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Mechanistic Insights into C(sp^2)-C(sp)N Reductive Elimination from Gold(III) Cyanide Complexes

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This paper is dedicated to the memory of our colleague and friend, Prof. Kilian Muñiz, who recently passed away.

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Abstract: A new family of phosphine-ligated dicyanoarylgold(III) complexes has been prepared and their reactivity towards reductive elimination has been studied in detail. Both, a highly positive entropy of activation and a primary $^{12/13}$C KIE suggest a late concerted transition state while Hammett analysis and DFT calculations indicate that the process is asynchronous. As a result, a distinct mechanism involving an asynchronous concerted reductive elimination for the overall C(sp^2)-C(sp)N bond forming reaction is characterized here for the first time complementing previous studies reported for C(sp^3)-C(sp^3), C(sp^2)-C(sp^2) and C(sp^3)-C(sp^2) bond formation processes taking place on gold(III) species.

Introduction

Gold-catalyzed cross-couplings have come to the forefront of synthetic methods to forge both C-C and C-X bonds in recent years.[1] An in-depth understanding of the reaction mechanisms as well as of the factors that affect the rate and selectivity of the elementary organometallic steps in these transformations has proven crucial to design more effective and selective processes.[2,3] Reductive elimination on gold(III) intermediates is a key step in these catalytic cycles as it precedes the formation of the new C-C or C-X bond towards the desired product and regenerates the gold(I) species that re-enter the catalytic cycle. Pioneering work from Kochi and Tobias on dialkylgold(III) complexes established a C(sp^3)-C(sp^3) reductive elimination via a high-energy T-shaped intermediate formed by ligand dissociation for both neutral [R$_3$PAu(alkyl)$_3$] and cationic [(R$_3$P)$_2$Au(alkyl)$_2$]$^+$ complexes.[4] An analogous mechanism was proposed by Komiya for gold(III) complexes yielding C(sp^2)-C(sp^3) bonds (Scheme 1, left).[5] Years later, Vicente reported the first examples of C(sp^2)-C(sp^2) reductive elimination from diarylgold(III) complexes, a process that has been characterized in detail by Toste and co-workers.[6,7] These seminal studies revealed a concerted mechanism from a tetracoordinated gold(III) center (Scheme 1, right). In contrast to the aforementioned extensive investigations on C(sp^3)-C(sp^3) and C(sp^2)-C(sp^2) bond forming reactions, no mechanistic study on the analogous C(sp^2)-C(sp) reductive elimination has been reported yet despite the demonstrated

efficiency of gold to trigger the formation of these type of bonds.[8] Among other factors, the scarce number of available methods to access [C(sp^2),C(sp)-Au(III)] species has significantly limited the in depth mechanistic characterization of these transformations.[8a, 8e, 9] To address this gap, and in line with on-going efforts in our group to understand the reactivity of gold(III) species relevant in synthetic contexts,[10] we report here the synthesis and characterization of a new family of [(Ph$_3$P)Au(aryl)(CN)$_2$] complexes together with a detailed mechanistic study towards C(sp^2)-C(sp)N bond formation to produce the corresponding polyfluorinated benzonitriles. The experimental and computational data reveal a novel asynchronous concerted reductive elimination mechanism operating on these gold(III) species that contrasts with classical dissociative or synchronous concerted processes previously reported for C(sp^3)-C(sp^3) and C(sp^2)-C(sp^2) bond forming reactions (Scheme 1, bottom).
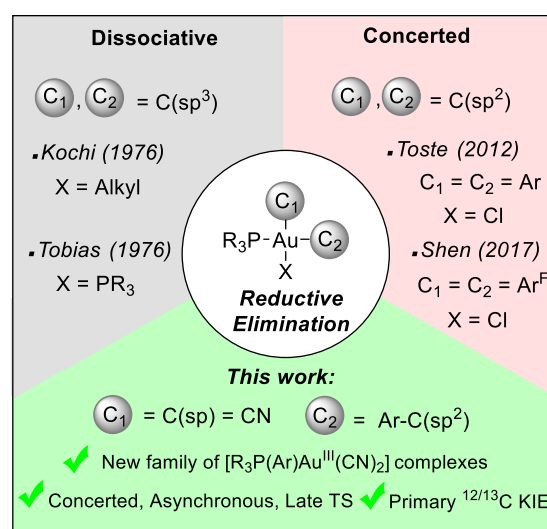
Scheme 1. Summary of reductive elimination mechanisms characterized on gold(III) species.

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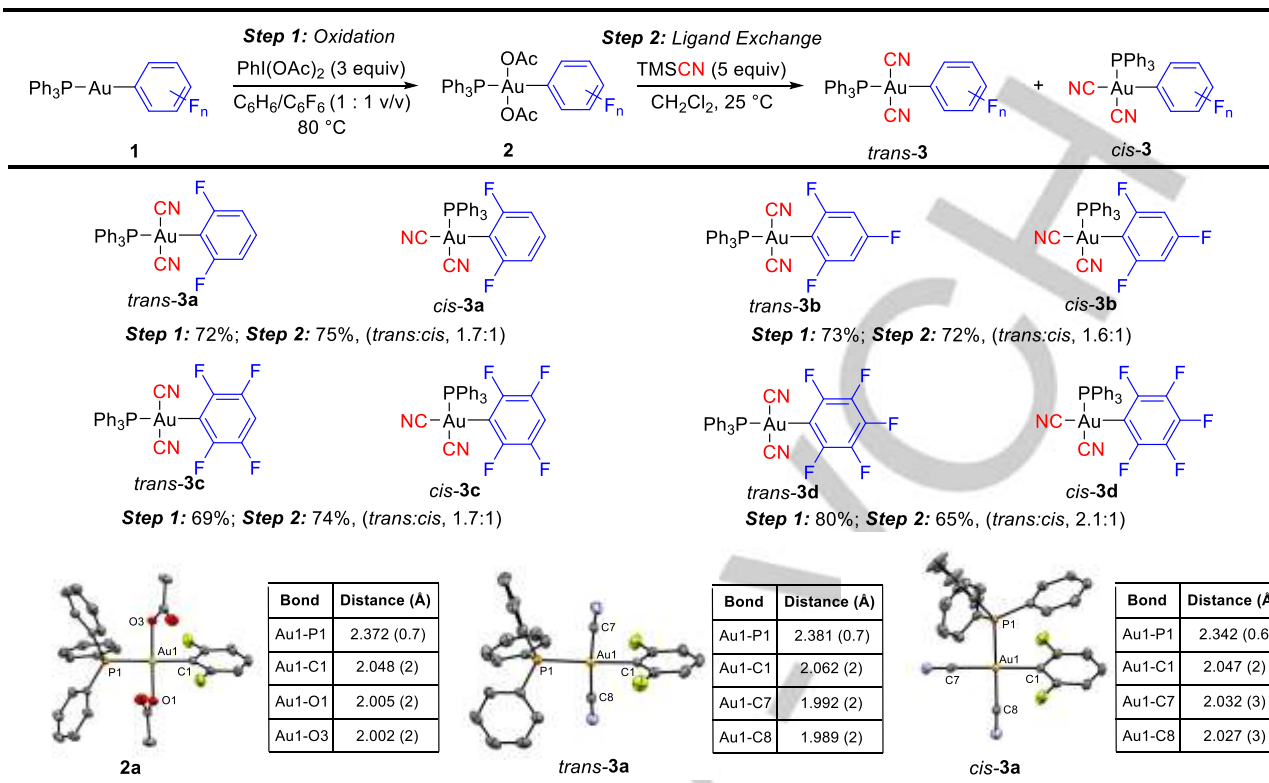
Scheme 2. Synthesis of phosphine-ligated dicyanoarylgold(III) complexes; X-ray crystal structure shown as 50% ellipsoids. Hydrogens were omitted for clarity.

Results and Discussion

First, we set out to prepare and characterize stable phosphine-ligated dicyanoarylgold(III) complexes (Scheme 2).[11] To this end, polyfluoroarylgold(I) species **1a-d** were oxidized with PhI(OAc)$_2$ at 80 °C to obtain the corresponding *trans*-diacetatoarylgold(III) complexes **2a-d** in moderate to good yields. The use of a 2,6-difluoro substitution pattern on the aryl moiety is crucial to impart the required stability to the resulting gold(III) complexes. The presence of more electron-rich aryl ligands (*p*-F-C$_6$H$_4$, *p*-*t*Bu-C$_6$H$_4$) yielded a competitive C(sp^2)-O bond formation process during the oxidation step, in line with the observations reported by Ribas *et al.* [12] (For additional information on these and related control experiments, see Supporting Information) [11]. Subsequent ligand exchange on complexes **2** with TMSCN at room temperature furnished two main products, *cis*- and *trans*-**3a-d**, which could be separated by column chromatography on silica gel and whose structures were unambiguously established by X-ray diffraction of single crystals of *trans*- and *cis*-**3a** (Scheme 2). In all cases, the *trans*- isomer, predicted to be thermodynamically more stable according to DFT calculations (ΔG$_{trans-cis}$ ca. -1.0 kcal/mol at 25 ºC), is obtained as the major product in these transformations.[11]

The thermal and bench-top stability of complexes **3a-d** set the basis for the subsequent study on the reductive elimination to form C(sp^2)-C(sp)N bonds.[13] At 100 ºC, quantitative conversion of *trans*-**3a-d** to the corresponding polyfluorinated benzonitriles

4a-d alongside Ph$_3$PAuCN (**5**) was successfully achieved (Table 1).

Table 1. Thermally-induced reductive elimination from phosphine-ligated dicyanoarylgold(III) complexes.
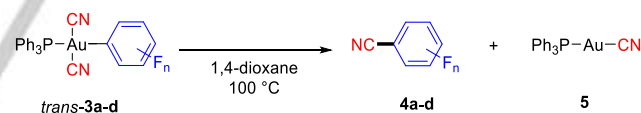
Entry	Compound	Time (h)	Product (%)[a]
1	*trans*-**3a**	2	**4a**, 99
2	*trans*-**3b**	3	**4b**, 98
3	*trans*-**3c**	19	**4c**, 97
4	*trans*-**3d**	30	**4d**, 95

[a] Yield calculated by ^{19}F NMR using 3,3'-difluorobenzophenone as internal standard

Subsequent kinetic studies focused on the reductive elimination of *trans*-**3a** (25 mM) in 1,4-dioxane at 100 ºC. This system provided homogeneous reaction mixtures amenable to reaction monitoring via ^{19}F NMR.[11] Temporal concentrations of both substrate (*trans*-**3a**) and product (**4a**) were calculated using 3,3'-difluorobenzophenone as internal standard. The consumption of *trans*-**3a** followed a first-order irreversible decay {-d[*trans*-**3a**]/d*t* = k_1[*trans*-**3a**]} up to conversions higher than 95 % with no intermediate species detected (< 2%). Thus, the average first-order rate constant (k_1) at 100 ºC was calculated to be 6.88 x 10^{-4} s^{-1} $\pm$ 2.34 x 10^{-5} s^{-1} over three separate experiments (Figure 1a).

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First-order kinetics imply either a concerted mechanism where the Csp^2-C(sp)N bond is formed at the rate-determining step or a dissociative mechanism in which a high-energy T-shaped intermediate is formed by ligand dissociation (PPh_3 or CN^-). Phosphine decoordination was ruled out since the addition of Ph_3P (10 equiv) to a solution of *trans*-**3a** did not significantly influence the rate of formation of **4a**.[11,14,15]

[*trans*-**3a**]$_0$ = 25 mM

Figure 1. a) Kinetics of reductive elimination of *trans*-**3a** at 100 °C (representative example shown).[10] Left: Evolution of concentrations of *trans*-**3a** and **4a** over time. Right: Plot of ln{[*trans*-**3a**]$_t$ / [*trans*-**3a**]$_0$} *vs* time indicating a first-order decay on *trans*-**3a**. The error bars represent the inherent error in quantifying ^{19}F NMR signal intensity. b) Eyring analysis for reductive elimination in *trans*-**3a** (80, 90, 95 and 100 °C). The error bars represent the standard deviation over three separate experiments.[11]

This result is in striking contrast to observations made by Kochi and co-workers for the reductive elimination of trialkylgold(III) species, in which the presence of external phosphine inhibits the $C(sp^3)$-$C(sp^3)$ reductive elimination[4] as well as with observations made by Toste and co-workers for the reductive elimination on diarylgold(III) species, where an excess of external phosphine accelerates the formation of the $C(sp^2)$-$C(sp^2)$ bond by associative ligand exchange.[6b] Interestingly, the addition of one equivalent of anionic cyanide reagents (NBu_4CN or KCN) to a solution of *trans*-**3a** at 25 °C leads to the displacement of the phosphine ligand, thus illustrating the affinity of cyanide ligands for gold and deeming unlikely their potential dissociation from the gold(III) complexes.[11,16,17,18] Additionally, an experiment at a lower initial concentration of *trans*-**3a** (5 mM) showed no effect on the rate of reductive elimination at 100 ºC (6.75×10^{-4} s^{-1}), which

seems to exclude a bimolecular process.[11] Interestingly, *cis*-**3a** undergoes reductive elimination under the same reaction conditions, yielding **4a** and **5** at a similar rate (6.96×10^{-4} s^{-1}) to that of *trans*-**3a** (see Figure 2a). This result is rather surprising in light of the strong *trans* effect associated with cyano ligands.[19] Thus, to further characterize the reductive elimination mechanism, activation parameters were determined from the first-order rate constants obtained at different temperatures. A $\Delta G^{\ddagger}$ value of 27.4 kcal mol^{-1} at 100 °C was obtained together with a significant positive entropy of activation ($\Delta S^{\ddagger}$ = +27 cal K^{-1}mol^{-1}) (Figure 1b).[11] As a dissociative pathway was previously ruled out, we rationalize this value as a result of a late transition state in which at least one of the Au-C bonds is significantly weakened, thus increasing the degrees of freedom in the system. This observation contrasts with the early transition state characterized by Toste and co-workers for the concerted $C(sp^2)$-$C(sp^2)$ reductive elimination ($\Delta S^{\ddagger}$ = +2.0 cal K^{-1}mol^{-1}).[6b] In order to verify our hypothesis experimentally, *cis*-**3a**-{$^{13}C_{2-CN}$} was synthesized to determine the $^{12/13}C$ kinetic isotope effect (KIE).[20,21]

[*cis*-**3a**]$_0$

+

[*cis*-**3a**-{$^{13}C_{2-CN}$}]$_0$

in-situ $^{31}P\{^1H\}$ NMR
1,4-dioxane-d_8
65 °C
25 mM

4a   **5**

4a-$^{13}C_{CN}$ **5**-$^{13}C_{CN}$

Figure 2. Kinetics of reductive elimination of *cis*-**3a**. a) Plot of ln{[*cis*-**3a**]/[*cis*-**3a**]$_0$} vs time indicating a first-order decay at 100 °C. The error bars represent the inherent error in quantifying ^{19}F NMR signal intensity. b) Intermolecular competition between *cis*-**3a** and *cis*-**3a**-{$^{13}C_{2-CN}$} to determine $^{12/13}C$ KIE. The $^{12/13}C$ KIE was calculated to be 1.032 ± 0.005. The dotted line represents the simulated profile.

The isotopic labelling synthesis was achieved using commercially available TMSCN-{$^{13}C_{-CN}$}.[11] Upon isolation, the $^{12/13}C$ KIE was determined by an intermolecular competition experiment using an equimolar mixture of the isotopologues *cis*-**3a** and *cis*-**3a**-{$^{13}C_{2-CN}$} which was monitored by *in-situ* $^{31}P\{^1H\}$ NMR at 65 °C (Figure 2b). A value of 1.032 ± 0.005 was obtained, which is indicative of a primary KIE for carbon and suggests that the cleavage of the Au-C(sp)N bond occurs during the rate-limiting step. This value is

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also in good agreement with the theoretically calculated one (1.042 via DFT).[11] To the best of our knowledge, no experimental $^{12/13}$C KIE values have been reported on reductive elimination from late transition metals, which makes this study a precedent for further investigations in the field.

Additional experiments were designed to verify whether a common mechanism operates across the different substrates. The effect of the aryl group on the kinetics of the reductive elimination for *trans*-**3a-d** complexes (25 mM) in 1,4-dioxane at 100 ºC was therefore investigated. The first-order rate constants were analyzed by a linear free-energy relationship (LFER) using the standard Hammett σ-function,[22] affording a ρ value of -1.9 (Figure 3a). The observed trend is consistent with a conserved reaction mechanism across the different complexes. Additionally, it suggests that the cyano ligand acts as an electrophile and the nucleophilicity of the aryl ligand is decreased in presence of electron withdrawing substituents, thus reducing the rate of reductive elimination in electron deficient systems.

(kcal/mol) were calculated at 100 °C with the B3LYP/ def2-QZVPP functional. Distances indicated in Å.

Ground- and transition-state structures were computed for both *trans*- and *cis*-**3a** isomers using DFT calculations (Figure 3b). The $\Delta G^{\neq}$ values predicted computationally at 100 °C for both complexes are very similar, in line with the very close first-order rate constants determined experimentally. The analysis of bond distances showed the lengthening of the Au-C(sp^2) bond in the TS for both *trans*-**3a** (from 2.08 to 2.20 Å) and *cis*-**3a** (from 2.07 to 2.17 Å) compared to the minimized ground state geometries. Further, a significant shortening of the C(sp^2)-C(sp)N distance is also observed in both compounds. Surprisingly, the Au-C(sp) bond remains almost unchanged between ground state and transition state. This is in sharp contrast with computed transition states for C(sp^2)-C(sp^2) reductive elimination where both Au-C(sp^2) bonds are synchronously elongated.[7a] Both structural features confirm the primary $^{12/13}$C KIE and the positive entropy of activation determined experimentally and support the vision of an asynchronous reductive elimination. To the best of our knowledge, such a scenario has not yet been reported for gold(III) species and thus confirms the mechanistic diversity underlying transformations mediated by this late transition metal. Further, these findings highlight the similarity with other d^{10} metals such as Pd, for which a "migratory" reductive elimination has been proposed on cyanide derivatives based on their similarity with CO insertion processes.[13b]
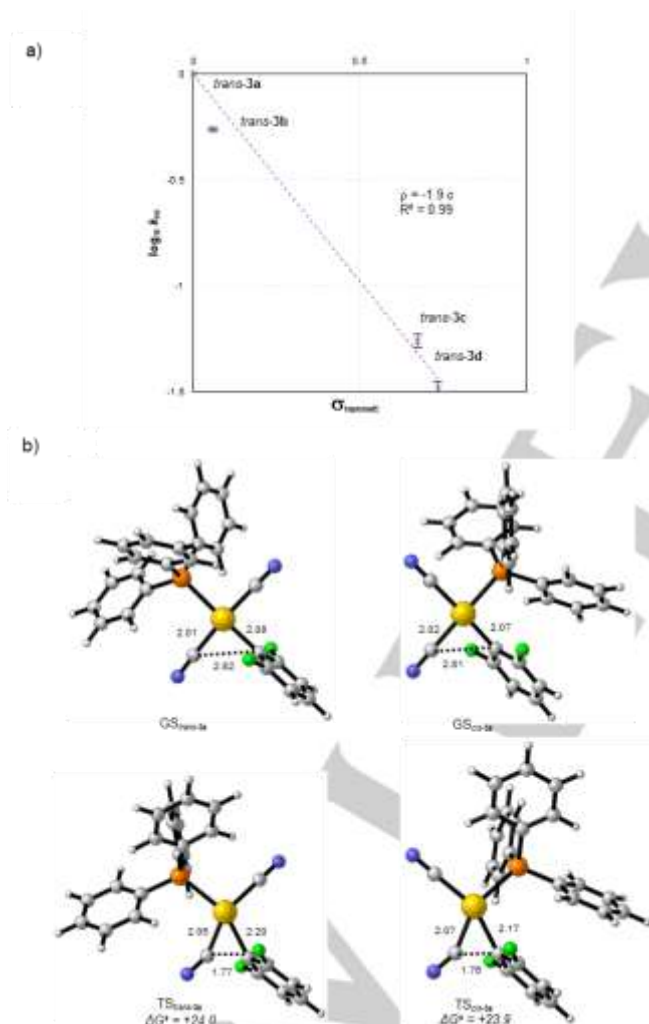
Conclusion

We report here the synthesis of stable phosphine-supported dicyanopolyfluoroarylgold(III) complexes, which under thermal conditions, deliver the corresponding polyfluorinated benzonitriles. This novel compound class gave us the opportunity to unravel the underlying mechanism of the C(sp^2)-C(sp)N reductive elimination from gold(III), which occurs through an unprecedented asynchronous concerted pathway analogous to the "migratory" reductive elimination reported for Pd(II) complexes. Our results have the potential to streamline the development of new catalytic methods to access arylnitriles as well as to improve other gold-catalyzed couplings involving C(sp)-hybridized groups.

Acknowledgements

Figure 3. a) Hammett plot of the rates of the reductive elimination from *trans*-**3a-d** at 100 °C in 1,4-dioxane. The error bars represent the standard deviation over three separate experiments.[10] b) Computed ground states (GS) and transition states (TS) for the reductive elimination of *trans*-**3a** and *cis*-**3a** and Gibbs Free Energy values

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[15] The formation of **4a** is not affected by the presence of TEMPO (5 equiv) in the reaction media (See Supporting Information, ref. 11).

[16] Reductive elimination was never observed from the mixture (See Supporting Information, ref. 11).

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[21] For *trans*-**3a**, the ^{31}P NMR signals of the ^{12}C and ^{13}C-labeled compounds fully overlap. As such, and since *cis*-**3a** and *trans*-**3a** have been proved to undergo reductive elimination at similar rates by a similar mechanism, it was decided to use the *cis* isomer for the KIE study (See Supporting Information, ref. 11).

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RESEARCH ARTICLE

Entry for the Table of Contents
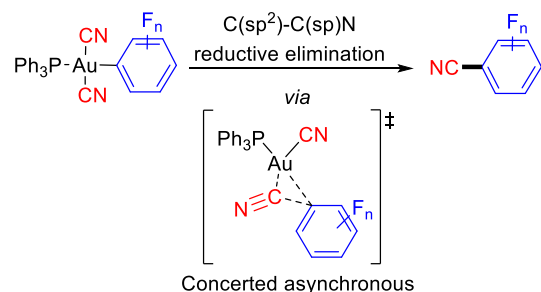
A detailed mechanistic study on the C(sp^2)-C(sp)N reductive elimination from gold(III) complexes is reported here. The kinetic and computational data from a new family of well-defined phosphine-ligated dicyanoarylgold(III) complexes unravel a novel asynchronous concerted reductive elimination process operating in these transformations.

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