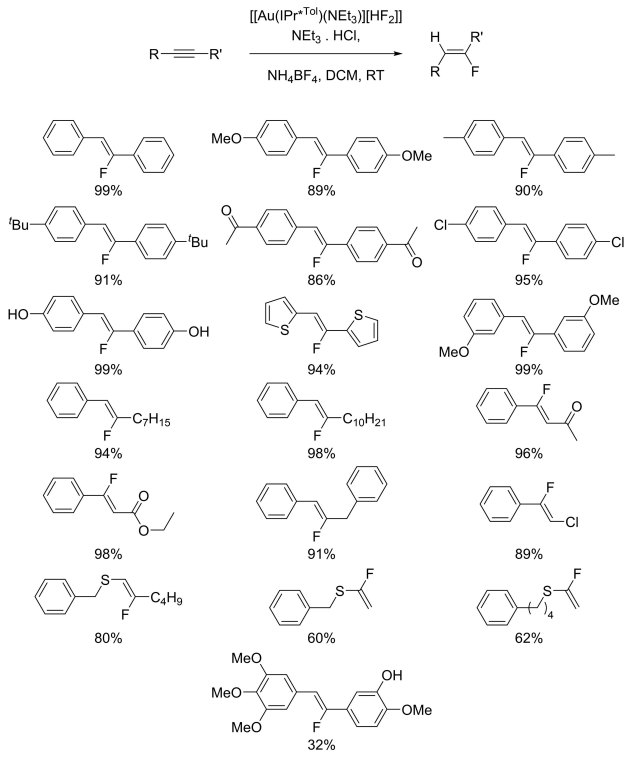
Scheme 78. Silane mediated hydrogen fluoride exchange to form a gold hydride complex.



Scheme 79. Reductive elimination on gold(III) fluoride complexes.



Scheme 80. Application of gold(III) fluoride complexes in cross-coupling reactions with boronic acids.



Scheme 81. Gold bifluoride supported hydrofluorination of alkynes.

ment were recently observed and characterized, with the use of a special HF source.[144a]

An additionally interesting class of Au-NHC species are trifluoromethyl gold complexes. Trifluoromethyl groups are also very important in medicinal chemistry for their physical similarity to methyl or chlorine groups and for the stability they impart.[150] Gold-mediated reactions have attracted considerable attention so it is only natural that the reactivity of these complexes has also been examined in the field of trifluoromethylation,[151] therefore interest has grown for trifluoromethyl gold-NHC complexes. A scope of [Au-(NHC)(CF_3)] complexes (**119a–f**), prepared from gold-NHC halides and $TMSCF_3$ in the presence of silver fluoride (Scheme 82) was reported in 2014.[152]

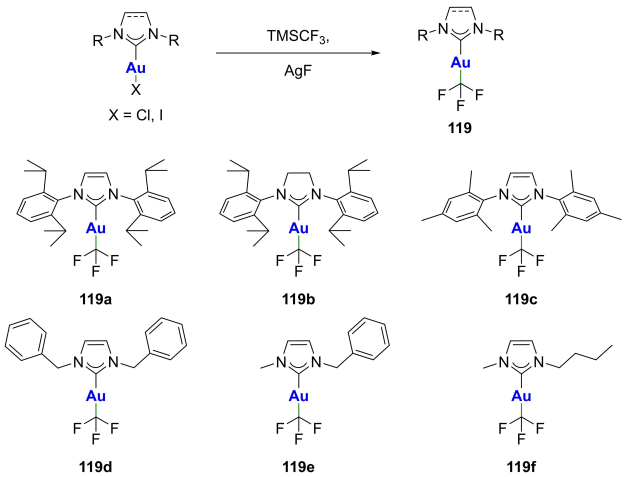
Recently, Nolan and co-workers have extended this work to a wider range of NHCs, thus obtaining also complexes **119g–k**, and showed that their bifluoride complexes were powerful alternative precursors for trifluoromethyl gold complexes (Scheme 83).[39]

Along this scope expansion, and following up on Bertrand's work on α-hydride abstraction from alkyl-gold complexes,[100] Nolan and colleagues also explored the α-fluorine abstraction from the trifluoromethyl gold complexes. As mentioned in the gold-hydroxide section, this α-fluoride abstraction led to the observation of novel difluorocarbene complexes, that could act as entryway into ^{18}F labelled trifluoromethylations (see Scheme 12).[39]

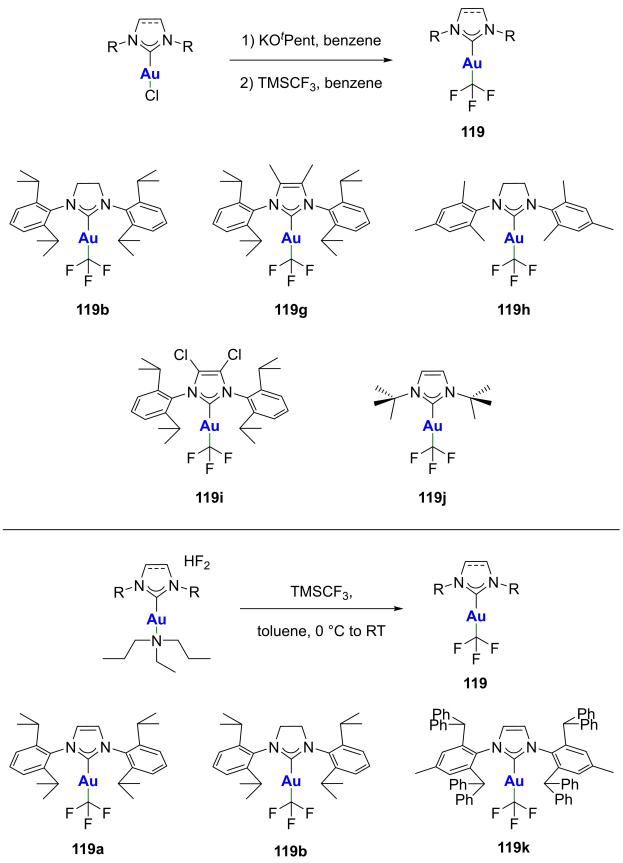
As for fluoride-containing complexes, gold(III) complexes with trifluoromethyl groups have been reported (**120–122**). Several reports show that such compounds can be accessed by oxidation of [Au(NHC)(CF_3)] complexes,[152] by trifluoromethylation of [Au(NHC)F_3] with $TMSCF_3$ or by the action of a free carbene on [Au(CF_3)$_3$(CH_3CN)] (Scheme 84).[153]

The reductive elimination reactivity of gold(III) already observed on fluorides could be observed on some of these complexes, offering access to trifluoromethyl halides under photo-irradiation (Scheme 85).[152]

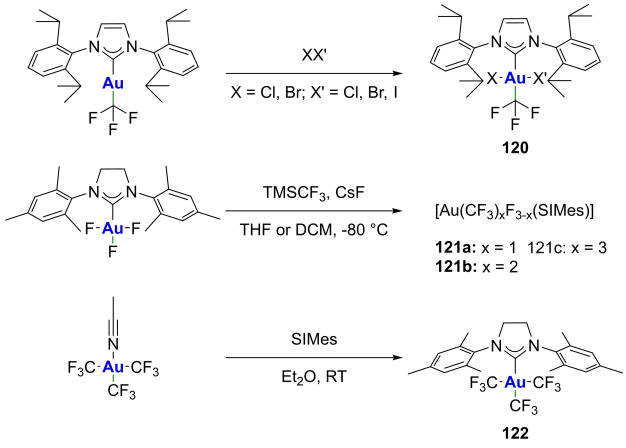
An alternative access to gold mediated trifluoromethylation was developed by Toste in the form of a photoredox



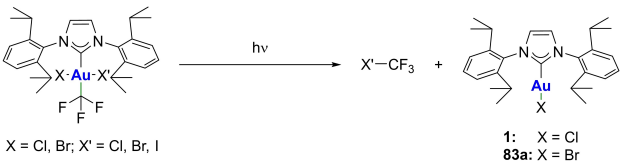
Scheme 82. Silver assisted synthesis of trifluoromethyl gold-NHC complexes.



Scheme 83. Expanded scope of trifluoromethyl gold-NHC complexes.



Scheme 84. Access to trifluoromethyl gold(III)-NHC complexes.



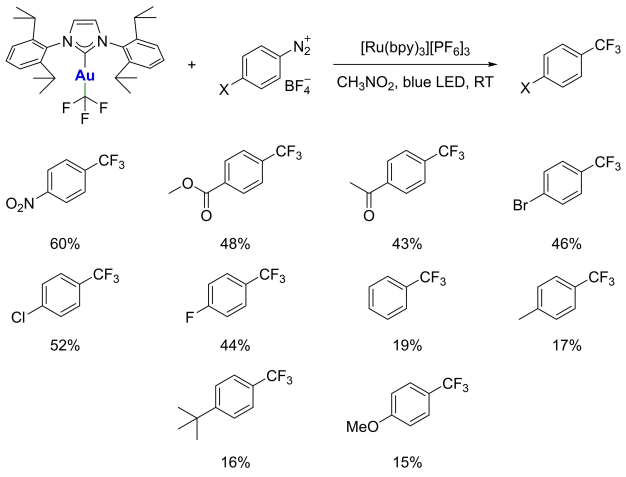
Scheme 85. Reductive elimination from trifluoromethyl gold(III)-NHC complexes.

initiated reaction between [Au(NHC)(CF$_3$)] complexes and aryl radicals generated from diazonium salts (Scheme 86).[151e]

13. Summary and Outlook

We believe that this overview of the most widely used gold-NHC complexes employed in organometallic synthesis shows how the selection of starting materials can significantly facilitate expedient and selective access to a wide range of gold-NHC complexes with exciting (photo)catalytic, biological or photoemissive properties.

The knowledge of the mechanistic aspects of the different synthetic processes has permitted the discovery of new valuable intermediates as well as key target compounds, accessible under very mild conditions, with the use of inexpensive reagents and green solvents. Curiously, most of the golden synthons presented in this review have themselves demonstrated interesting applications in homogeneous catalysis, medicinal chemistry, and materials science. This establishes such derivatives as extremely attractive for both academia and industry. A variety of golden synthons is now at the disposal of gold catalysis practitioners, offering a range of options for pre-catalyst screening and fundamental organometallic reactivity studies for the isolation or observation of intermediates of catalytic cycles. An important aspect of many golden synthons is the scalability of their synthesis, which has been demonstrated and thoroughly presented in recent reports for the widely used [Au(IPr)(OH)] and its digold analogue, [{Au(IPr)}$_2$(μ-OH)][BF$_4$].[154] Many advances are expected in the applications of such compounds, as well as improvements on their synthesis, while the discovery of new golden synthons will always be a worthwhile endeavour.



Scheme 86. Photoredox initiated trifluoromethylation of aryl diazonium tetrafluoroborate.

Acknowledgements

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: anticancer activity · gold complexes · luminescence · *N*-heterocyclic carbenes · organometallic synthesis · (photo)catalysis

[1] D. Pflästerer, A. S. K. Hashmi, *Chem. Soc. Rev.* **2016**, *45*, 1331–1367.
[2] a) R. P. Herrera, M. C. Gimeno, *Chem. Rev.* **2021**, *121*, 8311–8363; b) T. A. C. A. Bayrakdar, T. Scattolin, X. Ma, S. P. Nolan, *Chem. Soc. Rev.* **2020**, *49*, 7044–7100.
[3] D. Marchione, L. Belpassi, G. Bistoni, A. Macchioni, F. Tarantelli, D. Zuccaccia, *Organometallics* **2014**, *33*, 4200–4208.
[4] a) M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius, *Nature* **2014**, *510*, 485–496; b) Q. Zhao, G. Meng, S. P. Nolan, M. Szostak, *Chem. Rev.* **2020**, *120*, 1981–2048; c) S. Witzel, A. Stephen, K. Hashmi, J. Xie, *Chem. Rev.* **2021**, *121*, 8868–8925.
[5] C. A. Smith, M. R. Narouz, P. A. Lummis, I. Singh, A. Nazemi, C.-H. Li, C. M. Crudden, *Chem. Rev.* **2019**, *119*, 4986–5056.
[6] a) G. M. -Alcántar, P. Picchetti, A. Casini, *Angew. Chem.* **2023**, *62*, e202218000; b) T. Lazarević, A. Rilak, Ž. D. Bugarčić, *Eur. J. Med. Chem.* **2017**, *142*, 8–31; c) T. Scattolin, V. A. Voloshkin, F. Visentin, S. P. Nolan, *Cell Rep. Phys. Sci.* **2021**, *2*, 100446.
[7] S. A. Patil, A. P. Hoagland, S. A. Patil, A. Bugarin, *Future Med. Chem.* **2020**, *12*, 2239–2275.
[8] J. V. Fontes, I. A. Santos, L. B. Rosa, R. L. A. Lima, A. C. G. Jardim, D. C. Miguel, C. Abbehausen, *ChemistrySelect* **2022**, *7*, e20220156.
[9] P. de Frémont, N. M. Scott, E. D. Stevens, S. P. Nolan, *Organometallics* **2005**, *24*, 2411–2418.
[10] a) H. M. J. Wang, I. J. B. Lin, *Organometallics* **1998**, *17*, 972–975; b) M. R. L. Furst, C. S. J. Cazin, *Chem. Commun.* **2010**, *46*, 6924–6925.
[11] a) A. Collado, A. Goméz-Suárez, A. R. Martin, A. M. Z. Slawin, S. P. Nolan, *Chem. Commun.* **2013**, *49*, 5541–5543; b) T. Scattolin, N. V. Tzouras, L. Falivene, L. Cavallo, S. P. Nolan, *Dalton Trans.* **2020**, *49*, 9694–9700.
[12] a) T. Scattolin, S. P. Nolan, *Trends Chem.* **2020**, *2*, 721–736; b) E. A. Martynova, N. V. Tzouras, G. Pisanò, C. S. J. Cazin, S. P. Nolan, *Chem. Commun.* **2021**, *57*, 3836–3856; c) T. Scattolin, A. Simoens, C. V. Stevens, S. P. Nolan, *Trends Chem.* **2022**, *4*, 584–607.
[13] A. Annunziata, G. Ferraro, M. E. Cucciolito, P. Imbimbo, A. Tuzi, D. M. Monti, A. Merlino, F. Ruffo, *Dalton Trans.* **2022**, *51*, 10475–10485.
[14] a) C. Topf, C. Hirtenlehner, U. Monkowius, *J. Organomet. Chem.* **2011**, *696*, 3274–3278; b) L. Huang, F. Rominger, M. Rudolph, A. S. K. Hashmi, *Chem. Commun.* **2016**, *52*, 6435–6438.
[15] a) C. Hirtenlehner, C. Krims, J. Hölbling, M. List, M. Zabel, M. Fleck, R. J. F. Berger, W. Schoefberger, U. Monkowius, *Dalton Trans.* **2011**, *40*, 9899–9910; b) R. De Marco, M. Dal Grande, M. Baron, L. Orian, C. Graiff, T. Achard, S. Bellemin-Laponnaz, A. Pothig, C. Tubaro, *Eur. J. Inorg. Chem.* **2021**, 4196–4206.
[16] S. Diez-Gonzalez, N. Marion, S. P. Nolan, *Chem. Rev.* **2009**, *109*, 3612–3676.
[17] a) A. Collado, J. Bohnenberger, M.-J. Oliva-Madrid, P. Nun, D. B. Cordes, A. M. Z. Slawin, S. P. Nolan, *Eur. J. Inorg. Chem.* **2016**, 4111–4122; b) H. Sivaram, J. Tan, H. V. Huynh, *Dalton Trans.* **2013**, *42*, 12421–12428; c) T. Martinez, A. Vanitcha, C. Troufflard, N. Vanthuyne, J. Forté, G. Gontard, G. Lemière, V. Mouriès-Mansuy, L. Fensterbank, *Angew. Chem. Int. Ed.* **2021**, *60*, 19879–19888.
[18] a) J. F. Arambula, R. McCall, K. J. Sidoran, D. Magda, N. A. Mitchell, C. W. Bielawski, V. M. Lynch, J. L. Sessler, K. Arumugam, *Chem. Sci.* **2016**, *7*, 1245–1256; b) F. Chotard, A. S. Romanov, D. L. Hughes, M. Linnolahti, M. Bochmann, *Eur. J. Inorg. Chem.* **2019**, 4234–4240.
[19] S. Gaillard, P. Nun, A. M. Z. Slawin, S. P. Nolan, *Organometallics* **2010**, *29*, 5402–5408.
[20] L. Canovese, F. Visentin, C. Levi, V. Bertolasi, *Organometallics* **2011**, *30*, 875–883.
[21] V. Stoppa, T. Scattolin, M. Bevilacqua, M. Baron, C. Graiff, L. Orian, A. Biffis, I. Menegazzo, M. Roverso, S. Bogialli, F. Visentin, C. Tubaro, *New J. Chem.* **2021**, *45*, 961–971.
[22] a) M. Baron, C. Tubaro, M. Basato, M. M. Natile, C. Graiff, J. Organomet, *Chem.* **2013**, *723*, 108–114; b) M. Baron, M. Dalla Tiezza, A. Carlotto, C. Tubaro, C. Graiff, L. Orian, *J. Organomet. Chem.* **2018**, *866*, 144–152; c) F. J.-B. dit Dominique, H. Gornitzka, A. Sournia-Saquet, C. Hemmert, *Dalton Trans.* **2009**, 340–352; d) A. H. Mageed, B. W. Skelton, A. N. Sobolev, M. V. Baker, *Eur. J. Inorg. Chem.* **2018**, 109–120.
[23] a) M. Baron, C. Tubaro, M. Basato, A. Ahmed Isse, A. Gennaro, L. Cavallo, C. Graiff, A. Dolmella, L. Falivene, L. Caporaso, *Chem. Eur. J.* **2016**, *22*, 10211–10224; b) C. Tubaro, M. Baron, M. Costante, M. Basato, A. Biffis, A. Gennaro, A. Ahmed Isse, C. Graiff, G. Accorsi, *Dalton Trans.* **2013**, *42*, 10952–10963; c) M. Baron, C. Tubaro, M. Basato, A. Biffis, C. Graiff, *J. Organomet. Chem.* **2012**, *714*, 41–46.
[24] a) C. Schmidt, B. Karge, R. Misgeld, A. Prokop, M. Brönstrup, I. Ott, *MedChemComm* **2017**, *8*, 1681–1689; b) J. Tan, H. Sivaram, H. V. Huynh, *Appl. Organomet. Chem.* **2018**, *32*, e4441.
[25] a) V. K. Kulkarni, B. N. Khiarak, S. Takano, S. Malola, E. L. Albright, T. I. Levchenko, M. D. Aloisio, C.-T. Dinh, T. Tsukuda, H. Häkkinen, C. M. Crudden, *J. Am. Chem. Soc.* **2022**, *144*, 9000–9006; b) P. A. Lummis, K. M. Osten, T. I. Levchenko, M. S. A. Hazer, S. Malola, B. Owens-Baird, A. J. Veinot, E. L. Albright, G. Schatte, S. Takano, K. Kovnir, K. G. Stamplecoskie, T. Tsukuda, H. Häkkinen, M. Nambo, C. M. Crudden, *J. Am. Chem. Soc. Au* **2022**, *2*, 875–885; c) H. Yi, K. M. Osten, T. I. Levchenko, A. J. Veinot, Y. Aramaki, T. Ooi, M. Nambo, C. M. Crudden, *Chem. Sci.* **2021**, *12*, 10436–10440; d) M. Bevilacqua, M. Roverso, S. Bogialli, C. Graiff, A. Biffis, *Inorg. Chem.* **2023**, *62*, 1383–1393.
[26] S. Gaillard, J. Bosson, R. S. Ramón, P. Nun, A. M. Z. Slawin, S. P. Nolan, *Chem. Eur. J.* **2010**, *16*, 13729–13740.
[27] I. I. F. Boogaerts, S. P. Nolan, *J. Am. Chem. Soc.* **2010**, *132*, 8858–8859.
[28] R. M. P. Veenboer, D. Gasperini, F. Nahra, D. B. Cordes, A. M. Z. Slawin, C. S. J. Cazin, S. P. Nolan, *Organometallics* **2017**, *36*, 3645–3653.
[29] S. Gaillard, A. M. Z. Slawin, S. P. Nolan, *Chem. Commun.* **2010**, *46*, 2742–2744.
[30] A. Goméz-Suárez, R. S. Ramón, A. M. Z. Slawin, S. P. Nolan, *Dalton Trans.* **2012**, *41*, 5461–5463.
[31] F. Nahra, S. R. Patrick, A. Collado, S. P. Nolan, *Polyhedron* **2014**, *84*, 59–62.
[32] S. R. Patrick, A. Goméz-Suárez, A. M. Z. Slawin, S. P. Nolan, *Organometallics* **2014**, *33*, 421–424.
[33] D. Hueber, M. Hoffmann, B. Louis, P. Pale, A. Blanc, *Chem. Eur. J.* **2014**, *20*, 3903–3907.
[34] F. Sirindil, S. P. Nolan, S. Dagorne, P. Pale, A. Blanc, P. de Frémont, *Chem. Eur. J.* **2018**, *24*, 12630–12637.
[35] S. Gaillard, D. Rix, A. M. Z. Slawin, J. Lacour, S. P. Nolan, *Dalton Trans.* **2012**, *41*, 8235–8237.
[36] A. Collado, S. R. Patrick, D. Gasperini, S. Meiries, S. P. Nolan, *Beilstein J. Org. Chem.* **2015**, *11*, 1809–1814.
[37] S. Hase, Y. Kayaki, T. Ikariya, *ACS Catal.* **2015**, *5*, 5135–5140.
[38] J. Weaver, S. Gaillard, C. Toye, S. Macpherson, S. P. Nolan, A. Riches, *Chem. Eur. J.* **2011**, *17*, 6620–6624.
[39] S. M. P. Vanden Broeck, D. J. Nelson, A. Collado, L. Falivene, L. Cavallo, D. B. Cordes, A. M. Z. Slawin, K. Van Hecke, F. Nahra, C. S. J. Cazin, S. P. Nolan, *Chem. Eur. J.* **2021**, *27*, 8461–8467.
[40] F. Nahra, S. R. Patrick, D. Bello, M. Brill, A. Obled, D. B. Cordes, A. M. Z. Slawin, D. O'Hagan, S. P. Nolan, *ChemCatChem* **2015**, *7*, 240–244.
[41] S. Dupuy, F. Lazreg, A. M. Z. Slawin, C. S. J. Cazin, S. P. Nolan, *Chem. Commun.* **2011**, *47*, 5455–5457.
[42] G. C. Fortman, A. Poater, J. W. Levell, S. Gaillard, A. M. Z. Slawin, I. D. W. Samuel, L. Cavallo, S. P. Nolan, *Dalton Trans.* **2010**, *39*, 10382–10390.

[43] A. S. Romanov, M. Bochmann, *Organometallics* **2015**, *34*, 2439–2454.
[44] S. Guo, H. Sivaram, D. Yuan, H. V. Huynh, *Organometallics* **2013**, *32*, 3685–3696.
[45] S. Guo, J. C. Bernhammer, H. V. Huynh, *Dalton Trans.* **2015**, *44*, 15157–15165.
[46] B. W. Gung, L. N. Bailey, D. T. Craft, C. L. Barnes, K. Kirschbaum, *Organometallics* **2010**, *29*, 3450–3456.
[47] M. Farooq, N. A. Taha, R. R. Butorac, D. A. Evans, A. A. Elzatahry, M. A. M. Wadaan, S. S. Al-Deyab, A. H. Cowley, *Int. J. Mol. Sci.* **2015**, *16*, 24718–24731.
[48] R. R. Butorac, S. S. Al-Deyab, A. H. Cowley, *Molecules* **2011**, *16*, 2285–2292.
[49] D. Gasperini, A. Collado, A. Goméz-Suaréz, D. B. Cordes, A. M. Z. Slawin, S. P. Nolan, *Chem. Eur. J.* **2015**, *21*, 5403–5412.
[50] I. I. Hashim, N. V. Tzouras, X. Ma, L. Bourda, K. Van Hecke, S. P. Nolan, C. S. J. Cazin, *Dalton Trans.* **2022**, *15*, 13246–13254.
[51] A. M. Al-Majid, S. Yousuf, M. I. Choudhary, A. Collado, F. Nahra, S. P. Nolan, *ChemistrySelect* **2016**, *1*, 76–80.
[52] S. Sen, S. Hufnagel, E. Y. Maier, I. Aguilar, J. Selvakumar, J. E. DeVore, V. M. Lynch, K. Arumugam, Z. Cui, J. L. Sessler, J. F. Arambula, *J. Am. Chem. Soc.* **2020**, *142*, 20536–20541.
[53] N. V. Tzouras, A. Gobbo, N. B. Pozsoni, S. G. Chalkidis, S. Bhandary, K. Van Hecke, G. C. Vougioukalakis, S. P. Nolan, *Chem. Commun.* **2022**, *58*, 8516–8519.
[54] N. Ibrahim, M. H. Vilhelmsen, M. Pernpointner, F. Rominger, A. S. K. Hashmi, *Organometallics* **2013**, *32*, 2576–2583.
[55] A. S. Romanov, C. R. Becker, C. E. James, D. Di, D. Credgington, M. Linnolahti, M. Bochmann, *Chem. Eur. J.* **2017**, *23*, 4625–4637.
[56] E. Y. Tsui, P. Müller, J. P. Sadighi, *Angew. Chem.* **2008**, *120*, 9069–9072.
[57] C. P. Stow, R. A. Widenhoefer, *Organometallics* **2020**, *39*, 1249–1257.
[58] R. Gauthier, N. V. Tzouras, Z. Zhang, S. Bédard, M. Saab, L. Falivene, K. Van Hecke, L. Cavallo, S. P. Nolan, J. Paquin, *Chem. Eur. J.* **2022**, *28*, e202103886.
[59] M. Pažický, A. Loos, M. J. Ferreira, D. Serra, N. Vinokurov, F. Rominger, C. Jäkel, A. S. K. Hashmi, M. Limbach, *Organometallics* **2010**, *29*, 4448–4458.
[60] a) D. V. Partyka, M. Zeller, A. D. Hunter, T. G. Gray, *Angew. Chem. Int. Ed.* **2006**, *45*, 8188–8191; b) D. V. Partyka, J. B. Updegraff, M. Zeller, A. D. Hunter, T. G. Gray, *Organometallics* **2009**, *28*, 1666–1674; c) L. Gao, M. A. Peay, D. V. Partyka, J. B. Updegraff, T. S. Teets, A. J. Esswein, M. Zeller, A. D. Hunter, T. G. Gray, *Organometallics* **2009**, *28*, 5669–5681; d) H. K. Lenker, T. G. Gray, R. A. Stockland, *Dalton Trans.* **2012**, *41*, 13274–13276; e) D. V. Partyka, M. Zeller, A. D. Hunter, T. G. Gray, *Inorg. Chem.* **2012**, *51*, 8394–8401; f) M. E. Richard, D. V. Fraccica, K. J. Garcia, E. J. Miller, R. M. Ciccarelli, E. C. Holahan, V. L. Resh, A. Shah, P. M. Findeis, R. A. S. Jr, *Beilstein J. Org. Chem.* **2013**, *9*, 2002–2008.
[61] S. Dupuy, L. E. Crawford, M. Bühl, A. M. Z. Slawin, S. P. Nolan, *Adv. Synth. Catal.* **2012**, *354*, 2380–2386.
[62] S. Dupuy, A. M. Z. Slawin, S. P. Nolan, *Chem. Eur. J.* **2012**, *18*, 14932–14928.
[63] N. V. Tzouras, M. Saab, W. Janssens, T. Cauwenbergh, K. Van Hecke, F. Nahra, S. P. Nolan, *Chem. Eur. J.* **2020**, *26*, 5541–5551.
[64] A. Simoens, T. Scattolin, T. Cauwenbergh, G. Pisanò, C. S. J. Cazin, C. V. Stevens, S. P. Nolan, *Chem. Eur. J.* **2021**, *27*, 5653–5657.
[65] T. Cauwenbergh, N. V. Tzouras, T. Scattolin, S. Bhandary, A. Simoens, K. Van Hecke, C. V. Stevens, S. P. Nolan, *Chem. Eur. J.* **2021**, *27*, 13342–13345.
[66] F. J. L. Ingner, A. Schmitt, A. Orthaber, P. J. Gates, L. T. Pilarski, *ChemSusChem* **2020**, *13*, 1359–1366.
[67] J. Cornella, M. Rosillo-Lopez, I. Larrosa, *Adv. Synth. Catal.* **2011**, *353*, 1359–1366.
[68] J. J. Mihaly, D. J. Stewart, T. A. Grusenmeyer, A. T. Phillips, J. E. Haley, M. Zeller, T. G. Gray, *Dalton Trans.* **2019**, *48*, 15917–15927.
[69] T. Li, D. S. Muthiah Ravinson, R. Haiges, P. I. Djurovich, M. E. Thompson, *J. Am. Chem. Soc.* **2020**, *142*, 6158–6172.
[70] T. Li, P. I. Djurovich, M. E. Thompson, *Inorg. Chim. Acta* **2021**, *517*, 120188.
[71] S. Singh, S. S. Kumar, V. Jancik, H. W. Roesky, H. Schmidt, M. Noltemeyer, *Eur. J. Inorg. Chem.* **2015**, *2015*, 3057–3062.
[72] H. M. J. Wang, C. Y. L. Chen, I. J. B. Lin, *Organometallics* **1999**, *18*, 1216–1223.
[73] a) L. Gao, D. V. Partyka, J. B. Updegraff, N. Deligonul, T. G. Gray, *Eur. J. Inorg. Chem.* **2009**, *2009*, 2711–2719; b) A. L. F. Chow, M. H. So, W. Lu, N. Zhu, C. M. Che, *Chem. Asian J.* **2011**, *6*, 544–553.
[74] L. Canovese, C. Levi, F. Visentin, C. Santo, V. Bertolasi, *Inorg. Chim. Acta* **2013**, *404*, 105–112.
[75] K. Klauke, S. Werner, F. Mohr, *Eur. J. Inorg. Chem.* **2018**, *2018*, 1053–1056.
[76] M. M. Hansmann, F. Rominger, A. S. K. Hashmi, *Chem. Sci.* **2013**, *4*, 1552–1559.
[77] N. Kim, R. A. Widenhoefer, *Angew. Chem. Int. Ed.* **2018**, *57*, 4722–4726.
[78] G. F. Manbeck, M. C. Kohler, M. R. Porter, R. A. Stockland Jr, *Dalton Trans.* **2011**, *40*, 12595–12606.
[79] a) D. V. Partyka, L. Gao, T. S. Teets, J. B. Updegraff, N. Deligonul, T. G. Gray, *Organometallics* **2009**, *28*, 6171–6182; b) J. E. Heckler, N. Deligonul, A. L. Rheingold, T. G. Gray, *Chem. Commun.* **2015**, *49*, 5990–5992.
[80] T. J. Robilotto, N. Deligonul, J. B. Updegraff, T. G. Gray, *Inorg. Chem.* **2013**, *52*, 9659–9668.
[81] a) J. A. Garg, O. Blacque, J. Heier, K. Venkatesan, *Eur. J. Inorg. Chem.* **2012**, *2012*, 1750–1763; b) J. J. Mihaly, A. T. Phillips, J. T. Malloy, Z. M. Marsh, M. Zeller, J. E. Haley, K. De La Harpe, T. A. Grusenmeyer, T. G. Gray, *Organometallics* **2012**, *39*, 489–494; c) J. J. Mihaly, S. M. Wolf, A. T. Phillips, S. Mam, Z. Yung, J. E. Haley, M. Zeller, K. De La Harpe, E. Holt, T. A. Grusenmeyer, S. Collins, T. G. Gray, *Inorg. Chem.* **2022**, *61*, 1228–1235.
[82] T. Seki, K. Kashiyama, H. Ito, *Dalton Trans.* **2019**, *48*, 7105–7109.
[83] E. S. Gauthier, M. Cordier, V. Dorcet, N. Vanthuyne, L. Favereau, J. A. G. Williams, J. Crassous, *Eur. J. Org. Chem.* **2021**, *2021*, 4769–4776.
[84] F. Yu, X. Song, G. Liu, X. Chang, K. Li, Y. Wang, G. Cui, Y. Chen, *Chem. Eur. J.* **2018**, *28*, e202202439.
[85] J. Zhang, H. Zou, J. Lei, B. He, X. He, H. H. Y. Sung, R. T. K. Kwok, J. W. Y. Lam, L. Zheng, B. Z. Tang, *Angew. Chem. Int. Ed.* **2020**, *59*, 7097–7105.
[86] D. Konkolewicz, A. Gray-Weale, S. Perrier, *J. Am. Chem. Soc.* **2009**, *131*, 18075–18077.
[87] D. Konkolewicz, S. Gaillard, A. G. West, Y. Y. Cheng, A. Gray-Weale, T. W. Schmidt, S. P. Nolan, S. Perrier, *Organometallics* **2011**, *30*, 1315–1318.
[88] Y. Long, B. Cao, X. Xiong, A. S. C. Chan, R. W. Sun, T. Zou, *Angew. Chem. Int. Ed.* **2021**, *60*, 4133–4141.
[89] N. Estrada-Ortiz, F. Guarra, I. A. M. de Graaf, L. Marchetti, M. H. de Jager, G. M. M. Groothuis, C. Gabbiani, A. Casini, *ChemMedChem* **2017**, *12*, 1429–1435.
[90] S. M. Meier-Menches, B. Aikman, D. Döllerer, W. T. Klooster, S. J. Coles, N. Santi, L. Luk, A. Casini, R. Bonsignore, *J. Inorg. Biochem.* **2020**, *202*, 110844.
[91] J. Oberkofler, B. Aikman, R. Bonsignore, A. Pöthig, J. Platts, A. Casini, F. E. Kühn, *Eur. J. Inorg. Chem.* **2020**, *2020*, 1040–1051.
[92] B. Kemper, M. von Gröning, V. Lewe, D. Spitzer, T. Otremba, N. Stergiou, D. Schollmeyer, E. Schmitt, B. J. Ravoo, P. Besenius, *Chem. Eur. J.* **2013**, *23*, 6048–6055.
[93] A. Vellé, R. Maguire, K. Kavanagh, P. J. Sanz Miguel, D. Montagner, *ChemMedChem* **2017**, *12*, 841–844.
[94] T. Scattolin, P. Lippmann, M. Beliš, K. Hecke, I. Ott, S. P. Nolan, *Appl. Organomet. Chem.* **2022**, e6624.
[95] I. Mármol, J. Quero, P. Azcárate, E. Atrián-Blasco, C. Ramos, J. Santos, M. C. Gimeno, M. J. Rodríguez-Yoldi, E. Cerrada, *Pharmaceutica* **2022**, *14*, 2064.
[96] E. Y.-H. Hong, H.-L. Wong, V. W.-W. Yam, *Chem. Eur. J.* **2015**, *21*, 5732–5735.
[97] A. Pinto, M. Echeverri, B. Gómez-Lor, L. Rodríguez, *Dalton Trans.* **2022**, *51*, 8340–8349.
[98] a) J. Gil-Rubio, V. Cámara, D. Bautista, J. Vicente, *Organometallics* **2012**, *31*, 18075–18077; b) A. A. Penney, G. L. Starova, E. V. Grachova, V. V. Sizov, M. A. Kinzhalov, S. P. Tunik, *Inorg. Chem.* **2017**, *56*, 14771–14787; c) V. Stoppa, E. Battistel, M. Baron, P. Sgarbossa, A. Biffis, G. Bottaro, L. Armelao, C. Tubaro, *Molecules* **2022**, *27*, 4317.
[99] N. P. Mankad, F. D. Toste, *J. Am. Chem. Soc.* **2010**, *132*, 12859–12861.
[100] G. Ung, G. Bertrand, *Angew. Chem. Int. Ed.* **2013**, *52*, 11388–11391.
[101] a) G. Ciancaleoni, L. Biasiolo, G. Bistoni, A. Macchioni, F. Tarantelli, D. Zuccaccia, L. Belpassi, *Organometallics* **2013**, *32*, 4444–4447; b) N. Salvi, L. Belpassi, D. Zuccaccia, F. Tarantelli, A. Macchioni, *J. Organomet. Chem.* **2010**, *965*, 2679–2686; c) R. Dorel, A. M. Echavarren, *Chem. Rev.* **2015**, *115*, 9028–9072; d) T. J. Brown, R. A. Widenhoefer, *J. Organomet. Chem.* **2011**, *696*, 1216–1220; e) S. Ferrer, A. M. Echavarren, *Organometallics* **2018**, *37*, 781–786; f) T. J. Brown, M. G. Dickens, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2009**, *131*, 6350–6351.
[102] D. H. Ringger, P. Chen, *Angew. Chem. Int. Ed.* **2013**, *52*, 4686–4689.
[103] N. Kim, R. A. Widenhoefer, *Chem. Sci.* **2019**, *10*, 6149–6156.

[104] C. Dash, P. Kroll, M. Yousufuddin, H. V. R. Dias, *Chem. Commun.* **2011**, *47*, 4478–4480.
[105] S. Shekhar, P. Ryberg, J. F. Hartwig, J. S. Mathew, D. G. Blackmond, E. I. Strieter, S. L. Buchwald, *J. Am. Chem. Soc.* **2006**, *128*, 3584–3591.
[106] C. Munro-Leighton, E. D. Blue, T. B. Gunnoe, *J. Am. Chem. Soc.* **2006**, *128*, 1446–1447.
[107] M. W. Johnson, S. L. Shevick, F. D. Toste, R. G. Bergman, *Chem. Sci.* **2013**, *4*, 1023–1027.
[108] D. Mulryan, J. Rodwell, N. A. Phillipsw, M. R. Crimmin, *ACS Catal.* **2022**, *12*, 3411–3419.
[109] A. S. Romanov, M. Linnolahti, M. Bochmann, *Dalton Trans.* **2021**, *50*, 17156–17164.
[110] R. Hamze, S. Shi, S. C. Kapper, D. Sylvinson, M. Ravinson, L. Estergreen, M.-C. Jung, A. C. Tadle, R. Haiges, P. I. Djurovich, J. L. Peltier, R. Jazzar, G. Bertrand, S. E. Bradforth, M. E. Thompson, *J. Am. Chem. Soc.* **2019**, *141*, 8616–8626.
[111] A. S. Romanov, L. Yang, S. T. E. Jones, D. Di, O. J. Morley, B. H. Drummond, A. P. M. Reponen, M. Linnolahti, D. Credgington, M. Bochmann, *Chem. Mater.* **2019**, *31*, 3613–3623.
[112] J.-G. Yang, X.-F. Song, J. Wang, K. Li, X. Chang, L. -Y- Tan, C.-X. Liu, F.-H. Yu, G. Cui, G. Cheng, W.-P. To, C. Yang, C.-M. Che, Y. Chen, *Chem. Eur. J.* **2021**, *27*, 17834–17842.
[113] T.-Y. Li, D. G. Shlian, P. I. Djurovich, M. E. Thompson, *Chem. Eur. J.* **2021**, *27*, 6191–6197.
[114] F. Chotard, V. Sivchik, M. Linnolahti, M. Bochmann, A. S. Romanov, *Chem. Mater.* **2020**, *32*, 6114–6122.
[115] J.-G. Yang, X.-F. Song, G. Cheng, S. Wu, X. Feng, G. Cui, W.-P. To, X. Chang, Y. Chen, C.-M. Che, C. Yang, K. Li, *ACS Appl. Mater. Interfaces* **2022**, *14*, 13539–13549.
[116] A. S. Romanov, S. T. E. Jones, Q. Gu, P. J. Conaghan, B. H. Drummond, J. Feng, F. Chotard, L. Buizza, M. Foley, M. Linnolahti, D. Credgington, M. Bochmann, *Chem. Sci.* **2020**, *11*, 435–446.
[117] A.-P. M. Reponen, F. Chotard, A. Lempelto, V. Shekhovtsev, D. Credgington, M. Bochmann, M. Linnolahti, N. C. Greenham, A. S. Romanov, *Adv. Opt. Mater.* **2022**, *10*, 2200312.
[118] a) I. I. Hashim, N. V. Tzouras, W. Janssens, T. Scattolin, L. Bourda, S. Bhandary, K. V. Hecke, S. P. Nolan, C. S. J. Cazin, *Chem. Eur. J.* **2022**, *28*, e202201224; b) N. V. Tzouras, E. A. Martynova, X. Ma, T. Scattolin, B. Hupp, H. Busen, M. Saab, Z. Zhang, L. Falivene, G. Pisanò, K. Van Hecke, L. Cavallo, C. S. J. Cazin, A. Steffen, S. P. Nolan, *Chem. Eur. J.* **2021**, *27*, 11904–11911; c) E. A. Martynova, V. A. Voloshkin, S. G. Guillet, F. Bru, M. Beliš, K. V. Hecke, C. S. J. Cazin, S. P. Nolan, *Chem. Sci.* **2022**, *13*, 6852; d) M. Zhu, C. Zheng, X. Zhang, S.-L. You, *J. Am. Chem. Soc.* **2019**, *141*, 2636–2644.
[119] T. Cauwenbergh, N. V. Tzouras, T. Scattolin, A. Slmoens, C. V. Stevens, C. S. J. Cazin, S. P. Nolan, *Chemistry-Methods* **2022**, *2*, e202100098.
[120] C. N. Muniz, J. Schaab, A. Razgoniaev, P. I. Djurovich, M. E. Thompson, *J. Am. Chem. Soc.* **2022**, *144*, 17916–17928.
[121] N. V. Tzouras, T. Scattolin, A. Gobbo, S. F. Rizzolio, E. Cavarzerani, V. Canzonieri, K. V. Hecke, G. C. Vougioukalakis, C. S. J. Cazin, S. P. Nolan, *ChemMedChem* **2022**, *17*, e202200135.
[122] E. A. Martynova, T. Scattolin, E. Cavarzerani, M. Peng, K. Van Hecke, F. Rizzolio, S. P. Nolan, *Dalton Trans.* **2022**, *51*, 3462–3471.
[123] L. Ricard, F. Gagosz, *Organometallics* **2007**, *26*, 4704–4707.
[124] S. Arndt, M. M. Hansmannm, P. Motloch, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Chem. Eur. J.* **2017**, *23*, 2542–2547.
[125] M. W. Hussong, F. Rominger, P. Krämer, B. F. Straub, *Angew. Chem. Int. Ed.* **2014**, *53*, 9372–9375.
[126] A. Gómez-Suárez, R. S. Ramón, O. Songis, A. M. Z. Slawin, C. S. J. Cazin, S. P. Nolan, *Organometallics* **2011**, *30*, 5463–5470.
[127] S. G. Weber, D. Zahner, F. Rominger, B. F. Straub, *ChemCatChem* **2013**, *5*, 2330–2335.
[128] M. R. Fructos, M. Mar Díaz-Requejo, P. J. Pérez, *Chem. Commun.* **2016**, *52*, 7326–7335.
[129] D. Zhang, G. Xu, D. Ding, C. Zhu, J. Li, J. Sun, *Angew. Chem. Int. Ed.* **2014**, *53*, 11070–11074.
[130] J. Beerhues, R. R. M. Walter, H. Aberhan, M. Neubrand, M. Porré, B. Sarkar, *Organometallics* **2021**, *40*, 1077–1085.
[131] G. Seidel, B. Gabor, R. Goddard, B. Heggen, W. Thiel, A. Fürstner, *Angew. Chem. Int. Ed.* **2014**, *53*, 879–882.
[132] P. de Frémont, E. D. Stevens, M. R. Fructos, M. M Díaz-Requejo, P. J. Pérez, S. P. Nolan, *Chem. Commun.* **2006**, 2045–2047.
[133] L. Rocchigiani, W. T. Klooster, S. J. Coles, D. L. Hughes, P. Hrobárik, M. Bochmann, *Chem. Eur. J.* **2020**, *26*, 8267–8280.
[134] M. Landrini, E. De Paolis, A. Macchioni, L. Tensi, P. Hrobárik, L. Rocchigiani, *Eur. J. Inorg. Chem.* **2022**, 202200373.
[135] M. Delgado-Rebollo, C. García-Morales, C. Maya, A. Prieto, A. M. Echavarren, P. J. Pérez, *J. Organomet. Chem.* **2019**, *898*, 120856–120864.
[136] R. Ma, J. Yang, S. Kelley, B. W. Gung, *J. Organomet. Chem.* **2019**, *898*, 120865.
[137] M. Jin, R. Ando, M. J. Jellen, M. A. Garcia-Garibay, H. Ito, *J. Am. Chem. Soc.* **2021**, *143*, 1144–1153.
[138] Y. Hattori, R. Kitajima, R. Matsuoka, T. Kusamoto, H. Nishihara, K. Uchida, *Chem. Commun.* **2022**, *58*, 2560–2563.
[139] P. Font, H. Valdés, G. Guisado-Barrios, X. Ribas, *Chem. Sci.* **2022**, *13*, 9351–9360.
[140] P. de Frémont, H. Clavier, V. Rosa, T. Avilés, P. Braunstein, *Organometallics* **2011**, *30*, 2241–2251.
[141] C. Dash, M. Yousufuddin, T. R. Cundari, H. V. Rasika Dias, *J. Am. Chem. Soc.* **2013**, *135*, 15479–15488.
[142] a) W. J. Wolf, F. D. Toste, *The Chemistry of Gold Fluoride Complexes in Organogold Complexes PATAI'S Chemistry of Functional Groups* John Wiley & Sons, Ltd **2014**; b) N. J. Rijs, R. A. J. O'Hair, *Dalton Trans.* **2012**, *41*, 3395–3406; c) M. Baya, A. Pérez-Bitrián, S. Martínez-Salvador, J. M. Casas, B. Menjón, J. Orduna, *Chem. Eur. J.* **2017**, *23*, 1512–1515; d) E. Bernhardt, M. Finze, H. Willner, *J. Fluorine Chem.* **2004**, *125*, 967–973; e) X. Wang, L. Andrews, K. Willmann, F. Brosi, S. Riedel, *Angew. Chem. Int. Ed.* **2012**, *51*, 10628–10632.
[143] D. S. Laitar, P. Müller, T. G. Gray, J. P. Sadighi, *Organometallics* **2005**, *24*, 4503–4505.
[144] a) S. G. Rachor, R. Müller, M. Kaupp, T. Braun, *Eur. J. Inorg. Chem.* **2023**, *26*, e2022006; b) G. Yang, Z. Su, C. Qin, Y. Zhao, *J. Chem. Phys.* **2005**, *123*, 134302; c) N. T. Daugherty, T. J. Robilotto, J. Bacsa, T. G. Gray, J. P. Sadighi, *Polyhedron* **2020**, *181*, 114464.
[145] M. A. Ellwanger, S. Steinhauer, P. Golz, T. Braun, S. Riedel, *Angew. Chem. Int. Ed.* **2018**, *57*, 7210–7214.
[146] M. A. Ellwanger, C. von Randow, S. Steinhauer, Y. Zhou, A. Wiesner, H. Beckers, T. Braun, S. Riedel, *Chem. Commun.* **2018**, *54*, 9301–9304.
[147] J. A. Akana, K. X. Bhattacharyya, P. Müller, J. P. Sadighi, *J. Am. Chem. Soc.* **2007**, *129(25)*, 7736–7737.
[148] H. Lv, J.-H. Zhan, Y.-B. Cai, Y. Yu, B. Wang, J.-L. Zhang, *J. Am. Chem. Soc.* **2012**, *134(39)*, 16216–16227.
[149] N. P. Mankad, F. D. Toste, *Chem. Sci.* **2012**, *3*, 72–76.
[150] H. L. Yale, *J. Med. Chem.* **1958**, *1(2)*, 121–133.
[151] a) M. S. Winston, W. J. Wolf, F. D. Toste, *J. Am. Chem. Soc.* **2015**, *137*, 7921; b) M. S. Winston, W. J. Wolf, F. D. Toste, *J. Am. Chem. Soc.* **2014**, *136*, 7777; c) M. D. Levin, T. Q. Chen, M. E. Neubig, C. M. Hong, C. A. Theulier, I. J. Kobylianskii, M. Janabi, J. P. O'Neil, F. D. Toste, *Science* **2017**, *356*, 1272; d) S. Liu, K. Kang, S. Liu, D. Wang, P. Wei, Y. Lan, Q. Shen, *Organometallics* **2018**, *37*, 3901; e) S. Kim, F. D. Toste, *J. Am. Chem. Soc.* **2019**, *141(10)*, 4308–4315.
[152] M. Blaya, D. Bautista, J. Gil-Rubio, J. Vicente, *Organometallics* **2014**, *33(22)*, 6358–6368.
[153] M. Winter, N. Limberg, M. A. Ellwanger, A. Pérez-Bitrián, K. Sonnenberg, S. Steinhauer, S. Riedel, *Chem. Eur. J.* **2020**, *26*, 16089–16097.
[154] F. Nahra, N. V. Tzouras, A. Collado, S. P. Nolan, *Nat. Protoc.* **2021**, *16*, 1476–1493.

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