[C^N]-Alkenyl Gold(III) Complexes by Proximal Ring-Opening of (2-Pyridyl)alkylidenecyclopropanes: Mechanistic Insights

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[C^N]-Alkenyl Gold(III) Complexes by Proximal Ring-Opening of (2-Pyridyl)alkylidenecyclopropanes: Mechanistic Insights

Jorge A. González,[a] Felipe Verdugo,[b] José Luis Mascareñas*,[b] Fernando López*[b,c] and Cristina Nevado*,[a]

Abstract: Pyridine-substituted alkylidenecyclopropanes (Py-ACPs) react with gold(III) salts under mild reaction conditions via an unprecedented, proximal ring-opening pathway, to generate highly appealing, catalytically active pyridine alkenyl [C^N]-gold(III) species. Mechanistic studies reveal that the activation of the C-C bond in the cyclopropyl ring takes place through an unusual concerted, σ-bond metathesis type-process.

Alkylidenecyclopropanes (ACPs) are readily accessible motifs that have found widespread application in organic synthesis.[1] The simultaneous presence of a highly strained cyclopropane and a C–C double bond makes these structures especially reactive in the presence of suitable transition metal complexes. Thus, a large number of metal-promoted transformations of ACPs have been reported in recent years.[2] From a mechanistic perspective, most of these reactions are initiated by oxidative insertion of the metal into the distal or proximal bonds of the cyclopropyl ring, as demonstrated in numerous reports involving Pd, Ni, Rh, Ru, Os, Al and Mg complexes (Scheme 1, a,b).[3] Alternatively, pathways based on the initial activation of the C–C double bond by a carbophilic catalyst, usually leading to highly reactive carbocationic intermediates, have also been disclosed (Scheme 1c).[4] In particular, cationic gold(I) species have been shown to promote this reactivity enabling ring expansions to cyclobutenes,[5] or nucleophilic ring-opening functionalization processes, among other reactions.[6,7] Although in these transformations the gold atom does not change the oxidation state, Toste and Bourissou have independently shown that gold(I) species can undergo oxidative addition processes with related strained systems like biphenylenes or cyclobutanones, to deliver stable [C^C]-gold(III) species.[8] These contributions highlight the interest that gold redox catalysis has received in last decade as a complementary tool in cross-coupling reactions.[9] Considering these results, and the well-known ability of coordinating groups to facilitate the activation of otherwise inert C-H bonds in the presence of gold salts,[10] we questioned whether the presence of a pyridine moiety adjacent to an ACP could enable a gold-promoted direct cleavage of the C-C bonds, and/or uncover new reactivity patterns.[11] Further, fostered by the lack of reports on the performance of ACPs in the presence of gold(III) salts, we set out to explore the reactivity of pyridine-substituted ACPs with highly oxidized gold species.

Herein we demonstrate that, in contrast to gold(I) complexes (e.g. AuCl), which simply coordinate to the pyridine-ACP ligands (Py-ACP, **1**), gold(III) salts unleash an unprecedented proximal ring opening that generates appealing [Csp²^N]-gold(III) species (**2**). More importantly, our mechanic studies reveal that the ring opening to produce **2** takes place by an unusual concerted, σ-bond metathesis-type process (Scheme 1d). To the best of our knowledge, pyridine alkenyl [C^N]-gold(III) complexes of this type are unknown, thus our research not only uncovers new transformations of ACPs, but also provides a practical and simple entry to a novel family of stable gold(III) complexes. Finally, we also demonstrate that these species are catalytically competent in alkene hydroarylation reactions, opening the way for further applications in synthesis.

ACP Activation: Distal and Proximal Metal Insertion *vs* Carbophilic Activation
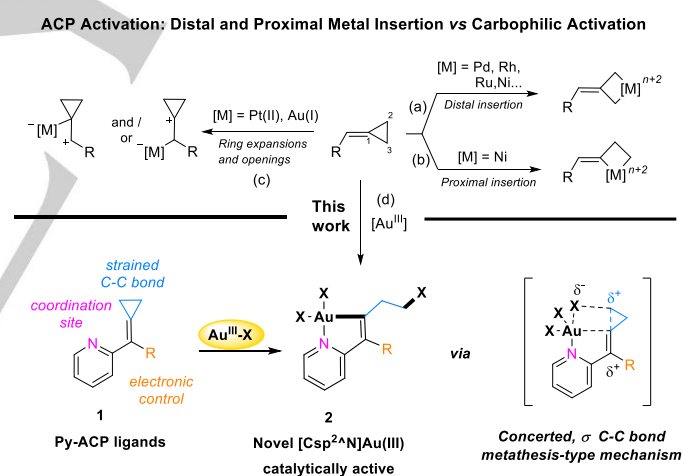
Scheme 1. Top: Reported activation of ACPs with transition metals. Bottom: new reactivity profiles of pyridine-ACP derivatives with gold(III) species.

Our investigation started with the synthesis of the desired pyridine-substituted ACPs of type **1** following previously reported procedures.[12,13] At the outset, the reaction of **1a** with (Me₂S)AuCl resulted in coordination of the gold chloride to the pyridine nitrogen to form complex **1a´**, which could be isolated and characterized by spectroscopic techniques as well as by single crystal X-ray diffraction analysis (Scheme 2). All attempts to promote a C–C bond cleavage, including longer reaction times (t > 24 h) and higher temperatures (40 °C), led to decomposition of **1a´**, with no evidence for C-C bond activation. Likewise, treatment of a solution of **1a´** in CD₂Cl₂ at 25 °C with different silver salts resulted in decomposition of the complex.[13]

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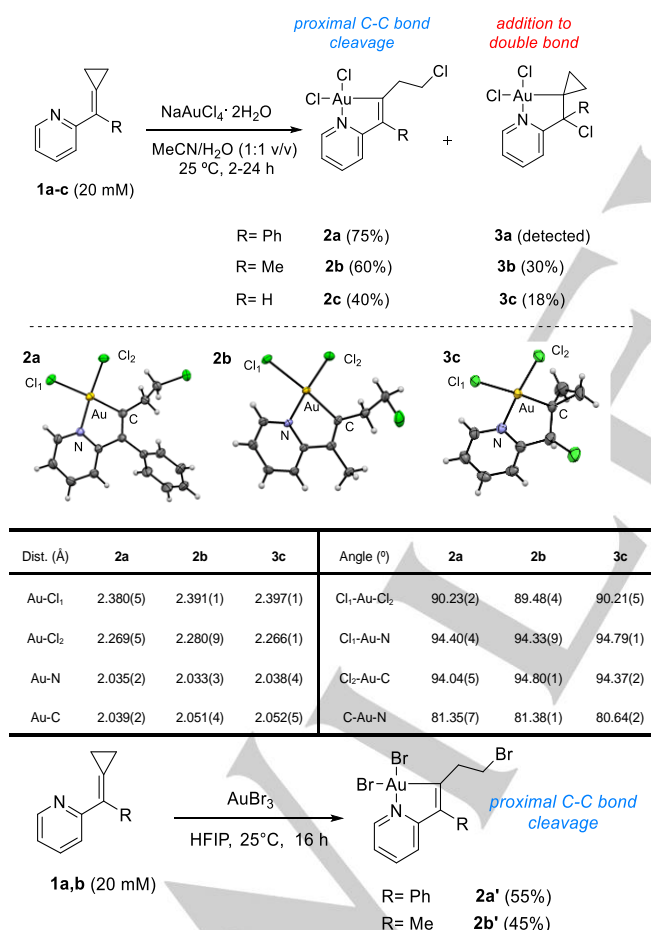[c] Instituto de Química Orgánica General (CSIC). Madrid, Spain

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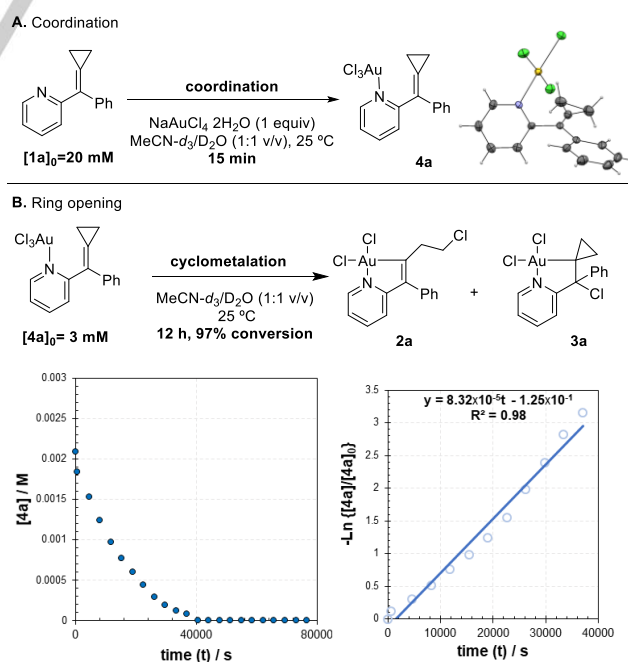
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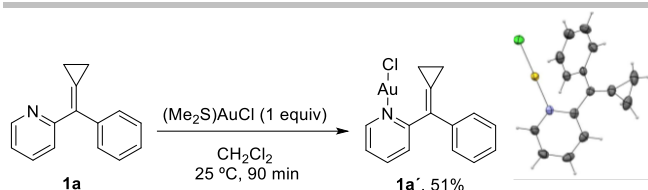
Scheme 2. Reactivity of Au(I) with pyridino-substituted ACPs and X-ray structure (50% probability ellipsoids) of the complex **1a'**. Bond lengths (Å): Au-Cl = 2.043(5) and Au-N = 2.247(2), respectively.

We then turned our attention to the behaviour of the Py-ACP precursors **1** in presence of gold(III) salts (Scheme 3). In contrast to the reaction with gold(I) salts, when **1a** was exposed to one equivalent of sodium tetrachloroaurate at 25 °C in a mixture MeCN:H$_2$O (1:1 v/v), for 16 h, we observed the clean formation of two cyclometalated products. Upon standard purification of the reaction mixture by flash column chromatography, [Csp^2^N]-gold(III) complex **2a** could be isolated in 75% yield. Interestingly, we observed that **2a** is stable in acidic media as well as under thermal conditions.[13]

Dist. (Å)	**2a**	**2b**	**3c**	Angle (º)	**2a**	**2b**	**3c**
Au-Cl$_1$	2.380(5)	2.391(1)	2.397(1)	Cl$_1$-Au-Cl$_2$	90.23(2)	89.48(4)	90.21(5)
Au-Cl$_2$	2.269(5)	2.280(9)	2.266(1)	Cl$_1$-Au-N	94.40(4)	94.33(9)	94.79(1)
Au-N	2.035(2)	2.033(3)	2.038(4)	Cl$_2$-Au-C	94.04(5)	94.80(1)	94.37(2)
Au-C	2.039(2)	2.051(4)	2.052(5)	C-Au-N	81.35(7)	81.38(1)	80.64(2)

Scheme 3. Top: Reactivity of pyridine-substituted ACPs **1a-c** with NaAuCl$_4$.[13] Middle: X-ray structures and table summarizing the relevant bond distances (Å) and angles for **2a**, **3b**, and **3c** (50% probability ellipsoids). Bottom: Reactivity of pyridine-substituted ACPs **1a-b** with AuBr$_3$.[13] The products were purified by flash column chromatography. Isolated yields reported.

Albeit the minor product of the reaction could not be isolated due to its low stability, it was unambiguously identified by NMR (from the crude mixture) as the cyclopropylpyridine gold complex **3a** (vide infra). Related pyridine-ACPs bearing a methyl (**1b**) or a hydrogen substituent (**1c**) at the internal position of the olefin reacted under similar conditions delivering the homologous alkenyl gold complexes **2b** and **2c** in 60 and 40% yield, respectively. In these cases, small amounts of products of type **3**, arising from a chloroauration of the double bond were also obtained. Gratifyingly, complexes **3b** and **3c** proved to be more stable than **3a**, and could be isolated in 30 and 18% yield, respectively. The structures of cyclometalated adducts **2a**, **2b** and **3c** could be unambiguously confirmed by X-ray diffraction analysis of single crystals. In these three complexes, the gold(III) center adopts a distorted square-planar geometry with a reduced C-Au-N angle (from 80.64(2) to 81.38(1)°), imposed by the geometry of the newly created five-membered ring [C^N] ligand. Interestingly, the C-Au distance in **2a** is shorter (2.039(2) Å) than in its homologue **2b** (2.051(4) Å, probably as a result of the extended conjugation offered by the phenyl substituent attached to the olefin. The reaction is not limited to the synthesis of chloride derivatives. Indeed, the analogous bromide complexes **2a'** and **2b'** could also be obtained in moderate yields by treating the pyridino-ACPs **1a** and **1b** with AuBr$_3$, using HFIP as solvent.[14] Importantly, a substrate similar to **1a**, but bearing a phenyl instead of a pyridine group, gave no conversion when treated with gold(III) salts under analogous reaction conditions, thus demonstrating that gold chelation by the pyridine moiety is key to achieve the observed C-C bond cleavage under mild reaction conditions.[11,15] In fact, careful monitoring by ^{1}H NMR of the reaction of **1a** with NaAuCl$_4$ under the abovementioned conditions, revealed an initial coordination of pyridine to the gold(III) in the reaction media yielding the pyridino-gold(III) complex (**4a**), which could also be isolated and unambiguously characterized by NMR and single crystal X-ray diffraction analysis (Scheme 4A).[13]
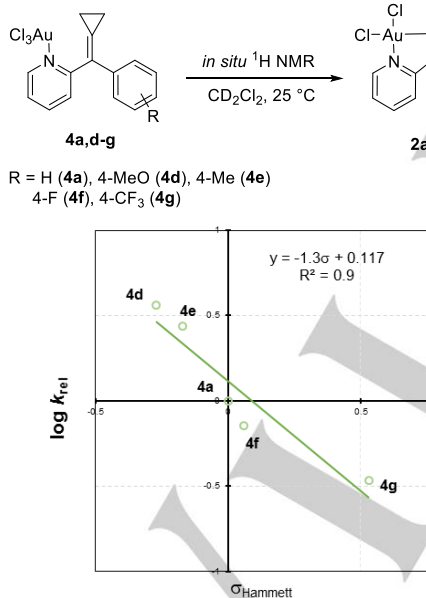

Scheme 4. Upper: **A**) Synthesis of gold(III) complex **4a**. **B**) Reactivity of **4a** to give **2a** and **3a**. Bottom: Kinetics of consumption of **4a**. As a result of the high

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dilution and since complex **4a** was used as direct precursor, a 1:2.5 ratio of **2a**/**3a** was observed in this experiment. [13]
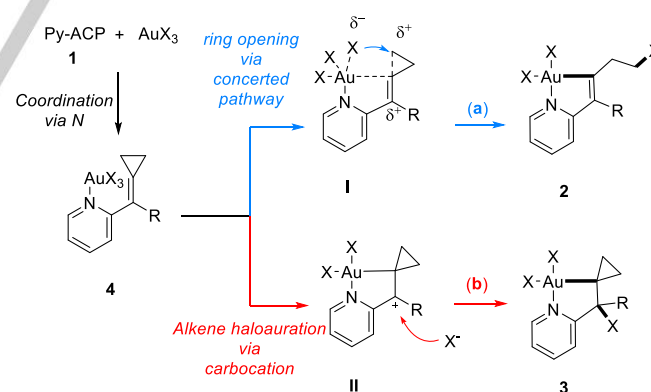
The question at hand next was whether or not **4a** was a productive intermediate in the formation of the cyclometalated adducts **2** and **3**. In order to answer this question, **4a** was re-submitted to the standard reaction conditions overnight, furnishing the expected adducts **2a** and **3a** (Scheme 4B). Kinetics of this reaction showed that the cyclometalation process occurs much slower ($t_{1/2}$ = 2.3 h, see SI) compared to the coordination of **1a** to gold(III) ($t_{1/2}$ = 18 s, see SI, Scheme 4, bottom).[13] These results thus confirm that the cyclometalation is the rate limiting step in these transformations. Given that, to the best of our knowledge, there were no precedents in the literature for this type of gold mediated rearrangements, we sought to shed further light on the underlying mechanism of these reactions. We first assessed the effect of the electronic properties of the aryl substituent on the ring opening process by introducing electron-donating and electron-withdrawing groups in the *para* position of the aromatic ring. The transformation of complexes **4a,d-f**, obtained from the corresponding ACP precursors, to the cyclometalation products **2a,d-f**, was monitored under the standard reaction conditions.[13,16] When plotting logk_{rel} against neutral Hammett values,[17] we could observe a modest correlation (ρ= -0.9) that indicates that the reaction is only moderately sensitive to electronic effects on the aromatic ring of the ACP moiety (Scheme 5). These results suggest that the cyclometalation reaction is not involving the formation of benzylic carbocations, as in that case a much higher ρ value would be expected according to previous studies reported for related systems.[18]

BHT or TEMPO, the reaction proceeded with comparable efficiency, thus ruling out a radical mechanism underlying these transformations.[13] Remarkably, when **4a** was dissolved in solvents with a high dielectric constants, such as DMSO, we observed a fast and exclusive formation of the secondary alkene chloroauration product **3a** ($t_{1/2}$ = 0.14 h).[13] Additional control experiments also confirmed that [Csp3^N]-gold(III) complexes **3** were not intermediates in the formation of the Csp2-cyclometalated adducts **2**.[19],[13]

Based on the abovementioned results, several mechanistic considerations can be made. First, the observation of a pseudo-first order decay for **4a**, and given that no intermediate species were detected, suggests that the cyclometalation reaction follows an unimolecular pathway.[19] Second, the formation of alkenyl gold(III) complexes **2** through a step-wise mechanism involving a benzylic carbocation is deemed unlikely based on the Hammett value, and on the control experiments in the presence of excess of Cl⁻.[13] Therefore, for the formation of **2a** from **4** we favor a mechanism involving a proximal Csp3-Csp2 bond activation with concerted Au-Cl cleavage so that the partial positive charge generated in the homoallylic position is intercepted by the nascent nucleophilic chloride (Scheme 6, path a). This process resembles a C-C σ-bond metathesis in which a concerted exchange takes place between the Au-X and the proximal cyclopropyl C-C σ-bond (**I**) so that all occupied orbitals are engaged in bonding along the course of the reaction. Such σ-C-C bond metathesis-type processes with transition metals are rare and therefore, our results, in addition to uncover a new type of transformation, revealed a mechanistic mode unprecedented in the field of gold chemistry.[20] In contrast, the formation of adducts **3** seems to proceed via carbocation intermediate **II** (Scheme 6, path b), a route that is strongly favored in the presence of highly polar solvents such as DMSO, in which the exclusive formation of adducts **3** is observed.[13]


R = H (**4a**), 4-MeO (**4d**), 4-Me (**4e**)
4-F (**4f**), 4-CF₃ (**4g**)

Scheme 5. Kinetics of cyclometalation with different substitution patterns on the pyridine-ACPs at 25 °C. Hammett plot for compounds **4a**, **4d-g**.[13]

Scheme 6. Possible mechanisms for pyridine-ACP ring-opening.

Interestingly, when the reaction of **1a** was carried out under the conditions shown in Scheme 3, but in the presence an external source of chloride (Me₄NCl, 10 equiv), we observed the exclusive formation of alkenyl gold(III) complex **2a**. Further, when the reaction was carried out in the presence of radical traps such as

Aryl-pyridine gold(III) complexes have found application as cytotoxic agents,[21] bioorthogonal reagents,[22] and luminescent materials.[23] In addition, some of these systems have also been used as catalysts.[24] However, striking the right balance between stability and catalytic activity for gold(III) species still represents a major challenge. The main difficulty stems from the intrinsically high redox potential that leads to the facile reduction of Au(III) complexes to Au(I) or metallic Au(0) species in the presence of electron-rich reagents. In addition, even when the ligands are able

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to stabilize the highly oxidized metal, the resulting complex is often catalytically inert.[8a,25] We thus wondered whether the stable and easy to handle [C^N] alkenyl gold(III) complexes of type **2** could be useful in this context. The hydroarylation of alkenes represents an ideal transformation to benchmark the catalytic potential of these novel species, as the resulting derivatives are extremely valuable building blocks in organic synthesis and materials science.[26] To our delight, **2a** in combination with AgSbF$_6$ catalyzed the hydroarylation of different olefins under mild reaction conditions with yields and selectivities comparable to those previously reported for other cationic gold(I) and gold(III) salts (Scheme 7).[13],[27]
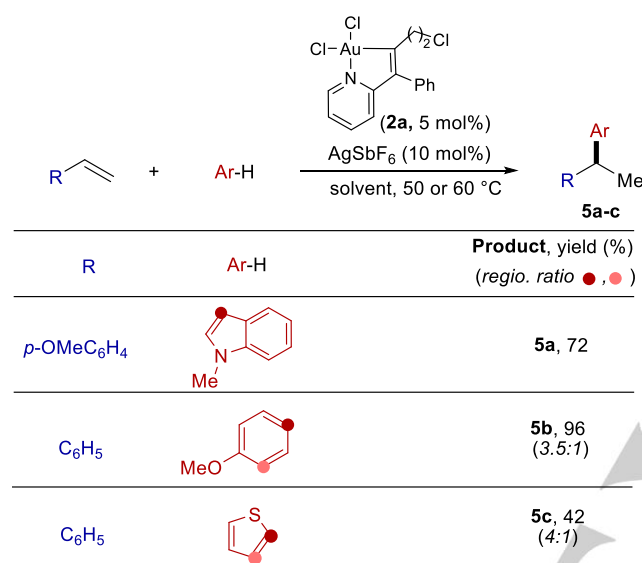
Scheme 7. Catalytic application of complex **2a** in alkene hydroarylation reactions. Comparative experiments with more standard Au(III) catalysts are described in the Supporting Information.[13]

In summary, we have uncovered here novel ways of manipulating ACPs in the presence of gold(III) salts that resulted in the preparation of previously unknown cyclometalated [C^N]-alkenyl gold(III) complexes. Key for the observed reactivity is the presence of a neighboring pyridine moiety that, by coordination to the highly oxidized metal, facilitates the C-C bond cleavage process. Our mechanistic studies suggest that the ring opening proceeds via activation of the proximal single C-C bond in the cyclopropyl moiety through a unimolecular concerted process that resembles a C-C σ-bond metathesis. This type of mechanism is underdeveloped not only in gold chemistry, but also for other transition metals. Finally, we also demonstrate that these novel [C^N]Au(III)Cl$_2$ species, despite being rather stable, present interesting catalytic properties, and therefore can be added to the toolbox of gold catalysts for synthetic applications.

Acknowledgements

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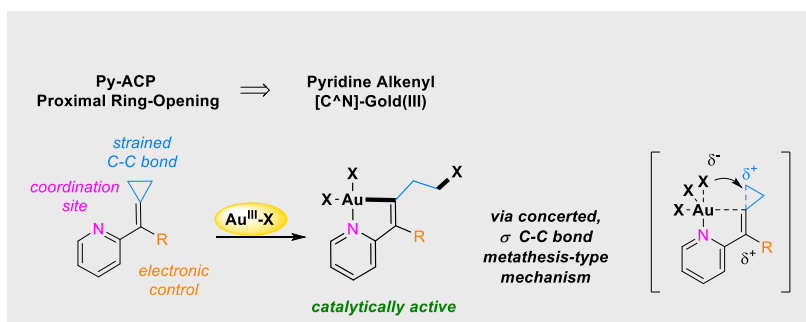
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[C^N]-Alkenyl Gold(III) Complexes by Proximal Ring-Opening of (2-Pyridyl)alkylidenecyclopropanes: Mechanistic Insights

Knock, Knock: Pyridine-substituted alkylidenecyclopropanes (Py-ACPs) react with gold(III) salts via an unprecedented, proximal ring-opening pathway, to generate highly appealing, catalytically active pyridine alkenyl [C^N]-gold(III) species. Mechanistic studies reveal that the activation of the C-C bond in the cyclopropyl ring takes place through an unusual concerted, σ-bond metathesis type-process under very mild reaction conditions aided by coordination of the pyridine ligand to the highly oxidized metal center