The Gold(I)-Catalyzed Protodecarboxylation Mechanism

Stéphanie Dupuy, Luke Crawford, Michael Bühl and Steven P. Nolan^{*[a]}

Abstract: A mechanistic study of the gold-catalyzed protodecarboxylation is described. Each reaction step has been investigated experimentally and computationally. More specifically, the activation parameters for the decarboxylation step have been determined through kinetic studies. Further experimental studies on the hydrolysis of the arylgold intermediate have revealed that the protodeauration can become competitive with the decarboxylation process at high conversions. This switch in rate-limiting step has been shown to be pK_a -dependent. These studies have been supported by DFT calculations and permit a better understanding of which prevalent features of the reaction mechanism account for the decarboxylation process.

Introduction

Transition metal catalyzed cross-couplings have become staple methodologies in modern chemistry.¹ In this context, the use of carboxylic acids as carbon-nucleophile sources has recently emerged as an appealing alternative approach to waste-intensive traditional cross-couplings from both environmental and step- and atom-economical perspectives.² In addition, these promising raw materials are inexpensive, easy to handle, accessible in great structural diversity and ensure a complete chemoselectivity and regioselectivity in the coupling reactions. The viability of these processes has been illustrated in recent years with the development of multiple novel methodologies for the construction of C-C bonds in decarboxylative coupling reactions using mono or bimetallic catalyst systems.^{2a,3}

Among these methodologies, a variety of transition metals including Cu,^{3h,4} Ag,⁵ Rh,⁶ Pd⁷ and Au⁸ have been efficiently utilized to extrude CO₂ from aromatic carboxylic acids.^{3b,8b,9} It is now widely established that a common initiation step in these reaction relies on the formation of a metal carboxylate species.¹⁰ This intermediate, upon heating, releases a molecule of CO₂ to generate an arylmetal species that can subsequently be coupled with a variety of electrophiles. Mechanistic investigations of the decarboxylation step have been performed with Cu,^{4a,11} Ag^{11e,11f} and Pd¹² as well as uncatalyzed systems.^{4a,11e,13} Nilsson,^{11a,11b,14} Sheppard¹⁰ and Cohen^{11c,11d} pioneered the exploration of the Cu-mediated decarboxylation mechanism as early as 1970 and provided evidence for the formation of an organocopper intermediate in the protodecarboxylation reaction. In early 2000, Gooßen and co-workers further investigated the intrinsic mechanism on the formation of this key intermediate from Cu- and Ag-benzoates using DFT calculations.^{4a,11e} These studies

confirmed the beneficial effect of the presence of a substituent in the *ortho* position on the aryl ring and a reduced energy barrier for Ag over Cu-mediated decarboxylation. Electron-rich ligands, such as nitrogen donors, were found to enhance the rate of the decarboxylation process. Finally, the decarboxylation step was found to proceed *via* a concerted mechanism with only one transition state (Figure 1). Likewise, based on DFT calculations, Sue and Lin reported that the *ortho*-substituent on the aryl ring produces an intrinsically steric effect which destabilizes the starting carboxylate complex and reduces the overall barrier of the decarboxylation process.^{3h,13d}

Scheme 1. Mechanistic pathways for decarboxylative metalation using Cu, Ag and Pd

In contrast, Pd-catalyzed systems allow for low-temperature (70–80 °C) decarboxylation reactions but possess limited reactivity, being restricted to mainly bis-*ortho*-substituted electron-rich substituents.^{7a,13b,15} Recently, Kozłowski *et al.* reported a Pd-catalyzed protodecarboxylation using [Pd(TFA)₂] (TFA = trifluoroacetic acid) catalyst.^{12b} Subsequent advanced experimental and theoretical studies of the palladium-mediated protodecarboxylation of 2,6-dimethoxybenzoic acid revealed the protodepalladation as the rate-limited step that justified the need of 10 equivalents of TFA for the process to occur. Furthermore, both decarboxylation and protodepalladation were found to proceed *via* a stepwise mechanism involving an electrophilic aromatic substitution (Scheme 1). Further theoretical studies investigated the effect of Pd salts, DMSO and TFA in the carboxyl exchange and the decarboxylation processes.^{12c}

Based on these studies, we reasoned that with the same electronic configuration as silver, gold could represent an appealing mediator to extrude CO₂ from aromatic carboxylic acids. Furthermore, if electron-rich ligands at the metal center enhance the decarboxylation process with other coinage metals, *N*-heterocyclic carbenes (NHC) would represent the ideal candidates as supporting ligands. In this context, we reported, in 2011, the first decarboxylation of *ortho*-substituted benzoic acids mediated by Brønsted base [Au(IPr)(OH)] (IPr = 1,3-bis(2,6-diisopropyl)phenyl-imidazol-2-ylidene) (pK_a (DMSO) = 30.3).^{9c} A catalytic version of the protodecarboxylation reaction was developed last year using low catalyst loadings of [Au(SIPr)(O₂CAd)] **1a** (SIPr = 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolin-2-ylidene) (Ad = 1-adamantyl).^{8b} This methodology was successfully applied to not only *ortho*-substituted carboxylic acids but also *meta*- and *para*-substituted

[a] S. Dupuy, L. Crawford, Prof. M. Bühl, Prof. Dr. S. P. Nolan
EastCHEM, School of Chemistry
University of St Andrews
North Haugh, St Andrews, Fife, KY16 9ST (UK)
E-mail: snolan@st-andrews.ac.uk

Supporting information for this article is given via a link at the end of the document.

compounds, making the (NHC)gold system competitive with the copper and silver systems. A similar catalytic cycle was proposed and supported by experimental studies leading to the isolation of the proposed intermediates formed *in situ* (gold benzoate **4** and aryl gold complex **5**) (Scheme 2).

Scheme 2. Proposed mechanism for gold(I)-catalyzed protodecarboxylation

With the growing number of mechanistic studies reported on decarboxylation reactions, the unique features that each metal possesses have begun to become clearer. To our knowledge, no in-depth mechanistic investigation has yet seen light for the gold(I)-catalyzed protodecarboxylation reaction. As previously reported, a considerable difference in reactivity was observed between benzoic acids bearing electron-donating and electron-deficient substituents. To elucidate the origin of this effect, kinetic studies and density functional theory calculations were performed on two different benzoic acids on the basis of their reactivity profile in the gold(I)-catalyzed protodecarboxylation.

The determination of thermodynamic activation parameters as well as calculations on the transition state structures would permit access to a more detailed mechanistic picture that could explain how the electronic properties of benzoic acid substituents affect the rate of each catalytic step and provide insights into the role of gold in the overall reaction.

Results and Discussion

In order to gain insights into each individual step, our attention focused on initial stoichiometric reactions. Our first target substrate, 2,6-dimethoxybenzoic acid (**2a**), was selected primarily on the basis of its favourable reactivity profile and secondly due to its recent use in Kozłowski's mechanistic studies on the palladium promoted protodecarboxylation, which would facilitate comparison with this system.^{12b}

Evidence of equilibrium for the carboxyl exchange: Step 1

In order to gain insights into each individual step, our attention focused on initial stoichiometric reactions. Our first target substrate, 2,6-dimethoxybenzoic acid (**2a**), was selected

primarily on the basis of its favourable reactivity profile and secondly due to its recent use in Kozłowski's mechanistic studies on the palladium promoted protodecarboxylation, which would facilitate comparison with this system.^{12b}

The reaction reached equilibrium within minutes of mixing and resulted in a mixture of **4a/1a** in a 1/1 ratio. Prolonged reaction time did not displace the equilibrium further; equilibrium had indeed been reached after this time. We reasoned that the molecule of adamantane-1-carboxylic acid (**3**) ($pK_a = 4.86$)¹⁶ generated during the course of reaction was most likely responsible for the cleavage of the newly formed gold-carboxylate bond and did make the process reversible. A similar equilibrium had been observed by Sheppard when studying the carboxyl displacement from $[\text{Cu}(\text{OAc})]$ to $[\text{Cu}(\text{O}_2\text{CR})]$ ($\text{R} = \text{C}_6\text{F}_5$, $\alpha\text{-NO}_2\text{-C}_6\text{H}_4$, CClF_2 and CCF_3).¹⁰ In contrast, the $\text{RC}(\text{O})\text{O-Hg}$ bond was found to be resistant to AcOH .¹⁷ Interestingly, repeating the reaction using 2-nitrobenzoic acid (**2b**) with **1a** led to 90% conversion to the corresponding gold(I) 2-nitrobenzoate intermediate (**4b**). Ultimately, these data suggested that the displacement of the equilibrium is likely pK_a -dependent with respect to the benzoic acid employed. To probe the existence of such a correlation, a series of *ortho*-substituted benzoic acids of varying acidities was next examined.¹⁶ Reactions were conducted in $\text{THF-}d_8$, monitored by ^1H NMR, and the complex distribution was analyzed after a few minutes after mixing. The results clearly show a linear correlation between the concentration of **4** to the pK_a of **2** (Figure 2). These results underline the fact that the more acidic benzoic acids lead to a higher propensity of the newly formed O-Au bond to proceed to protodeauration in the presence of acids.¹⁸

Figure 1. Influence of the pK_a of **2** on the reversibility of the carboxyl exchange reaction.¹⁶

Unsurprisingly, adding larger quantities of 2,6-dimethoxybenzoic acid **2a** displaced the equilibrium toward the formation of the gold benzoate **4a**. In this regard, K for the equilibrium depicted in eq. 2 was determined. **2a** and $[\text{Au}(\text{SIPr})(\text{O}_2\text{CAd})]$ **1a** were mixed in THF- d_8 at room temperature and the composition of the gold complex was analyzed by ^1H NMR spectroscopy. The equilibrium constant was determined to be 1.16 ± 0.3 (Figure 3). This value indicates that, during the catalytic reaction, where **2a** is present in a 50 fold excess over gold, the gold carboxylate intermediate **4a** will be proportionally present in ca. 60 fold excess over **1a**. Therefore, this should have a negligible effect on the overall catalytic process.

Figure 2. a) Effect of added **2a** on the carboxyl exchange reaction conversion. b) Determination of the equilibrium constant.

Gold-Induced Decarboxylation: Step 2

Having established the electronic influence of the benzoic acids on the carboxyl exchange, attention next focused on the influence in the decarboxylation process.

A series of kinetic experiments in combination with DFT calculations were performed for the decarboxylation step in order to rationalize the reactivity difference obtained using gold compared to other metals, as well as allow for a better understanding of the results of the present reaction scope.

At the outset, this exploration was continued with model substrates gold 2,6-dimethoxybenzoate **4a** and gold 2-nitrobenzoate **4b**, representing the most and the least rapid to undergo decarboxylation, respectively. Indeed, since our first study on the synthesis of aryl gold(I) complexes via decarboxylation, it was observed that, while being the most facile substrate in copper/silver¹⁹ and even phosphine Au-mediated^{9d} decarboxylation reactions, 2-nitrobenzoic acid **2b** represented the most challenging substrate from which to extrude CO_2 using our (NHC)-gold systems. This peculiar lack of reactivity was an additional motivation for the current study and the reason for this substrate to be initially selected as a comparison to benchmark model **2a** in our kinetic studies.

Figure 4 illustrates kinetic profiles for the catalytic decarboxylation of three model substrates. Under these reaction conditions, the plot of the formation of 1,3-dimethoxybenzene **6a** versus time clearly shows no effect of the concentration of 2,6-dimethoxybenzoic acid **2a** on the rate of the reaction and establishes a zero-order behavior for this component. The protodecarboxylation of **2a** proceeded smoothly and formed 1,3-dimethoxybenzene **6a** in quantitative yield after 9 h. The reaction of **2b** exhibited, in comparison, a very slow decarboxylation rate and stalled after ca 20 h with a product yield of 55%.

Figure 3. Reaction profile for the protodecarboxylation of **2** with **1a** in DMAc (1.5 mL). (♦) Using **2a** (0.5 mmol) and **1b** (2 mol%) at 120 °C. (□) Using 2,4-dichlorobenzoic acid **2i** and **1a** (5 mol%) at 140 °C. (Δ) Using **2b** and **1b** (5 mol%) at 140 °C.

A series of experiments were conducted to probe the origin of this lack of reactivity with **2b** (Table 1).

Upon further heating, no additional product formed. Increasing the catalyst loading did not facilitate the decarboxylation process, even using stoichiometric amounts (Table 1, entries 1-3). Adding catalyst to the reaction mixture did not convert more substrate (Table 1, entry 4). Suspecting that finally the product itself, and in particular its nitro moiety, was poisoning our catalyst, various amounts of nitrobenzene **6b** were introduced at the start of the reaction (Table 1, entries 5-6). Adding 0.5 equivalents of nitrobenzene **6b** led to a dramatic

drop in yield (Table 1, entry 5). The reaction was almost fully inhibited with the addition of a stoichiometric amount of product (Table 1, entry 6).

Table 1. Investigation of the protodecarboxylation of 2-nitrobenzoic acid (**2a**) with **1a**^[a]

Entry	1a (mol%)	6b (equiv.)	Yield ^[b]
1	5	-	53
2	10	-	61
3	100	-	55
4	5 + 5	-	54
5	5	0.5	26
6	5	1	8

[a] Reactions were conducted on a 0.5 mmol scale. [b] GC yields using *n*-tetradecane as internal standard.

However, addition of 0.5 mmol of 2,6-dimethoxybenzoic acid **2a** to a reaction having appeared to have stalled, followed by heating to 120 °C for 20 h, produced 1,3-dimethoxybenzene **6a** in quantitative GC yield (eq. 4). This result confirmed that the gold catalyst was still active.

From these series of experiments, two possible explanations can be proposed to account for the observed stagnation of the decarboxylation of 2-nitrobenzoic acid **2b**: (1) coordination of the gold center to the nitro moiety to form a stable complex appears reasonable and might become competitive with the carboxyl exchange process with the increased amount of nitrobenzene **6b** in solution. This can be related to the Su and Lin studies,^{11f} where the formation of a stable gold nitro complex would most likely increase the activation barrier for the decarboxylation process. (2) The overall process may be reversible *i.e.* C-H activation of the nitrobenzene by gold followed by a CO₂ insertion into the Csp²-Au bond. With an experimentally determined p*K*_a(DMSO) value of 36.2,²⁰ the C-H auration of nitrobenzene **6b** seems unlikely.

As an alternative to **2b**, 2,4-dichlorobenzoic acid (**2c**) was chosen as the acid substrate. The formation of gold 2,4-dichlorobenzoate (**4c**) from **1a** and **2c** was found to be irreversible. This result highlights the importance of making correlations between acidic hydrogen bonds of structurally related benzoic acids (p*K*_a(**2c**) = 2.44).^{16,21} Interestingly, the initial rate of the formation of the 1,3-dichlorobenzene product **6c** exhibited a zero order decay with an almost identical reaction profile as **2a** until reaching 80% yield of product and followed a first-order behaviour until the end of the protodecarboxylation reaction.

The progress of the decarboxylation reaction, from gold benzoate **4a** and **4c** to yield arylgold complexes **5a** and **5c**, respectively, can be monitored by ¹H NMR spectroscopy in toluene-*d*₈ (Scheme 2).²²

Scheme 3. Decarboxylation from gold benzoate **4** to arylgold **5**

Decarboxylation of **4a** was extremely rapid at 120 °C and furnished 2,6-dimethoxyphenylgold **5a** in 90% yield after only 30 min (Figure 5). In comparison, the process was much slower for **4c** and required 11 h to reach the same yield at the same temperature. The rate of decarboxylation for **4a** is almost 35-fold faster compared to **4c** (*k*_{4a} = 1.4 × 10⁻³ s⁻¹, *t*_{1/2} = 8 min vs *k*_{4c} = 4.5 × 10⁻⁵ s⁻¹, *t*_{1/2} = 257 min) (Figure 5). Noteworthy, both reactions proceeded cleanly and without involvement of any observable intermediates or side-products. The corresponding kinetic plots confirm that, in line with copper and palladium, the decarboxylation with gold is a first-order process under stoichiometric conditions.^{11d,12b}

Figure 4. Kinetic plots of the decarboxylation of gold benzoate complexes **4a** and **4c**.

The first-order rate constants were determined for each substrate at different temperatures. The kinetic data were collected in duplicate within 20 °C temperature range (see ESI).

The increase in temperature significantly accelerated the extrusion of CO₂ though this acceleration was more significant, within the 20 °C range, for the decarboxylation of **4a** compared to that of **4c** (5.5 vs 3.8 times faster) (see ESI). These data confirm that the rate of decarboxylation is not only dependent on temperature but that other parameters, such as electronic factors, play a crucial role, and notably the presence of a σ-donor substituent in the *ortho*-position promotes the release of CO₂ more efficiently than an electron-withdrawing substituent. It is worth mentioning that the rate constant for the decarboxylation of palladium 2,6-dimethoxybenzoate was found to be almost 35 times higher at 110 °C (*k*_{Pd} = 2.2 × 10⁻² s⁻¹, *k*_{4a} =

$6.6 \times 10^{-4} \text{ s}^{-1}$) (see ESI).^{12b} At all temperatures, the consumption of gold carboxylate **4** was found to occur via a first-order process. Further data on the composition of the highest energy transition state was obtained by carrying out an Eyring analysis of the observed rate constants at different temperatures (Figure 6).

Figure 5. Eyring analysis of the measured rate constants of gold benzoate **4** to arylgold **5**.

As expected, the extrusion of CO_2 from **4a** gave activation parameter values that are higher compared to the structurally related palladium complex ($\Delta G_{\text{Pd}}^\ddagger = 16.8 \text{ kcal/mol}$) and thus justifies the 40°C difference in operating temperature observed experimentally between the two systems.

Based on literature precedents, two possible reaction pathways were envisioned and are illustrated in Scheme 3.^{6b,12b,12d} By analogy to copper and silver, the first pathway (A) would proceed via intermediate **7** in which the gold center is positioned perpendicularly to the aryl ring and starts interacting with the *ipso* carbon of the aryl ring. Presumably, this intermediate would be stabilized by an *ortho*-donating substituent that would encourage loss of CO_2 by increasing electron density at the *ipso* carbon. Next, the concerted cleavage of the CO_2 bond and formation of the $\text{Csp}^2\text{-Au}$ bond would furnish **5** via a single transition state (TS) wherein the gold center is bound to the carbon bearing the carboxylate moiety.

Alternatively and in line with palladium, the second pathway (B) would involve an intermolecular electrophilic aromatic substitution that generates a Wheland-type intermediate **8** which would rearomatize with consecutive loss of CO_2 and formation of **5**.

Scheme 4. Proposed mechanistic pathways for the decarboxylation process

To assess the viability of these pathways, hybrid functional level DFT calculations were conducted (dispersion-corrected²³ PBE0-D3 level with toluene and DMAc as modelled via a polarisable continuum model, PCM, see ESI for full methodology). Additionally, several methoxy and chloro-substituted benzoic acids were examined for the decarboxylation in order to rationalize the steric and electronic influence on the free energy ($\Delta G^\ddagger$) of activation for this process (Table 2).

The calculated values for the thermodynamic activation parameters are in good agreement with our experimental findings. The activation energies for the decarboxylation of gold 2,6-dimethoxybenzoate **4a** and 2,4-dichlorobenzoate **4c** were found to differ by 2.3 kcal/mol at 25°C (Table 2, entries 1 and 6). The enthalpic difference between transition states was found to be similar with a value of 2.1 kcal/mol (see ESI).

Table 2. DFT computed free energies^[a] (kcal/mol) and geometric parameters relevant to decarboxylation.

Entry	R	$\Delta G^\ddagger(\text{TS4-5})$ (toluene)	$\Delta G^\ddagger(\text{TS4-5})$ (DMAc)	Distance ($\text{\AA}$) $\text{C}_{(\text{R})} - \text{C}_{(\text{COO})}$
1	2,6-(OMe) ₂ (4a)	21.8	22.5	1.77
2	2,5-(OMe) ₂ (4d)	23.3	23.5	1.77
3	2-OMe (4e)	20.9	20.8	1.77
4	2,6-Cl ₂ (4f)	26.8	27.8	1.82
5	2,5-Cl ₂ (4g)	24.8	24.5	1.78
6	2,4-Cl ₂ (4c)	23.6	23.2	1.73

[a] PBE0-D3/ECP2 – PCM // PBE0/ECP1 (see ESI for details)

Interestingly, 2-methoxybenzoic acid was found to offer a decarboxylation step that is more accessible than that of **4a** (Table 2, entry 2). This is apparently due to the lack of steric imposition preventing a “twist” of CO_2 at the associated transition

state (see ESI). By changing to a 2,5 substitution pattern, decoordinating CO₂ may rotate by a greater degree earlier in the reaction coordinate as a result of the decreased steric bulk at the *ortho* position. However, the activation energy differs primarily between methoxy and chloro substituents - the nature of the substituents ultimately appears to be of greater importance than steric bulk.

This difference in reactivity manifests itself due to the charge pattern present in the reactant complexes. The more electronegative *ortho* oxygens in **4a** serve to increase the negativity of the *ipso* carbon, activating it towards decarboxylation wherein upon forming a bond with gold it becomes more negatively charged. Further details and computed NPA charges are given in the ESI. Upon changing from a 2,6- to 2,5-substitution pattern, the energy barrier is predicted to increase with methoxy substituents (entries 1 and 2) but decrease with chloro-substituents (entries 4 and 5). Notably, gold 2,4-dichlorobenzoate complex **4c** is predicted to be considerably more active than the 2,6-substituted congener **4f** due to a decreased steric clash, but with retention of the activating electronic effects *via* the *ortho* moiety (entries 4 and 6).²⁴

As expected, the nature of the substituent affects the decarboxylation process significantly more when located in *ortho*- rather than in *meta*- or *para*-positions. Indeed, a 5 kcal/mol free energy difference in transition states was found between 2,6-dichloro and 2,6-dimethoxy derivatives (entries 1 and 4) which is reduced to 1.5 kcal/mol with the 2,5- derivatives (entries 2 and 5). Finally, the solvent effects are negligible in the decarboxylation and similar energy barriers were found using toluene and DMAc (≤ 1 kcal/mol differences). All Csp²-C_{COOH} bonds are within a 0.1 Å distance span and are shorter than the reported distances with copper (1.89 Å in the decarboxylation of copper 2-fluorobenzoate). This may contribute towards the reactivity difference within Cu and Au-mediated decarboxylation.

Figure 6. Left: PBE0/ECP1 optimized decarboxylation TS4a-5a with key distances highlighted (Å). Right: PBE0/ECP1 decarboxylation TS4c-5c with key distances highlighted (Å).

Our calculations predicted that the mechanism of the gold decarboxylation proceeds through a single concerted step involving one early transition state, **TS4-5**, similarly to copper and silver (Figure 7). Interestingly, the calculated transition state shows both gold and carboxylate group interacting with the fleeting aryl anion, characteristic of a process concerning loss of

a C – C bond and acquisition of an organogold bond. At the TS, the Au-O bond from gold benzoate **4** is effectively fully cleaved and no strong interaction between gold and the CO₂ molecule was found unlike for copper and silver systems (Au – O distances of > 2.7 Å). As such, an electrophilic aromatic substitution type mechanism, in analogy with palladium (though no Wheland-type intermediate could be located (see ESI)), seems reasonable to access this transition state. Furthermore, a mechanism exhibiting characteristics from routes typical to both Cu and Pd-mediated decarboxylation accounts for the requirement of *ortho*-substituents in addition to the crucial acceleration of the decarboxylation process with σ -donating *ortho*-substituents such as MeO and NMe₂.

Protodeauration: Step 3

The protodeauration is usually considered a routine step in gold homogenous catalysis.²⁵ It allows release of the desired final product and concomitantly regenerates the active gold catalyst. Being considered a fast process, it has often been neglected in mechanistic studies of gold-catalyzed reactions, as it is unlikely to be the turnover-limiting step.²⁶ Blum and coworkers have studied the relative kinetic basicity of organogold complexes toward protons and found that higher reactivity was observed for the more electron-rich aryl groups and that electron-rich ligands such as NHCs further enhanced the rate of protodemetalation.¹⁸ In our earlier report, we showed that the aryl gold complexes **5**, obtained after decarboxylation, are completely stable to water. It is thus reasonable to believe that, in our gold-catalyzed protodecarboxylation reaction, the proton source arises either from the benzoic acid substrate **2** or from the adamantane-1-carboxylic acid **3** generated *in situ* during the course of the reaction.

In this regard, we next examined the protodeauration of both 2,6-dimethoxyphenylgold **5a** and 2,4-dichlorophenylgold **5c** with one equivalent of carboxylic acid at room temperature in toluene-*d*₈. Initial attempts to follow the progress of these protodeauration reactions were thwarted by solubility issues that led to inconsistencies and reproducibility issues under these conditions. Subtle changes from the original conditions were warranted to address these concerns. Therefore, adamantane-1-carboxylic acid **3** ($pK_a = 4.8$) was replaced by AcOH ($pK_a = 4.9$)¹⁶ and the experiments were conducted in CDCl₃ as reaction solvent. The reactivity results of the protodeauration of **5a** and **5c** under these conditions are shown in Table 3. The following set of experiments directly supported the dependence of the protodeauration rate on the basicity of phenylgold species **5** and its important effect on the overall protodecarboxylation reaction. The addition of one equivalent of 2,6-dimethoxybenzoic acid **2a** to 2,6-dimethoxyphenylgold **5a** achieved the cleavage of the Csp²-Au bond in 2 h at room temperature (Table 3, entry 1). In contrast, a similar treatment of **5a** with one equivalent of AcOH, resulted in the rapid formation of 1,3-dimethoxybenzene **6a** in 50% conversion within 1 h but stalled from that point forward (Table 3, entry 2). The polarity of the solvent was found to slightly affect the rate of the hydrolysis reaction. The lack of reactivity persisted when using AcOH as proton source (Table 3, entries 2-3).

Interestingly, the protodeauration of **5c** proved much more challenging, regardless of the acid source, with only traces of 1,3-dichlorobenzene **6c** detected by ^1H NMR after hours (Table 3, entries 4-5). Increasing the temperature to 50 °C greatly accelerated the protodeauration of **5c** using **2c** but was

Table 3. Protodeauration of arylgold complexes **5a** and **5c** with stoichiometric amounts of AcOH or benzoic acid **2**^[a]

$\text{R}-\text{C}_6\text{H}_4-\text{Au}(\text{SiPr}) \xrightarrow[\text{T}]{\text{2 or AcOH}} \text{R}-\text{C}_6\text{H}_4-\text{H}$					
$\text{R} = 2,6\text{-(OMe)}_2$ 5a 6a $\text{R} = 2,4\text{-Cl}_2$ 5c 6c					
Entry	5	Acid (R-CO ₂ H) (pK _a)	t (h)	Solvent	6 (%) ^[a]
1	5a	2,6-(OMe) ₂ -C ₆ H ₃ (3.44) (2a)	2	CDCl ₃	>99
2	5a	AcOH (4.8)	0.6, 5	CDCl ₃	46, 67
3	5a	AcOH	0.6	toluene- <i>d</i> ₆	40
4	5c	AcOH	5	toluene- <i>d</i> ₆	-
5	5c	2,4-(Cl) ₂ -C ₆ H ₃ (2.44) (2c)	5	CDCl ₃	<10
6 ^[b]	5c	2c	3.5	CDCl ₃	41
7 ^[b]	5c	AcOH	3.5	CDCl ₃	-
8 ^[c]	5c	AdCO ₂ H	10	toluene- <i>d</i> ₆	60

[a] ^1H NMR conversion relative to consumption of **5**. [b] at 50 °C. [c] at 120 °C.

completely ineffective using AcOH as a proton source (Table 3, entries 6-7). This last result was particularly baffling considering that, under turnover conditions, the major acid source left, as **2** is being consumed, is adamantane-1-carboxylic acid **3**. Fascinated with these findings, we evaluated the reaction of **5c** with one equivalent of adamantane-1-carboxylic acid **3** at 120 °C. To our dismay, the protodeauration was found to be slower than the decarboxylation step with only 60% conversion, to the corresponding 1,3-dichlorobenzene **6c** being detected after 10 h (Table 2, entry 8). This plot twist pointed out a facet of the mechanism that was not envisaged at all. Since the beginning of our decarboxylation studies, the decarboxylation step was believed to be the rate-determining step and the culprit for the modest turnover observed during the catalytic process. To further support these findings, DFT calculations were also performed on the protodeauration step. AcOH was also used as a surrogate for **3** to simplify the model system. Energy profiles for the protodeauration of **5a** and **5c** using benzoic acid **2** or AcOH as proton source are shown in Figure 8.

Figure 7. DFT (PBE0-D3/ECP2/SDD PCM) computed free energy pathway for the protodeauration process using either benzoic acid **2** or AcOH as proton source. Energies given for species **5a-6a** and **5c-6c** relative to reactants **4a/4c** (in toluene).

Computations revealed that, similarly to the decarboxylation step, the protodeauration proceeds through a concerted mechanism, here with one 6-membered ring transition state, as illustrated in Figure 9.

Protodeauration can formally be characterized as a concerted proton transfer from the carboxylic acid moiety with combined Au – O bond formation (Figure 7). Concomitant cleavage of the Au – C_(aryl) bond occurs shortly afterwards, regenerating gold benzoate complex **4**, if the cleaving acid is benzoic acid **2**. Compared to the decarboxylation, the difference in reactivity between electronically and sterically distinct arylgold complexes is much more severe for the protodeauration step and is highly favoured with electron-rich aromatics that can activate the aurated carbon while being disfavoured by *meta* electron donating groups or large substituents at the *para* position (see ESI for full energetics). The former effect is exemplified by the activation energy necessary to overcome **TS(5+2)-6** for arylgold complexes **5a** and **5c**. Indeed, 2,6-dimethoxyphenylgold **5a** has a computed barrier of only 13.9 kcal/mol (ΔG), using **2a** as a proton source (ΔG relative to a **5a-2a** complex, Figure 8), which should be readily achievable at room temperature, in line with experimental findings. Comparatively, **5c** has a far more challenging barrier of 19.7 kcal/mol when using **2c** as an acid source (relative to **5a + 2a**, Figure 8), accounting for the need to apply heat for the reaction to proceed. Whilst these DFT values suggest that the rate-limiting step should remain decarboxylation, an activated acid is indeed needed for a facile and rapid protodeauration.

Figure 8. Left: Protodeauration **TS(5c+2c)-6c** with key distances highlighted (Å). Right: Protodeauration **TS(5c+AcOH)-6c** with key distances highlighted (Å).

With these first results in hand, the activation energies for the protodeauration of **5**, using AcOH as a surrogate to AdCO₂H **3**, were calculated (Figure 8). The differences in free energy barriers for the alternate acid sources are presented in Table 4.

In accordance with the experimental findings, the calculations show that this step becomes rate-limiting, in the case of 2,4-dichlorophenylgold **5c**, with a computed barrier of **25.9 kcal/mol** ($\Delta G^\ddagger$ in toluene) (Table 4, entry 2).

Table 4. DFT computed energies^[a] (kcal/mol) and geometric parameters relevant to decarboxylation.

$$\text{R}-\text{C}_6\text{H}_4-\text{Au}(\text{SIPr}) \xrightarrow[\text{T}]{\text{2 or AcOH}} \text{R}-\text{C}_6\text{H}_4-\text{H}$$

R = 2,6-(OMe)₂ **5a**

[a] PBE0-D3/ECP2 – PCM // PBE0/ECP1

This is 2.3 kcal/mol more challenging than the decarboxylation of the gold benzoate relative **4c** (see Table 2) and thus in the absence of suitable activated proton donors, the protodeauration becomes turnover-limiting. The protodeauration of 2,6-dimethoxyphenylgold **5a** by AcOH is less challenging at **19.9 kcal/mol** (Table 4, entry 1) and therefore decarboxylation still determines the overall reaction rate. From these computations we can conclude that protodeauration is sensitive to the aryl-gold substitution pattern and the pK_a of the acid used to cleave the Csp²-Au bond.

In view of these results, a clearer mechanistic picture has emerged that would most likely features, in regard to the benzoic acid employed, a shift of turnover-limiting step from the decarboxylation to the protodeauration process at the end of the catalytic cycle. Ultimately, this would transpire as a sudden and significant drop, stagnation or even inhibition in reactivity. This decrease in rate is predominantly correlated to the basicity of the arylgold intermediate. In view of the reactivity trend obtained in the carboxyl displacement, a similar correlation could be surmised for the hydrolysis final step with the following order of reactivity for the cleavage of the Csp²-Au bond:

In particular, the reactivity profile of the protodecarboxylation of the 2,4-dichlorobenzoic acid **2c** (Figure 1) clearly supports this hypothesis warranted by the first-order behaviour observed after 80% yield reached in 8 h and most likely accounts for the additional **14 h** required to protodecarboxylate the **20%** of acid **2c** left.

Finally, this provides an answer to the question of why electron-donating substituted benzoic acids prevail in the gold protodecarboxylation reaction. Indeed, the reaction rate of benzoic acids possessing a $pK_a \geq 4.8$ is only limited by the decarboxylation step and the final protonolysis step kinetically and thermodynamically drives the overall process. In contrast, electron-deficient substituted benzoic acids face two significant hurdles *i.e.* the decarboxylation step which is the rate-determining step, and particularly difficult with electron-poor substrates, until a 75-80% conversion is reached. Subsequently, the rate limiting-step can shift to becoming the protodeauration step depending on the basicity of the proton-donating acid. In all cases, the overall protodecarboxylation is much more energetically demanding with electron poor benzoic acids as supported by the kinetic data.

The results, extrapolated from this combination of kinetic and theoretical studies, allow us to formulate a refined mechanistic scenario illustrated in Scheme 5.

Initially, rapid carboxyl displacement occurs to form the active gold benzoate species, **4**, with loss of AdCO₂H. Upon heating, CO₂ is extruded from the gold benzoate **4** and aryl gold intermediate **5** is generated. At this stage, this species is poised for protodeauration that can proceed down two different pathways that involve either a cleavage of the Csp²-Au bond with AdCO₂H **3** or ArCO₂H **2**. In the first case, the pre-catalyst is regenerated with concomitant release of arene **6** (blue box). In the second case, the cleavage of the Csp²-Au would lead to the formation of arene **6** and would provide direct access to active species gold benzoate **4** (red box). The outcome would be linked to the pK_a of the benzoic acid employed and the concentration of benzoic acid material remaining in the reaction mixture. Our kinetic and computational studies have clearly established that the decarboxylation is predominantly the turnover-limiting step in the reaction but that toward the end of the reaction, the protodeauration can become competitive and rate limiting, notably with electron-deficient systems. This divergence hinges on the basicity of the arylgold intermediate and may account for the reaction not reaching completion.

Scheme 5. Refined mechanistic scenario for the Au(I)-catalyzed protodecarboxylation reaction.

Conclusion

This study of the mechanisms of the gold(I)-catalyzed protodecarboxylation reaction has enabled a clearer understanding of the fundamental factors controlling the overall reactivity. To our knowledge, this is the first in-depth investigation of protodecarboxylation with gold. A combination of stoichiometric experiments, kinetic and computational studies has answered several of our initial interrogations. In the case of gold, the carboxylate exchange step is an equilibrium that is pK_a -dependent. However, under catalytic conditions the exchange should not influence the reactivity. The formation of nitrobenzene is detrimental in (NHC)Au-mediated decarboxylation reactions as the nitro moiety likely coordinates to the gold in a side-reaction to form a stable complex. Kinetic studies allowed determination of thermodynamic activation parameters for both decarboxylation and protodeauration steps. These values are within the range of previously reported Late-Transition Metal decarboxylation reactions. The calculated barriers for the decarboxylation are in good quantitative agreement with the observed experimental values and confirmed that *ortho*-substituents that electronically enrich the aromatic ring reduce the activation energy barrier for the decarboxylation step significantly. These results suggest that, in contrast to silver and copper systems, the decarboxylation is governed by short-range mesomeric effects transmitted *via* the π -system. In addition, the calculated transition state gives both carboxylate and [(SIPr)Au]⁺ bound to the lone pair of the *ipso* carbon of the aryl and may result of an electrophilic aromatic substitution to gold type mechanism. Evidently, this outcome gives reasons for the more facile reactivity of electron-donating *ortho*-substituted benzoic acid with σ -donating effects. Unexpectedly, the protodeauration step is not trivial, as previously assumed. This portion of the cycle proceeds through a carboxylate-assisted proton transfer and is significantly influenced by the electronic properties (pK_a) of the substrates: electron-withdrawing groups dramatically slow the process whereas electron-donating groups like OMe increased the reaction rate substantially. Experimental and computational studies revealed that this process may emerge as a competitive rate-limiting step especially at low concentrations of benzoic acid.

These findings should be of general interest and could be used as a launching pad for the development of gold(I)-catalyzed decarboxylative coupling reactions where the protodeauration is the common side-reaction. We see here that the selection of an appropriate substrate in this specific transformation can promote one or the other of the two major reaction pathways enabled by gold catalysis.

Acknowledgements

We thank the EPSRC and the ERC (FUNCAT) for funding. SPN is a Royal Society Wolfson Merit Award holder. The University of St. Andrews School of Chemistry and EaStCHEM is also acknowledged and thanked for support and access to computing resources maintained by Herbert Früchtl.

Keywords: gold • decarboxylation • mechanism • NHC • protodeauration

- [1] Diederich, F.; Stang, P. J. *Metal-catalyzed Cross-coupling Reactions*; Wiley, 1998.
- [2] (a) Rodríguez, N.; Goossen, L. J. *Chem. Soc. Rev.* **2011**, *40*, 5030; (b) Baudoin, O. *Angew. Chem. Int. Ed.* **2007**, *46*, 1373.
- [3] (a) Gooßen, L. J.; Rodríguez, N.; Melzer, B.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824; (b) Becht, J.-M. *Org. Lett.* **2008**, *10*, 3161; (c) Gooßen, L. J.; Lange, P. P.; Rodríguez, N.; Linder, C. *Chem. Eur. J.* **2010**, *16*, 3906; (d) Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 11250; (e) Goossen, L. J.; Melzer, B. *J. Org. Chem.* **2007**, *72*, 7473; (f) Bhadra, S.; Dzik, W. I.; Goossen, L. J. *J. Am. Chem. Soc.* **2012**, *134*, 9338; (g) Xiaogang, L. *Org. Lett.* **2010**, *12*, 4134; (h) Zhao, D.; Gao, C.; Su, X.; He, Y.; You, J.; Xue, Y. *Chem. Commun.* **2010**, *46*, 9049; (i) Sunwoo, L. *Org. Lett.* **2008**, *10*, 945; (j) Duan, Z.; Ranjit, S.; Zhang, P.; Liu, X. *Chem. Eur. J.* **2009**, *15*, 3666; (k) Goossen, L. J. *Chem. Eur. J.* **2009**, *15*, 9336; (l) Miyasaka, M.; Fukushima, A.; Satoh, T.; Hirano, K.; Miura, M. *Chem. Eur. J.* **2009**, *15*, 3674.
- [4] (a) Gooßen, L. J.; Thiel, W. R.; Rodríguez, N.; Linder, C.; Melzer, B. *Adv. Synth. Catal.* **2007**, *349*, 2241; (b) Shang, R.; Fu, Y.; Wang, Y.; Xu, Q.; Yu, H.-Z.; Liu, L. *Angew. Chem. Int. Ed.* **2009**, *48*, 9350; (c) Cahiez, G.; Moyeux, A.; Gager, O.; Poizat, M. *Adv. Synth. Catal.* **2013**, *355*, 790.
- [5] (a) Cornella, J.; Sanchez, C.; Banawa, D.; Larrosa, I. *Chem. Commun.* **2009**, 7176; (b) Lu, P.; Sanchez, C.; Cornella, J.; Larrosa, I. *Org. Lett.* **2009**, *11*, 5710; (c) Grainger, R.; Nikmal, A.; Cornella, J.; Larrosa, I. *Org. Biomol. Chem.* **2012**, *10*, 3172; (d) Gooßen, L. J.; Linder, C.; Rodríguez, N.; Lange, P. P.; Fromm, A. *Chem. Commun.* **2009**, 7173.
- [6] (a) Sun, Z.-M.; Zhao, P. *Angew. Chem. Int. Ed.* **2009**, *48*, 6726; (b) Sun, Z.-M.; Zhang, J.; Zhao, P. *Org. Lett.* **2010**, *12*, 992; (c) Mochida, S.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 5776.
- [7] (a) Dickstein, J. S.; Mulrooney, C. A.; O'Brien, E. M.; Morgan, B. J.; Kozlowski, M. C. *Org. Lett.* **2007**, *9*, 2441; (b) Cornella, J.; Lu, P.; Larrosa, I. *Org. Lett.* **2009**, *11*, 5506; (c) Myers, A. G. *Org. Lett.* **2004**, *6*, 433; (d) Forgione, P.; Brochu, M.-C.; St-Onge, M.; Thesen, K. H.; Bailey, M. D.; Bilodeau, F. *J. Am. Chem. Soc.* **2006**, *128*, 11350.
- [8] (a) Dupuy, S.; Lazreg, F.; Slawin, A. M. Z.; Cazin, C. S. J.; Nolan, S. P. *Chem. Commun.* **2011**, 47, 5455; (b) Dupuy, S.; Nolan, S. P. *Chem. Eur. J.* **2013**, *19*, 14034; (c) Cornella, J.; Rosillo-Lopez, M.; Larrosa, I. *Adv. Synth. Catal.* **2011**, *353*, 1359.
- [9] (a) Neely, J. M.; Rovis, T. *J. Am. Chem. Soc.* **2014**, *136*, 2735; (b) Tunge, J. A. *Org. Lett.* **2004**, *6*, 2603; (c) Dupuy, S.; Lazreg, F.; Slawin, A. M. Z.; Cazin, C. S. J.; Nolan, S. P. *Chem. Commun.* **2011**, 47, 5455; (d) Larrosa, I. *Chem. Sci.* **2010**.
- [10] Cairncross, A.; Roland, J. R.; Henderson, R. M.; Sheppard, W. A. *J. Am. Chem. Soc.* **1970**, *92*, 3187.
- [11] (a) Chodowska-Palicka, J.; Nilsson, M. *Acta Chem. Scand.* **1970**, *24*, 3353; (b) Chodowska-Palicka, J.; Nilsson, M. *Acta Chem. Scand.* **1971**, *25*, 3451; (c) Cohen, T.; Schambach, R. A. *J. Am. Chem. Soc.* **1970**, *92*, 3189; (d) Cohen, T.; Berninger, R. W.; Wood, J. T. *J. Org. Chem.* **1978**, *43*, 837; (e) Gooßen, L. J.; Rodríguez, N.; Linder, C.; Lange, P. P.;

- Fromm, A. *ChemCatChem* **2010**, *2*, 430; (f) Xue, L.; Su, W.; Lin, Z. *Dalton Trans.* **2011**, *40*, 11926.
- [12] (a) Xue, L.; Su, W.; Lin, Z. *Dalton Trans.* **2010**, *39*, 9815; (b) Dickstein, J. S.; Curto, J. M.; Gutierrez, O.; Mulrooney, C. A.; Kozlowski, M. C. *J. Org. Chem.* **2013**, *78*, 4744; (c) Zhang, S.-L.; Fu, Y.; Shang, R.; Guo, Q.-X.; Liu, L. *J. Am. Chem. Soc.* **2009**, *132*, 638; (d) Tanaka, D.; Romeril, S. P.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 10323; (e) Svensson, F.; Mane, R. S.; Sävmarker, J.; Larhed, M.; Sköld, C. *Organometallics* **2013**, *32*, 490.
- [13] (a) Chuchev, K.; BelBruno, J. J. *J. Mol. Struct.* **2007**, *807*, 1; (b) Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 10323; (c) Xie, H.; Lin, F.; Lei, Q.; Fang, W. *Organometallics* **2013**, *32*, 6957; (d) Xue, L.; Su, W.; Lin, Z. *Dalton Transactions* **2011**.
- [14] Nilsson, M. *Acta Chem. Scand.* **1966**, *20*, 423.
- [15] Myers, A. G. *J. Am. Chem. Soc.* **2002**, *124*, 11250.
- [16] Calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02
- [17] Connett, J. E.; Davies, A. G.; Deacon, G. B.; Green, J. H. S. *J. Chem. Soc. C* **1966**, 106.
- [18] Roth, K. E.; Blum, S. A. *Organometallics* **2010**, *29*, 1712.
- [19] Indeed, computational investigations revealed that substituents that are capable of coordinating with the metal center such as NO₂ stabilizes the decarboxylation transition state and reduces the overall reaction barrier (see ref. x)
- [20] Shen, K.; Fu, Y.; Li, J.-N.; Liu, L.; Guo, Q.-X. *Tetrahedron* **2007**, *63*, 1568.
- [21] Wang, W.; Kumar, M.; Hammond, G. B.; Xu, B. *Org. Lett.* **2014**, *16*, 636.
- [22] During these first studies it was observed that maintaining the pressure in CO₂ was necessary to get accurate and reproducible results
- [23] Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. *J. Chem. Phys.* **2010**, *132*, 154104.
- [24] This is in accordance with our experimental observations as our initial attempts to stoichiometrically decarboxylate 2,6-dichlorobenzoic acid with [Au(IPr)(OH)] in reasonable time were unsuccessful (10% conversion after 5 h at 120 °C). Unpublished results.
- [25] (a) Kovács, G.; Ujaque, G.; Lledós, A. *J. Am. Chem. Soc.* **2008**, *130*, 853; (b) Wang, W.; Hammond, G. B.; Xu, B. *J. Am. Chem. Soc.* **2012**, *134*, 5697; (c) Zhu, Y.; Yu, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 8329.
- [26] Wang, Z. J.; Benitez, D.; Tkatchouk, E.; Goddard III, W. A.; Toste, F. D. *J. Am. Chem. Soc.* **2010**, *132*, 13064.

Entry for the Table of Contents (Please choose one layout)

Layout 1:

FULL PAPER

A mechanistic study of the gold-catalyzed protodecarboxylation reaction is described.

Stephanie Dupuy, Luke Crawford, Michael Bühl and Steven P. Nolan*

Page No. – Page No.

The Gold(I)-Catalyzed Protodecarboxylation Mechanism