Mercury-Free Synthesis of Pincer \([C^N\text{N}^C]\text{Au}^{III}\) Complexes by an Oxidative Addition/CH Activation Cascade

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Starting from the commercially available dimethyl sulfide-gold(I) chloride complex (DMSAuCl) and diazonium salts in the presence of 2,6-di-tert-butyl-4-methylpyridine as base, symmetric and unsymmetric \([C^N\text{N}^C]\text{Au}^{III}Cl\) complexes were synthesized in a selective, photosensitizer-free, photochemical reaction using blue LED light. This new protocol provides the first mercury-free synthesis of this type of pincer-complexes in moderate-to-excellent yields, starting from a readily available gold(I) precursor. Owing to the extraordinary properties of the target compounds, like excellent luminescence and high anti-cancer activities, the synthesis of such complexes is a highly active field of research, which might make its way to an industrial application. Owing to the disadvantages of the known protocols, especially the toxicity and the selectivity issues in the case of unsymmetric complexes, avoiding the use of mercury, should further accelerate this ongoing development.

With the first synthesis of a \([C^N\text{N}^C]\text{Au}^{III}\) complex by Che and co-workers in 1998, a fast rise of research concerning this privileged motif in gold(III) chemistry started. Complexes with these tridentate ligands represent the most actively explored privileged motif in gold(III) chemistry.

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gold precursor that allows a post-functionalization after oxidation through chloride replacement. During the proposed reaction, pyridine via ligand exchange replaces DMS, so it works just as weakly coordinating ligand. Thus, for the synthesis of \([\text{C}^\text{N}^\text{C}]\text{Au}^{\text{III}}\text{Cl}\) complexes any pre-functionalization step of the gold complex DMSAuCl can be avoided.

We started our investigation with an in situ activation of aniline 1a via diazotization, using tert-butyl nitrite (tBuONO) and tetrafluoroboric acid (HBF₄) in acetonitrile. Then, the photochemical step, the diazonium salt was directly subjected to the commercially available DMSAuCl in the presence of a base. An unselective reaction was observed, and no product could be isolated (Table 1, entries 1 and 2). With isolated diazonium salt 2a, the reaction without any base delivered a solid, but the measured proton NMR showed a mixture of several compounds (entry 3). With the sterically hindered organic Hünig base the reaction did proceed in the same manner. If sodium hydrogen carbonate was employed, the desired product 3a was produced in traces (entry 5). The yield of 3a dramatically increased to 86% when the organic base 2,6-di-tert-butyl-4-methylpyridine (DTBMP) was used (entry 6). This sterically hindered pyridine base does not compete as ligand with the substrate and in addition does not decompose the diazonium salt.

The identity of the product 3a was unambiguously confirmed by an X-ray single crystal structure analysis (Figure 1, top left picture for 3a). An up-scaling, starting from 602 mg (1.5 mmol) of 2-(6-(4-(tert-butyl)phenyl)pyridin-2-yl)benzenediazonium tetra-fluoroborate, resulted in 574 mg (1.1 mmol) of 3a in 73% yield. Under the optimized reaction conditions, various arendiazonium salts were converted. As shown in Table 2, arenediazonium salts with substituents of varying nature with electron-donating and withdrawing groups on the benzene ring, underwent the oxidative addition smoothly, affording the desired \([\text{C}^\text{N}^\text{C}]\text{Au}^{\text{III}}\text{Cl}\) complexes 3b–3e in moderate-to-good yields. A phenanthrene-substituted diazonium salt was also successfully converted to a gold(III) complex 3f. Next, we turned our focus on substrates bearing unsymmetrically substituted arene systems, which offer two possible positions for the final CH-activation step. Interestingly, both substrates 3g and 3h yielded only the sterically less hindered positional isomer.

In case of 3g, an X-ray structure analysis could be obtained. Most remarkably, the reaction also tolerated an alkyne-substituted precursor, which delivered complex 3i in 78%. This versatile functional group has never been included in this type of

Scheme 1. Synthetic strategies towards \([\text{C}^\text{N}^\text{C}]\text{gold(III)}\) and gold(III)[\text{C}^\text{N}] complexes.

![Scheme 1](image-url)

**Table 1. Optimization of reaction conditions**

| Entry | [Au] Base | Yield |
|-------|------|------|
| 1a    | DMSAuCl NaHCO₃ | unselective reaction |
| 2a    | DMSAuCl NET₃ | unselective reaction |
| 3a    | DMSAuCl Hünig base | unselective reaction |
| 4a    | DMSAuCl NaHCO₃ | traces |
| 5a    | DMSAuCl DBTP | 86% |

[a] Reaction conditions: aniline (1a, 100 μmol), tBuONO (220 μmol), HBF₄ (220 μmol), base (500 μmol), and DMSAuCl (100 μmol) in acetonitrile (1 mL, 0.1 M) were reacted at room temperature under irradiation with blue LEDs; [b] Reaction conditions: diazonium salt (2a, 100 μmol) and DMSAuCl (100 μmol) in acetonitrile (1 mL, 0.1 M) were reacted at room temperature under irradiation with blue LEDs; [c] Reaction conditions: diazonium salt (2a, 100 μmol), DMSAuCl (100 μmol) and base (120 μmol) in acetonitrile (1 mL, 0.1 M) were reacted at room temperature under irradiation with blue LEDs; [d] isolated yield.
complexes before, which might be explained by a competing mercuration of the triple bond (Glick et al. isolated mercurated products starting from diphenylacetylenes with a yield of 75% with mercury(II) acetate in acetic acid at room temperature) that would occur during the synthesis using the classical approach.\[29\] Furthermore, gold complexes are excellent catalysts for the conversion of alkynes.\[30,31\] Our protocol also opened up a route to the C$_2$-symmetric complex 3j, which in most of the named publications served as the [C^N^C]Au$^{\text{III}}$Cl precursor. To our delight, the replacement of the arene part by a thiophene ring, also led to the corresponding product 3k in an excellent yield of 97%. Also, a thiophene[3,2-b]thiophene 3l was tolerated, although the yield dropped to 57%. Complexes 3m and 3n show the limits of this synthesis. The corresponding gold complex of 3m was not isolable, whereas during the reaction of 3n elemental gold precipitated.

As already mentioned, compound 3a gave crystals suitable for an X-ray single-crystal structure analysis (Figure 1—left top picture for 3a). For 3b it was also possible to confirm this structure by a single X-ray crystal structure (Figure 1—right top picture for 3b). Furthermore, for 3g and 3l crystal structure determinations were possible, too. The structure of 3g very nicely shows the sterically less hindered isomer of the complex (Figure 1—left down picture for 3a). Owing to the additional alkyne moiety in 3l, (Figure 1—right picture for 3l), this structure features the first example of a [C^N^C]gold(III) complex including a triple bond in the backbone to be characterized by X-ray crystallography.

With the developed protocol, a direct entry to cationic [C^N^C]Au$^{\text{III}}$(NHC) complexes not dependent on mercury-containing reagents was achieved. By changing the gold(I) precursor, a direct mercury-free synthesis of anti-cancer agents like [C^N^C]Au$^{\text{III}}$(NHC)-complexes now is possible. Complex 4 was isolated in a 65% yield starting from IMesAu(I)Cl (IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene) and AgBF$_4$ by using diazonium salt 2k (Scheme 2a). In the last years, amongst other things the arylation of this class of pincer compounds was achieved with boronic acids in palladium-catalyzed reactions.\[14\] We now developed two different applications. First, we started from a DMS-gold(I)-pentafluorobenzene precursor,\[33\] which delivered complex 5 in good yield (Scheme 2b). Furthermore, we could show that at the gold(III) stage simple transmetallation with phenyl lithium is also a viable process. The reaction of complex 3a gave the desired product 6 in 62% yield (Scheme 2c).

A plausible mechanism that is in line with our previous reports,\[24,25\] is illustrated in Scheme 3. After irradiation of the diazonium salt I with blue-light LED, a cationic gold(III) intermediate II is formed, which directly undergoes CH-activation at
the aryl ring to generate Wheland complex III. Rearomatization under liberation of a proton then delivers the desired [C^N^C]AuCl complex (IV).

In conclusion, an operationally simple, visible light-mediated\cite{34} oxidative addition\cite{33} of diazonium salts to DMSAuCl, DMSAuCF$_3$, or NHCAuCl for the synthesis of [C^N^C]gold(III) complexes, not dependent on additional photosensitizers, was developed. This technology allows the first mercury-free synthesis of well-defined gold complexes, opening new gates especially for medical use. The mild reaction conditions, broad scope, and upscale opportunities suggest that this method could be a useful synthetic tool for the production of gold(III) anticancer drugs and gold(III)-based photo emitters without the generation of toxic mercury wastes.

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**Conflict of interest**

The authors declare no conflict of interest.

**Keywords:** gold(III) complexes • diazonium salts • photochemistry • photosensitizer-free • pincer complexes

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