Gold-Catalyzed Alkoxy-Carbonylation of Organohalides

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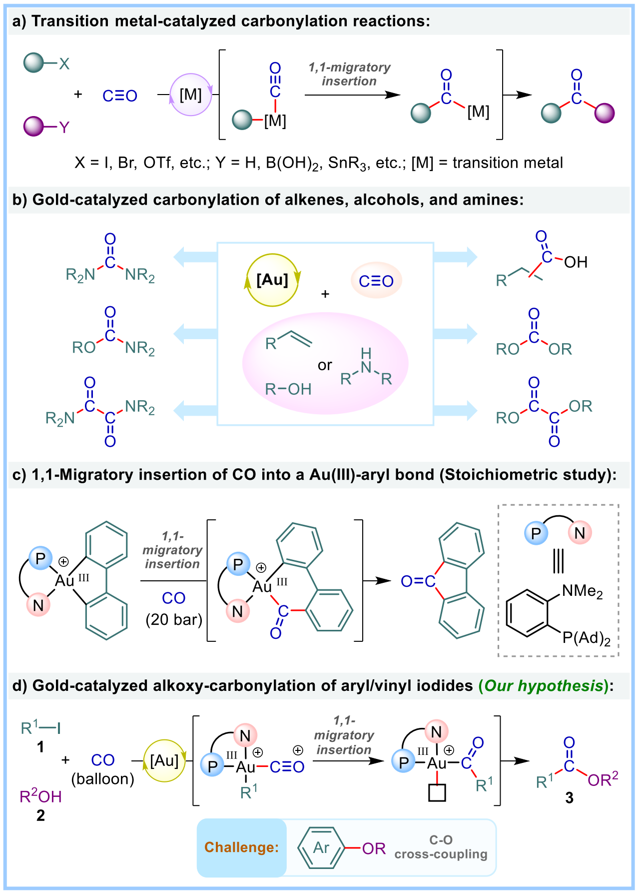
Abstract: Herein, for the first time, we disclose the gold-catalyzed alkoxy-carbonylation of organohalides utilizing ligand-enabled Au(I)/Au(III) redox catalysis. The present methodology is found to be general, efficient, employs mild reaction conditions and showcases a broad substrate scope even with structurally complex molecules. Density functional theory (DFT) calculations revealed unique mechanistic pathways, distinct from those of conventional transition metal-catalyzed carbonylation reactions.

Carbon monoxide (CO), one of the most readily available and cheapest C1 synthons, is utilized in the development of various transition metal-catalyzed carbonylation reactions of aryl halides, alkenes, alkynes, allylic derivatives, and so on (Scheme 1a).[1] These reactions afford a variety of carbonyl compounds such as acids, aldehydes, ketones, esters, amides, etc., serving as important intermediates in the total synthesis of natural products and pharmaceutically important molecules.[2] In principle, these reactions proceed through the 1,1-migratory insertion of CO into the transiently generated M–C bonds. Generally, these carbonylation reactions are known to be catalyzed by transition metals such as Pd, Ru, Rh, Ni, Ir, Fe, etc.

In recent years, gold redox catalysis has emerged as an important tool in organic synthesis.[3] The ability of gold to shuttle between two oxidation states [Au(I) and Au(III)] has placed it as a potential contender for transition metal catalysis. Numerous cross-coupling reactions have been reported, all of which involve oxidative addition, ligand exchange, and reductive elimination steps. However, the migratory insertion step remains less explored in gold chemistry.[4] A few stoichiometric studies have been carried out by Bochmann,[5] Bourissou,[6] and Tilset[7] to showcase the feasibility of migratory insertion of C–C multiple bonds into the Au(III)–H, Au(I)–Si/Au(III)–C, and Au(III)–O bonds. Recently, our group has demonstrated the viability of the migratory insertion of alkene into the Au(III)–Ar bond in a catalytic fashion by employing MeDalPhosAuCl as a catalyst.[8] Soon after, the Xie group showcased the feasibility of migratory insertion of benzyne into the Au(III)–C bond in a catalytic manner employing (2-furyl)$_3$PAuCl as a catalyst.[9]

As far as gold-catalyzed carbonylation reactions are concerned, there exist several reports in both homogeneous and heterogeneous catalytic systems where CO has been utilized as a C1 synthon (Scheme 1b).[10] In particular, the Souma group reported the synthesis of gold(I) carbonyl compounds, by treating Au_2O_3 with CO in concentrated H_2SO_4, and showed their catalytic activity for the carbonylation of alkenes.[11] Similarly, Yamanaka,[12] Angelici,[13] Friend,[14] Li,[15] Bertrand,[16] Echavarren,[17] Koper,[18] He,[19] and others[20] reported the gold-mediated carbonylation reaction of alcohols and amines. However, there exists no report on the carbonylation of organohalides which could be due to the lack of fundamental understanding of the migratory insertion of CO into the Au(III)–C bonds. In this regard, the pioneering studies conducted by the Bower/Russell group described the feasibility of migratory insertion of CO into the Au(III)–C bonds (Scheme 1d).[21] Inspired by this report[21] and the available literature on migratory insertion,[5,6,7,8,9] we hypothesized that the alkoxy-carbonylation of organohalides could be achieved in a catalytic fashion through a migratory insertion of CO into the Au(III)–C bond (Scheme 1d). Our endeavours in this direction led to the development of an efficient method for alkoxy-carbonylation of aryl/vinyl iodides and the details of reaction development, substrate scope, and mechanistic investigations are provided herein. Interestingly, under the established reaction conditions, C-O cross-coupling reaction[22] was not observed indicating the robustness of the developed method. To the best of our



Scheme 1. Transition metal-mediated carbonylation reactions: general overview and present work

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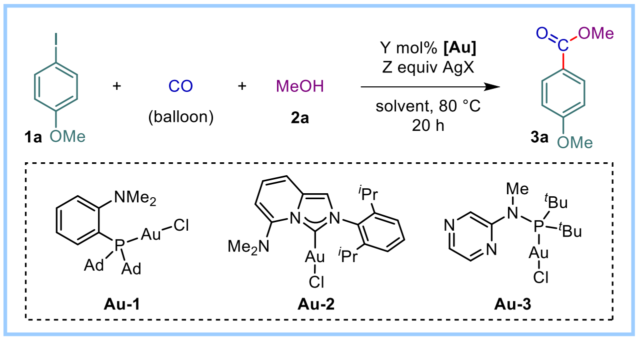
knowledge, this represents the first example of alkoxy-carbonylation of organohalides in gold chemistry.

Table 1. Optimization of reaction conditions[a]



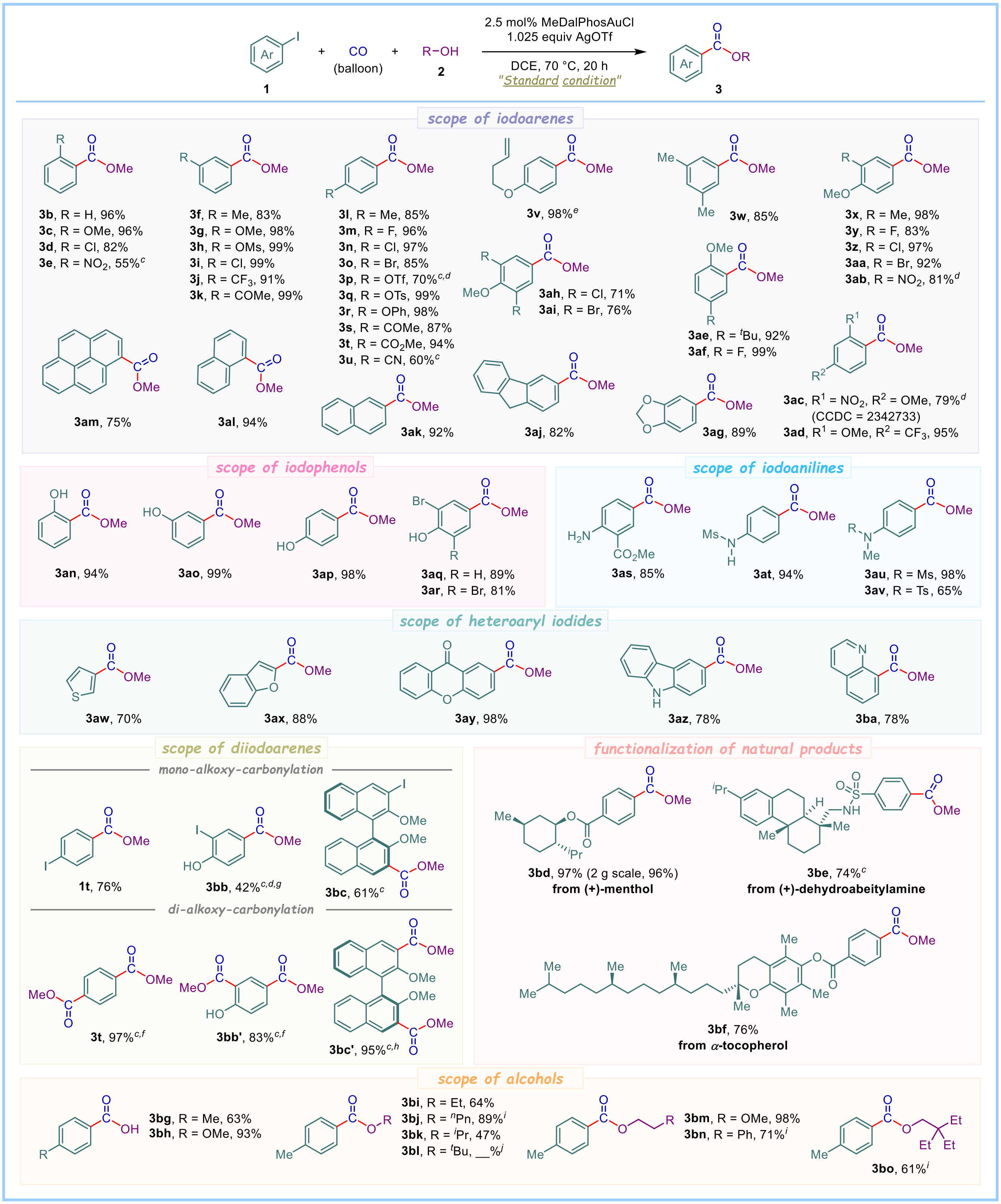
Entry	Y	[Au]	Z	AgX	Solvent	Isolated Yield (%)
1	10	**Au-1**	1.1	AgOTf	DCE	95[b]
2	10	**Au-1**	1.1	AgOTf	DCE	98
3	5	**Au-1**	1.05	AgOTf	DCE	98
4	2.5	**Au-1**	1.025	AgOTf	DCE	98
5	1	**Au-1**	1.01	AgOTf	DCE	75
6	2.5	**Au-1**	1.025	$AgNTf_2$	DCE	80
7	2.5	**Au-1**	1.025	$AgSbF_6$	DCE	88
8	2.5	**Au-1**	1.025	$AgBF_4$	DCE	81
9	2.5	**Au-1**	1.025	AgOTf	DCM	82[c]
10	2.5	**Au-1**	1.025	AgOTf	toluene	81
11	2.5	**Au-1**	1.025	AgOTf	1,4-dioxane	50
12	**2.5**	**Au-1**	**1.025**	**AgOTf**	**DCE**	**99**[d]
13	2.5	**Au-2**	1.025	AgOTf	DCE	91[e]
14	2.5	**Au-3**	1.025	AgOTf	DCE	95[e]

[a] Reaction conditions: 0.2 mmol **1a**, 2.0 mmol **2a**, Y mol% **[Au]**, Z equiv AgX, solvent (0.05 M), CO (balloon), 80 °C, 20 h. [b] 0.7 equiv pyridine was used. [c] Reaction temperature 40 °C. [d] Reaction temperature 70 °C. [e] Reaction time 36 h.

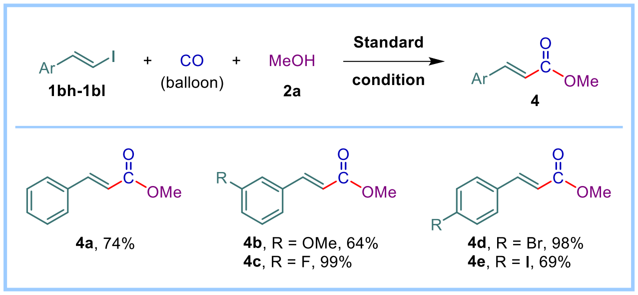
We initiated our investigations on the reaction of 4-iodoanisole with methanol and CO (balloon) under our previously established Heck reaction conditions (10 mol% MeDalPhosAuCl, 1.1 equiv AgOTf, 0.7 equiv pyridine, in DCE (0.05 M) at 80 °C).[8a] Pleasingly, the carbonylation product **3a** was obtained in 95% yield (Table 1, entry 1). Inspired by this result, we opted to understand the effect of silver salts, solvents, gold catalysts, and their loading. The reaction proceeded efficiently without base, delivering the product **3a** in 98% yield (entry 2). The study on the effect of catalyst loading (entries 3-5) revealed that the reaction exhibited equal efficiency with a reduced catalyst loading of 2.5 mol% **Au-1** (entry 4). Next, we found that varying the halide scavengers (entries 6-8) and solvents (entries 9-11) had a detrimental effect on the reaction outcome. Lowering the reaction temperature to 70 °C resulted in the formation of product **3a** in 99% yield (entry 12). The hemilabile (C,N)-ligated gold catalyst (**Au-2**) independently developed by Szostak[23] - Russell,[24] and KarPhos-ligated gold catalyst developed by Gagosz[25] (**Au-3**), exhibited equal efficiency in producing **3a**.

Having the optimized reaction conditions in hand, we next explored the scope of aryl iodides **1** for the gold-catalyzed alkoxy-carbonylation reaction by using methanol **2a** (Scheme 2). To our delight, a wide range of electron-rich, electron-neutral, and electron-deficient aryl iodides **1** reacted efficiently to deliver the alkoxy-carbonylation products **3** in excellent yield. For instance, aryl iodides **1b-1u** having different substituents at *ortho*, *meta*, and *para* positions reacted smoothly to deliver the products **3b-3u** in 55-99% yield. Next, the aryl iodide **1v** having a tethered alkene also delivered product **3v** in 98% yield under slightly higher CO pressure (10 bar). Interestingly, undesired 1,2-diarylation[26] and intermolecular oxy-arylation[27] products were not observed. Further, disubstituted aryl iodides **1w-1ag** also reacted well to afford the products **3w-3ag** in 79-99% yield. The products **3ah-3ai** were obtained in 71-76% yield when trisubstituted aryl iodides **1ah-1ai** were used as substrates. Besides, 3-iodo-9H-fluorene, 2-iodonaphthalene, 1-iodonaphthalene, and 1-iodopyrene also reacted efficiently under the standard reaction conditions to furnish the products **3aj-3am** in 75-94% yield. Differently substituted iodophenols **1an-1ar** also reacted with methanol to afford the products **3an-3ar** in 81-99% yield. Next, the products **3as-3av** were obtained in 65-98% yield when 4-iodoaniline derivatives **1as-1av** were used as substrates. Heteroaryl iodides such as 3-iodothiophene, 2-iodobenzofuran, 2-iodo-9H-xanthen-9-one, 3-iodo-9H-carbazole, and 8-iodoquinoline also reacted smoothly with methanol to deliver the corresponding products **3aw-3ba** in 70-98% yield. Notably, the gold catalyst exhibited excellent chemoselectivity for the C(sp^2)-I bond over other C(sp^2)-X (X = F, Cl, Br, OMs, and OTf) bonds (see: **3d**, **3h-3i**, **3m-3p**, **3y-3aa**, **3af**, **3ah-3ai**). Gratifyingly, the present methodology was also applicable for the selective functionalization of diiodoarenes to access both mono-esters (entries **1t**, **3bb**, and **3bc)** and di-esters (entries **3t**, **3bb'**, and **3bc'**). Additionally, the iodoarene-embedded natural products such as (+)-menthol (**1bd**), (+)-dehydroabeitylamine (**1be**), and *α*-tocopherol (**1bf**) also reacted efficiently to afford the desired carbonylation products **3bd-3bf** in 74-97% yield. Next, we turned to evaluate the scope of alcohols **2** by using 4-iodotoluene as a model substrate (Scheme 2). The products **3bg-3bh** were obtained in 63-93% yield when water was used instead of alcohols. Further, ethanol, 1-pentanol, and 2-propanol reacted smoothly under the standard reaction conditions to furnish the products **3bi-3bk** in 47-89% yield. However, tertiary butanol failed to deliver the corresponding alkoxy-carbonylation product **3bl**. Next, alcohols **1bm-1bo** also reacted smoothly to afford the products **3bm-3bo** in 61-98% yield. The practicality of the present methodology was demonstrated by undertaking the large-scale synthesis of **3bd** (5.17 mmol scale, 2 g of **1bd**, 96% yield).[28]

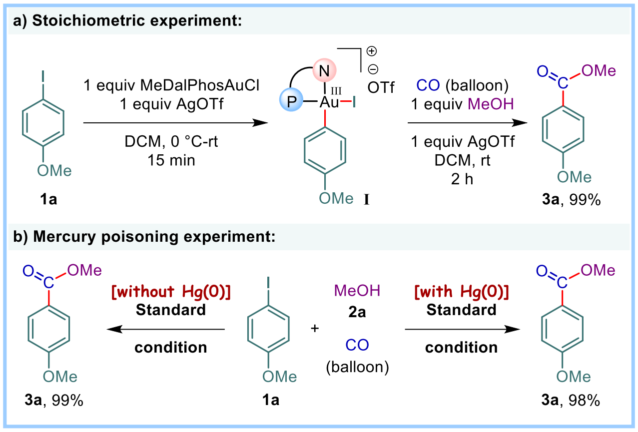
Interestingly, the present methodology was also applicable for accessing the alkoxy-carbonylation of vinyl iodides (Scheme 3). Particularly, treating vinyl iodides **1bh-1bl** with methanol under standard conditions delivered the desired product *α*,*β*-unsaturated carbonyl compounds **4a-4d** in 64-99% yield.



Scheme 2. Scope of the gold-catalyzed alkoxy-carbonylation of aryl iodides[a,b] [a]Reaction conditions: 0.2 mmol **1a**, 2.0 mmol **2a**, 0.005 mmol MeDalPhosAuCl, 0.205 mmol AgOTf, DCE (0.05 M), 70 °C, 20 h. [b]Isolated yield. [c]5 mol% MeDalPhosAuCl was used. [d]Reaction time 36 h. [e]10 bar CO pressure was used. [f]2.05 equiv AgOTf and 20 equiv **2a** was used. [g]Reaction temperature 30 °C and DCM was used as a solvent. [h]After stirring the reaction for 20 h, an additional 5 mol% MeDalPhosAuCl, 10 equiv of **2a**, and 1.05 equiv of AgOTf was added, and stirred the reaction mixture for 20 h. [i]2 equiv alcohol **2** was used. [j]No reaction.



Scheme 3. Gold-catalyzed alkoxy-carbonylation of vinyl iodides



Scheme 4. Mechanistic investigations

A few control experiments were carried out to gain mechanistic insights (Scheme 4). At first, the stoichiometric experiment was conducted to generate aryl-Au(III) species **I** by the reaction of MeDalPhosAuCl with 4-iodoanisole **1a**. The treatment of aryl-Au(III) species **I** with AgOTf and methanol under the CO atmosphere delivered the alkoxy-carbonylation product **3a** in 99% yield. This experiment clearly implies that the aryl-Au(III) species **I** intercepts CO and methanol to afford the product **3a**. Further, the plausible involvement of the catalysis by palladium traces was ruled out by the ICP-MS analysis which showed a negligible amount of Pd in the reaction.[28] Next, the mercury poisoning experiment was performed to rule out the possible involvement of catalysis by gold nanoparticles (Scheme 4b).[28]

Based on the mechanistic investigations and literature reports,[21,29] we initially proposed a mechanism involving migratory insertion step.[28] Next, DFT computations were performed using Gaussian 16 set of program (Figure 1). The putative carbonyl-gold complex **A** exhibiting a *para*-methoxyphenyl group was used as reference of the free energies. The positive charge of the Au(III) atom is actually largely delocalized over the electron-rich aryl group. The AuCO angle of 168° also indicates that the second positive charge is localized on the carbonyl carbon atom (a large LUMO lobe is located at this position). No migration of the aryl group to CO could be modeled, but a direct reductive elimination leading to complex **B** (-12.4 kcal/mol) in an exergonic fashion, at the expense of only 8.5 kcal/mol of free energy of activation to reach $\mathbf{TS_{AB}}$.[30] Species **B** converged as an acylium ion, in which the Au(I) atom is coordinated to the carbon *para* to the methoxy group (Au…C 2.46 Å). Addition of MeOH proved impossible to model, the approach of the alcohol infinitely raising the energy. Thus, TfO⁻ was used as a base to remove the proton of MeOH during the approach.[31,32] In such case, the formation of ester **C** (-44.2 kcal/mol) was obtained in a strongly exergonic manner without any activation barrier. In **C**, TfOH is H-bonded to the oxygen atom of the methoxy group. Elimination of TfOH further lowers the energy to -50.8 kcal/mol (complex **G**). Another scenario to explain the formation of **G** is the direct addition of the [MeOH…OTf]$^-$ adduct to **A**. This first gives the precomplex **D**, located at 5.1 kcal/mol on the free energy surface. The C–O bond formation takes place at $\mathbf{TS_{DE}}$, whose energy is very close to that of $\mathbf{TS_{AB}}$ (8.5 *vs* 8.4 kcal/mol). The resulting complex **E** is formed exergonically (-8.1 kcal/mol). Direct reductive elimination to give **C** requires 7.8 kcal/mol of free energy of activation to reach $\mathbf{TS_{EC}}$ (-0.3 kcal/mol). This barrier can be lowered to 6.0 kcal/mol by first eliminating TfOH to give **F** (-12.3 kcal/mol). Then, the reductive elimination transition state $\mathbf{TS_{FG}}$ can be found at -6.3 kcal/mol on the surface. Overall, the mechanism presented in Figure 1 shows the feasibility of the alkoxy-carbonylation of *para*-iodoanisole under the Au(I)/Au(III) catalysis. Once the carbonyl complex is reached, the barriers are quite low. However, it is not possible to make a clear distinction between the computed scenarios because the direct reductive elimination and the direct addition of MeOH face similar barriers.

In conclusion, we have developed the ligand-enabled gold-catalyzed alkoxy-carbonylation of aryl/vinyl iodides. This transformation operates under mild reaction conditions with low CO pressure (balloon) and exhibits excellent chemoselectivity for C(sp^2)-I bond over other C(sp^2)-X bonds (X = F, Cl, Br, I, OMs, and OTf). DFT studies suggested that the carbonyl-gold complex **A** follows two potential pathways: 1) direct reductive elimination, or 2) direct addition of MeOH, resulting in the formation of products. Clearly, these pathways are mechanistically distinct when compared with other transition metal-catalyzed carbonylation reactions, where the migratory insertion step is crucial. Considering the rich legacy of transition metal-catalyzed carbonylation reactions in academia and industries, and with gold now entering the realm of carbonylation reactions, we foresee tremendous potential of this work for the development of novel reactivities.

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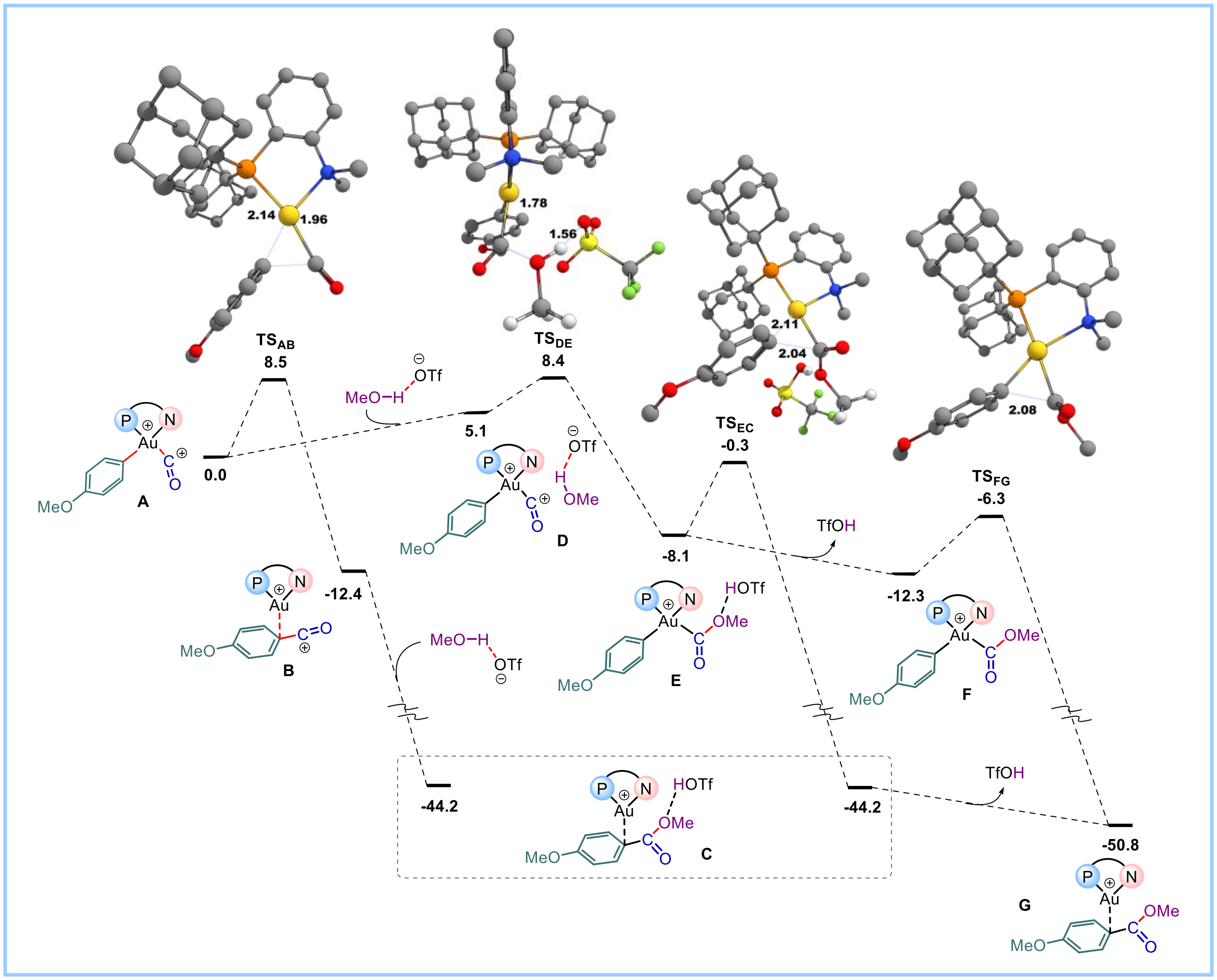

Figure 1. M11L/SDD+f(Au):6-311+G(d,p) free energy profile (ΔG$_{298}$, kcal/mol) of the formation of complex **G** from the *trans*-N/Ar gold complex **A** ((P,N) = MeDalphos; some hydrogen atoms have been omitted for clarity; selected distances in Å)

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