JOC The Journal of Organic Chemistry
Article
pubs.acs.org/joc

Computational Characterization of the Mechanism for Coinage-Metal-Catalyzed Carboxylation of Terminal Alkynes

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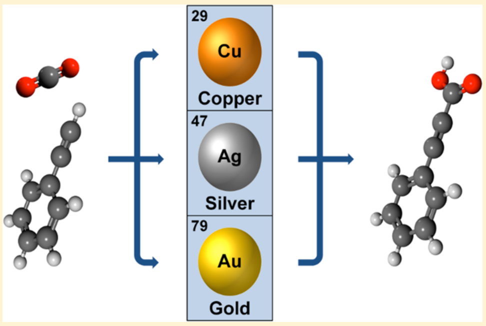
Supporting Information

ABSTRACT: Several experimentally reported copper-, silver-, and gold-catalyzed carboxylation processes of terminal alkynes are studied with DFT methods to find out the mechanism ruling these transformations. The computational results indicate that the reaction follows a very similar pathway for all three metals: the crucial step involves the electrophilic attack of an unactivated carbon dioxide unit on a metal−σ-acetylide complex. The calculations lead to the proposal of additional silver and gold catalytic systems that could perform this reaction at mild temperatures.



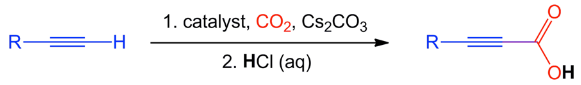
1. INTRODUCTION

Carbon dioxide is an inexpensive, nontoxic, and abundant chemical that is currently one of the most appealing C_1 building blocks for organic chemistry. Carbon dioxide is a thermodynamically stable and unreactive molecule, and traditional carbon dioxide activation strategies require quite harsh reaction conditions or specially designed organometallic species, preventing the widespread development of this process.[1] Things have been improving in recent years, and a variety of processes are now available for carbon dioxide activation. Catalytic applications for the direct C−H and N−H carboxylation have been developed[2] including gold,[3] copper,[4] rhodium,[5] and tin[6] catalysts as well as some other metal-free systems.[7] These methodologies allow the carboxylation of a wide variety of substrates such as epoxides,[2d] silanes,[7b] organometallic reagents,[2f] and olefins.[2i]

Among the substrates amenable to carboxylation, terminal alkynes have been shown to be rather convenient,[8] even if sometimes the resulting propiolic acids cannot be isolated and the products have to be trapped by other electrophiles.[9] Propiolic acids (or propiolates) constitute a valuable class of compounds; they can be found as motifs in biologically active molecules[10] and can be employed as substrates for other reactions such as cycloadditions, hydroarylations, and decarboxylative couplings.[11] Direct carboxylation seems to be a more efficient route to propiolic acids than alternatives such as oxidative carbonylation of alkynes, addition of alkynes to formaldehyde and subsequent oxidation, or reaction of alkynylmetal species with chloroformate or carbon dioxide.[12]

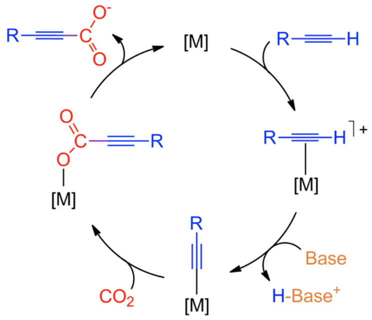
The typical reaction for direct carboxylation of terminal alkynes is summarized in Scheme 1, which can fit the systems experimentally reported by the groups of Gooßen[8b] and Zhang[8c] with copper and silver catalysts. No efficient gold catalysts have been reported for this process, although limited conversion has been observed.[8e]

Scheme 1. Metal-Catalyzed Carboxylation of Terminal Alkynes



No general mechanistic picture is available for these processes, but a plausible reaction scheme of the copper carboxylation process was put forward by Zhang and Lu[9b] (Scheme 2). The main steps are coordination of the alkyne to the metal center, deprotonation by an external base, insertion of

Scheme 2. Proposed Mechanism for the Metal-Catalyzed Carboxylation of Terminal Alkynes



Special Issue: Mechanisms in Metal-Based Organic Chemistry

Received: August 8, 2014
Published: September 22, 2014

dx.doi.org/10.1021/jo501837p | J. Org. Chem. 2014, 79, 11981−11987

carbon dioxide into the copper−acetylide bond, and departure of the propiolate product. A number of relevant mechanistic details are not addressed in this scheme, such as the identity of the rate-determining step and the detailed nature of the transition step for the carbon dioxide insertion into the metal−carbon bond. A computational study would be helpful to clarify these issues. Computational chemistry has been previously shown to be useful in the study of the reactivity of carbon dioxide with transition metal complexes.[13] The carboxylation of terminal alkynes has only been analyzed in a recent publication for the particular case of a silver-catalyzed process.[13e]

We herein report a computational mechanistic study for copper(I)-, silver(I)-, and gold(I)-catalyzed carboxylation of terminal alkynes. Whenever possible, comparison to experimental results has been made to assess the validity of the proposed catalytic cycles. Additional calculations on potential catalytic systems that have not yet been experimentally studied are also reported.

2. COMPUTATIONAL DETAILS

All of the structures were fully optimized with the B97D[14] density functional in the corresponding solvent with the Gaussian 09 package.[15] The Stuttgart triple-ζ basis set,[16] along with the associated electron core potentials, was employed for Cu, Ag, and Au, whereas the standard 6-31+G*[17] basis set was used for all H, C, N, O, and S atoms. Free energies in solution were computed with the (IEF-PCM) continuum dielectric solvation model;[18] the radii and non-electrostatic terms for Truhlar and co-workers' SMD solvation model were employed for this purpose.[19] In all cases, frequency calculations were carried out to ensure the nature of stationary points and transition states and to provide free energy corrections at 25 °C and 1 atm for all the species involved. Some of the experimental data being discussed were obtained at slightly different temperatures, but the effect on the barriers is very minor. For the case of the Cu(DMA) system, the change from 25 to 100 °C diminishes the free energy barrier from 24.4 to 24.0 kcal/mol, and in the case of the Ag(DMSO) system, the modification from 25 to 60 °C brings a change from 19.2 to 18.9 kcal/mol.

Additional single-point calculations on the previously optimized geometries were employed to obtain improved solvated free energy values with larger basis sets. The 6-311+G** all-electron basis set[17c] was used for all H, C, N, O, S, and Cl atoms, whereas the aug-cc-pVTZ[20] basis set including polarization and the associated electron core potential[21] was employed for copper, silver, and gold. The free energies supplied in the text are obtained by addition of the potential energies in solution obtained with the large basis set plus the free energy corrections obtained with the small basis set.

3. RESULTS AND DISCUSSION

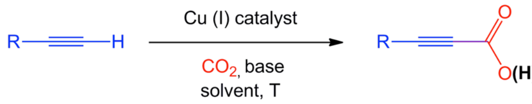
3.1. Copper-Catalyzed Carboxylations.

Several procedures for direct carboxylation of alkynes involving copper(I) complexes have been reported over the years, and they are summarized in Scheme 3. For their computational study, we are going to classify them in three blocks.

The first block is constituted by entry 1 in Scheme 3. It is the first example of this kind of reaction and consists specifically of a copper-mediated rather than copper-catalyzed process. Saegusa et al. showed that carbon dioxide was reversibly fixated by different $(PR_3)_3$−Cu−phenylacetylide systems (where R = Bu, Ph, OMe).[8a] They demonstrated that the better σ-donors produced the best carboxylating agents, and in addition, they proved that three P ligands remain on the metal center during the carboxylation reaction.

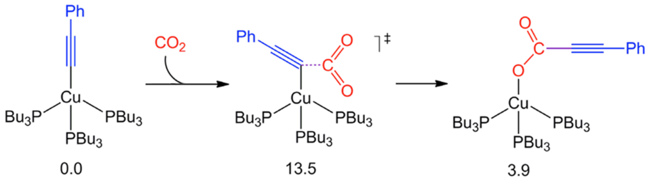
Although this is not a catalytic process, it constitutes a nice example of the seemingly more complicated step in the whole process. We carried out calculations on this step, and the results are summarized in Scheme 4. Two main conclusions can be extracted from these calculations; first, the energy difference between the copper−σ-acetylide and the copper−propiolate is less than 4 kcal/mol, indicating, as experiments pointed out, that the process is reversible. Additionally, the barrier for the process is low enough (only 13.5 kcal/mol is required) to allow the reaction to proceed at room temperature. An interesting feature of the carboxylation transition state is that there is no connection between the copper center and carbon dioxide (Figure 1), indicating that no additional activation of CO_2 is needed to push the reaction forward. A similar situation was found in a recent publication where a nickel−acetylide was found to directly attack CO_2 without any interaction with the metal.[13c] Additional four-membered transition states, corre-

Scheme 3. General Copper-Catalyzed Carboxylations and Their Reaction Conditions



Entry	Ligand	R	CO_2 pressure (bar)	Base	T (°C)	Solvent
1	$3PBu_3$	Ph	1	-	rt	DMF
2	-	Ph	1	K_2CO_3	100	DMA
3	TMEDA	Ph	1	K_2CO_3	rt	DMF
4	PEt_3	Ph	1	Cs_2CO_3	rt	DMA
5	IPr	Ph	15	K_2CO_3	60	DMF
6	phen + $2PPh_3$	Octyl	1	Cs_2CO_3	50	DMF
7	phen + 2P(*p*-F-Ph)$_3$	Ph	5	Cs_2CO_3	35	DMF

Scheme 4. Copper-Mediated CO_2 Insertion in the Cu−C≡CPh Bond (Free Energies in kcal/mol)



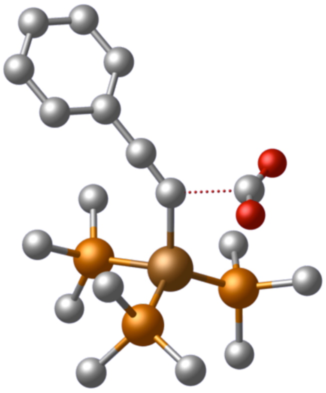
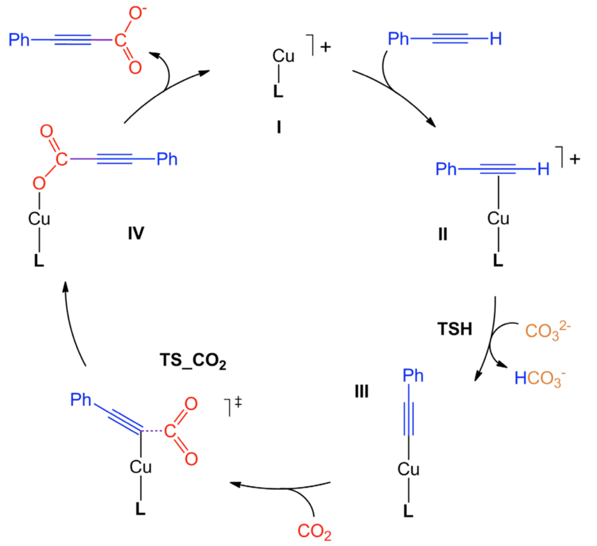


Figure 1. Detailed structure of the carboxylation transition state for the reaction between $Cu(PBu_3)_3$(phenylacetylene) and carbon dioxide (for clarity, butyl groups have been reduced to methyl, and hydrogen atoms are not shown).

sponding to complexes where an oxygen of CO_2 is bound to the copper before the carboxylation occurs, were sought, but it was not possible to locate any of them.

The second block of copper-catalyzed carboxylations is formed by entries 2−5 in Scheme 3. Entry 2 constitutes the first copper-catalyzed carboxylation; this ligand-free system allowed the synthesis of 2-alkynoates from terminal alkynes, carbon dioxide, and bromoalkanes.[9a] Entries 3−5 constitute more recent examples of this kind of carboxylation of terminal alkynes; the main difference between them is the ligand employed in the copper(I) catalyst, that is, TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylendiamine),[8c] triethylphosphine,[9c] or IPr (1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene).[9b] All of them use carbonates as bases, and the reaction is carried out at relatively low temperatures, ranging from room temperature to 60 °C. A joint theoretical analysis can be made for these reactions because their catalytic cycles for the carboxylation of phenylacetylene are quite similar. The general mechanism is shown in Scheme 5. The corresponding relative free energies for the key intermediates and transition states are collected in Table 1. In the case of the ligand-free system, a dimethylacetamide (DMA) solvent molecule bound through oxygen was employed as the ligand. The last line of Table 1 corresponds to the overall exergonicity of the process, the free energy change associated with the conversion from reactants to products. It does not depend on the catalyst, but it has a minor dependence on the solvent.

Scheme 5. General Mechanism for Copper-Catalyzed Carboxylation of Phenylacetylene[a]



[a]The ligand on copper is IPr, TMEDA, PEt_3, or a DMA molecule.

Table 1. Computed Free Energies (in kcal/mol) for Copper-Catalyzed Carboxylations with DMA, IPr, TMEDA, or PEt_3 on Copper

step	ligand			
		IPr	TMEDA	PEt_3
I	0.0	0.0	0.0	0.0
II	−9.8	−5.6	−15.9	−1.5
TSH	−31.2	−16.3	−24.6	−23.2
III	−56.6	−46.9	−49.9	−43.7
TS_CO$_2$	−32.2	−27.4	−30.4	−23.6
IV	−38.0	−35.2	−34.7	−32.4
overall	−24.0	−25.4	−25.4	−24.0

The computed mechanism (Scheme 5) is quite similar to that previously proposed from experimental considerations (Scheme 1) but provides additional insight into the way the reaction operates. The reaction starts with the alkyne π-coordination to the copper center of the catalyst (**I**); this step is exothermic for all studied systems. Once coordinated, the terminal proton acidity is increased and thus the C−H bond can be cleaved by the carbonate. The approach of the dianionic carbonate to the cationic complex is very favorable due mostly to electrostatic attraction, although there are also some favorable hydrogen bond interactions, resulting in an intermediate not reported in the table. This intermediate may involve, in some of the cases, previous coordination of the carbonate to the metal or not. However, the particular features of this intermediate have little general mechanistic implications, as it evolves via deprotonation through the low barrier TSH to the much more stable σ-acetylide−copper complex **III**.

The electrophilic attack of carbon dioxide on the acetylide forms the desired product that will, in principle, remain attached to the copper through the carboxylic oxygen. As shown above for the copper-mediated reaction, the transition state connecting species **III** and **IV** involves no bonding between the metal and the carbon dioxide. The free energy barrier for this step is the highest one in the catalytic cycle, and thus it is the rate-limiting step of the reaction. Barriers of 24.4, 19.5, 20.1, and 19.5 kcal/mol are obtained for DMA, TMEDA, PEt_3, and IPr, respectively. The reaction is thus feasible at low temperatures, the more difficult case being that of the ligand-free system. This is in agreement with the requirement of higher temperatures (100 °C) for the latter case. The catalyst is recovered by liberating the propiolate, either directly to the reaction mixture or by substitution with another terminal alkyne, which would take the catalytic cycle back to intermediate **II**.

A third block of copper-catalyzed carboxylations is that of entries 6 and 7 in Scheme 3. These reactions were reported by Goßen in 2010; in this case, the copper(I) catalyst contains a phenanthroline and two monodentate phosphine ligands such as PPh_3, $P(p\text{-F-Ph})_3$, $P(p\text{-Cl-Ph})_3$, PCy_3, etc. Their experiments show that PPh_3 allows the transformation of alkyl-substituted terminal alkynes into the corresponding propiolic acids at relatively low temperatures; in addition, employing the electron-poorer phosphine $P(p\text{-F-Ph})_3$ allows the synthesis of aryl-substituted propiolic acids at 35 °C, although a higher CO_2 pressure is needed. These two reactions have been computationally explored to determine the operating mechanism; in the case of alkyl-substituted alkynes, initial calculations reduced the size from the experimental octyl substrate to methyl in order to speed up the calculations. The proposed mechanism for these reactions is shown in Scheme 6, and the associated free energies can be found in Table 2.

The only qualitative difference with the mechanism discussed above for the second block of reactions is the need here of an additional step of phosphine dissociation before the active form of the catalyst is obtained. The phosphine dissociation is energetically disfavored, and this step requires around 10 kcal/mol for either catalyst. Once the tricoordinated complex **G2**, the real catalytic species, is formed, the reaction follows the path described above. The barrier for the electrophilic attack is

Scheme 6. Catalytic Cycle for the Carboxylation Reactions Developed by Gooßen

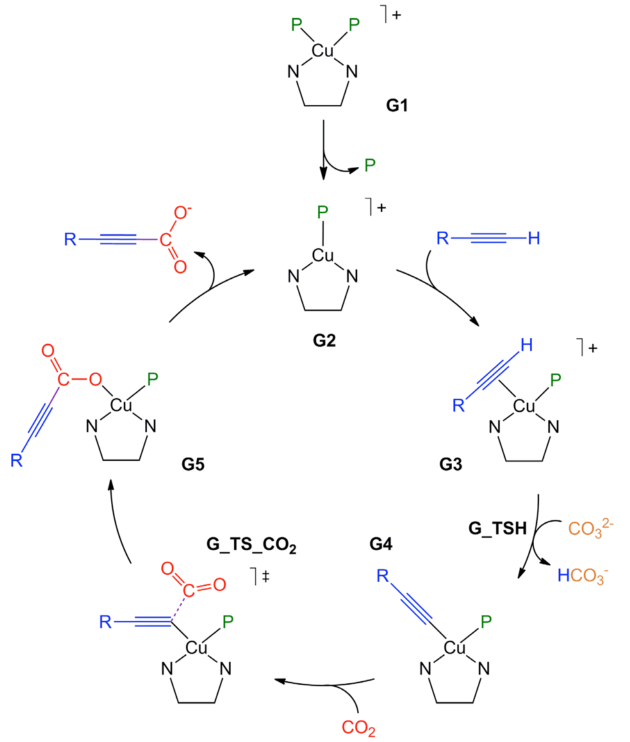


Table 2. Computed Free Energies (in kcal/mol) for Gooßen's Copper-Catalyzed Carboxylations

step	substrate	
	1-propyne	phenylacetylene
G1	0.0	0.0
G2	10.2	11.3
G3	11.9	0.0
G_TSH	11.0	8.8
G4	−19.6	−23.4
G_TS_CO$_2$	−4.1	−7.8
G5	−12.1	−11.8
overall	−24.8	−25.4

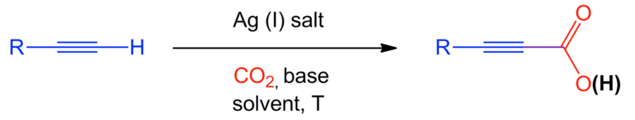
15.6 kcal/mol for both catalytic systems, again the rate-limiting step of the carboxylation process. In order to get the real barrier for 1-octyne, which is the original substrate employed in the experiments, **G4** and **G_TS_CO$_2$** were recomputed with this substrate. The barrier obtained for the reaction is 14.0 kcal/mol, indicating that the reaction should work smoothly at 50 °C.

All reactions considered for copper-catalyzed carboxylation follow a common pattern where the rate-determining step is the electrophilic attack of the acetylide ligand on the carbon dioxide and where the transition state for this step shows no strong interaction between carbon dioxide and copper.

3.2. Silver-Catalyzed Carboxylations.

Three reported examples of ligand-free silver-catalyzed carboxylation of terminal alkynes have been found in the literature;[8d,e,9a] Scheme 7 summarizes the general reaction for the studied catalytic systems. The main differences between those reactions stem from the solvent employed (DMA, DMF, or DMSO) and the product isolation, either esterification for the former or acid workup for the other two.

Scheme 7. General Silver-Catalyzed Carboxylations and Their Reaction Conditions



Entry	Ag source	R	CO_2 pressure (bar)	Base	T (°C)	Solvent
1	AgI/$AgNO_3$	Ph	1	K_2CO_3	100	DMA
2	AgI	Ph	2	Cs_2CO_3	50	DMF
3	$AgBF_4$	Bu	1	Cs_2CO_3	50	DMSO
4*	$Ag(PMe_3)^+$	Bu	-	CO_3^{2-}	25	DMSO
5*	$Ag(dmiy)^+$	Bu	-	CO_3^{2-}	25	DMSO

*Computationally proposed catalysts.

Since these catalytic systems look very alike, only one of them, the most recent one published by Arndt et al., has been computationally explored. As stated above, in these ligand-free reactions, the solvent may interact with the silver acting as a donor ligand. As observed in the copper-catalyzed carboxylations, the addition of other ligands may produce better catalysts; therefore, a couple of new silver catalytic systems using phosphine or carbene ligands are proposed here and were computationally tested. The simplest example of each ligand class has been selected, PMe_3 and 1,3-dimethylimidazol-2-ylidene (dmiy), to carry out the carboxylation of 1-hexyne in dimethylsulfoxide (DMSO).

The coordination number of the Ag(I) complexes is not a priori clear. Because of that, we made test calculations with more than two ligands (L, carbonate and alkyne, for instance) on the metal. All of these calculations led to spontaneous departure of one of the ligands. Because of that, we decided to settle on a maximum coordination number of two.

We carried out calculations thus on entries 3−5 of Scheme 7. In the case of the ligand-free catalyst (entry 3), a DMSO molecule bound through an oxygen atom was employed as the ligand.[22] Our calculations indicate that the catalytic cycle for these silver-promoted carboxylations (Scheme 8 and Table 3) is slightly different from that found for copper(I) catalysts. The difference is in the first part of the reaction, where a stable adduct between carbonate and silver (**Ag2**) replaces the π complex with the alkyne (**II**, Scheme 5) that was observed for copper. This result is in agreement with the computational results by Luo, Zhang, and co-workers,[13f] who found also that the carbonate bound silver in the initial step. We do not consider here the role of counterions as in their case, but their effect on the key steps should be minor. The difference between the behavior of copper and silver complexes can be probably attributed to the preference of the silver center for lower coordination numbers. Deprotonation of alkyne by this carbonate species takes place in any case with a low barrier, and the σ-acetylide intermediate **Ag4** is then reached. This species, already present in the copper reaction, can be considered as the resting state of the carboxylation reaction since it bears the lowest free energy throughout the catalytic cycle. The transition state for the electrophilic attack from carbon dioxide to the coordinated acetylide shows again no connection between the former and the silver center. The free energy barriers of the attack to CO_2 for the three studied ligands are practically

Scheme 8. General Mechanism for Silver-Catalyzed Carboxylation of 1-Hexyne

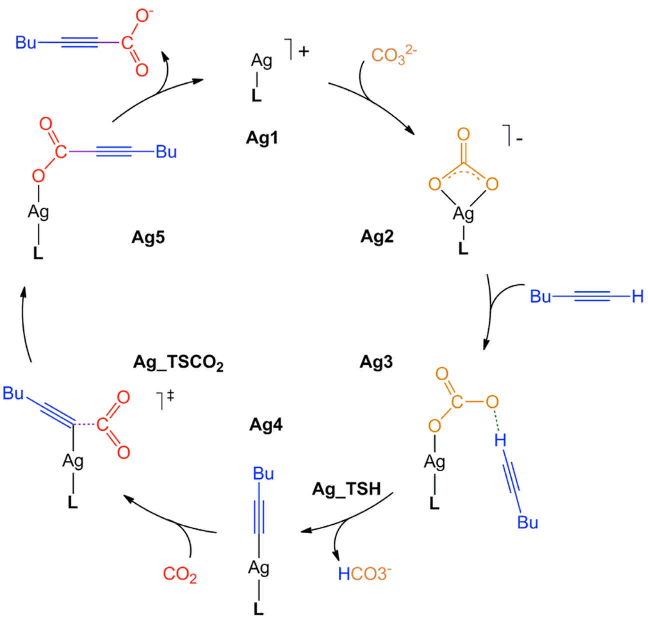


Table 3. Computed Free Energies (in kcal/mol) for Silver-Catalyzed Carboxylations

step	ligand		
	DMSO	PMe$_3$	dmiy
Ag1	0.0	0.0	0.0
Ag2	−37.3	−31.1	−31.9
Ag3	−28.2	−25.2	−24.6
Ag_TSH	−25.2	−17.7	−16.8
Ag4	−50.8	−43.0	−44.3
Ag_TSCO$_2$	−31.6	−23.4	−24.6
Ag5	−35.9	−34.2	−34.5
overall	−21.5	−21.5	−21.5

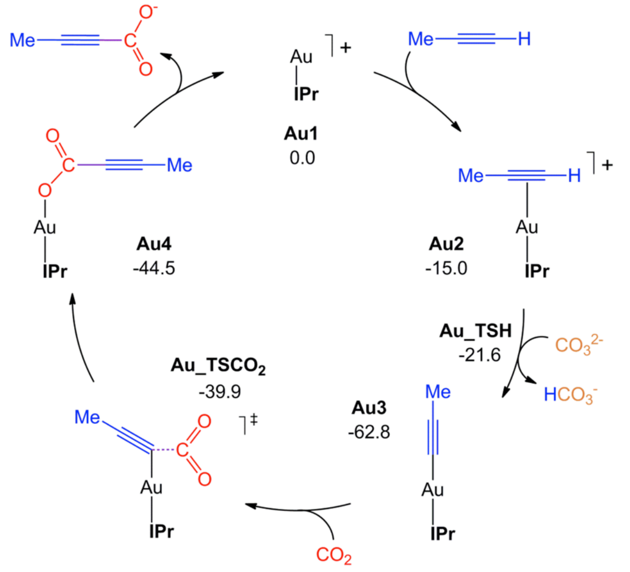
identical: 19.2, 19.6, and 19.8 kcal/mol for DMSO, PMe$_3$, and the carbene, respectively. These values, which correspond also to the overall barrier for the whole carboxylation process, indicate that the reaction should proceed in the low to moderate temperature range. It is remarkable that the barrier seems to be slightly lower for the system with a solvent molecule than for the ones with ligands. However, the differences are very small, 0.6 kcal/mol at most.

Usually, more complex ligands are employed in experiments; therefore, the carboxylation barriers of hexyne (i.e., **Ag4** and **Ag_TSCO$_2$**) were recomputed for P^{t}Bu$_3$ and IPr to check the energy requirement in more realistic catalytic systems. These calculations afforded barriers of 18.8 and 20.4 kcal/mol for the phosphine and carbene ligands, respectively, indicating that both systems should be able to carry out the carboxylation of 1-hexyne at low temperatures.

3.3. Gold-Catalyzed Carboxylations. Only one publication has been found dealing with the gold-catalyzed carboxylation of terminal alkynes.[8e] That report stated that poor yields (around 5%) were obtained when employing a Au(I)−IPr catalyst for the carboxylation of octyne in DMSO. Nevertheless, and because group 11 elements tend to behave in a similar way, it seems plausible to think of a gold catalyst able to carry out this kind of carboxylation reaction. First, a mechanistic study of the reported system was carried out to understand the reason for the experimental failure; afterward, another catalytic system based on a phosphine ligand was explored.

The computed catalytic cycle for the system published by Arndt et al. is shown in Scheme 9. The IPr ligand was maintained for calculations, while the original 1-octyne substrate was replaced by 1-propyne. Subsequent calculations with the original substrate were carried out afterward to obtain a better estimation of the reaction barrier.

Scheme 9. Proposed Mechanism for the Gold-Catalyzed Carboxylation of Arndt et al. Including Free Energies (in kcal/mol)



The catalytic cycle is very similar to those described above for copper and silver. It starts with the coordination of the alkyne to the gold center of the complex **Au1**. The coordinated alkyne can be easily deprotonated by the base; prior to this, an intermediate where the terminal proton and the carbonate establish a weak interaction is formed (**Au2_CO$_3$**) lying at −22.0 kcal/mol. The energy required for the deprotonation, computed as the free energy difference between **Au_TSH** and **Au2_CO$_3$**, is just 0.4 kcal/mol. The resulting σ-acetylide species **Au3** has the lowest free energy along the catalytic cycle. The electrophilic attack of carbon dioxide on the coordinated alkyne forms the final product through a transition state where the former is not connected to the gold. The energy requirement for this step, 22.9 kcal/mol, constitutes the overall barrier for the carboxylation. Recalculating the reaction barrier for the real 1-octyne substrate provides a value of 22.3 kcal/mol.

These barrier values are a little higher than most of those found for the copper- and silver-catalyzed carboxylation reactions studied above and thus are compatible with a more difficult process. Although a barrier of 22.3 kcal/mol can be strictly overcome at room temperature, our calculations are not sufficiently accurate to give quantitative values for absolute rate constants. On the other hand, our calculations are conclusive in indicating that all of these processes are near the limit of what can be feasible at room temperature, and the one with the Au(IPr) catalyst is the most difficult.

Because of this, we considered possible modifications that could bring down the barrier for the gold system. Replacement of the DMSO solvent by DMF could bring the value down to 21.4 kcal/mol. This may be sufficient to make the reaction feasible at mild temperatures. Replacing the carbene ligand by others may furnish an alternative catalyst for the gold-catalyzed carboxylation of terminal alkynes. The carboxylation barrier of 1-octyne in DMF was recomputed for a catalytic system bearing the electron-rich bulky P(^{t}Bu$_3$)$_3$ phosphine. As in other cases, the whole catalytic cycle was not recalculated because it was expected that the barrier corresponds to that between **Au3** and **Au_TSCO$_2$**. In this case, the barrier for the reaction is 20.3 kcal/mol, indicating that the proposed gold catalyst should be able to promote the carboxylation reaction.

4. CONCLUSIONS

The reaction mechanism for copper-, silver-, and gold-catalyzed carboxylation of terminal alkynes has been determined with DFT calculations. All of the catalytic systems follow a very similar pathway comprising the following common steps: alkyne coordination to the metal, deprotonation with an external base (normally a carbonate), and nucleophilic attack of the metal−acetylide complex on a carbon dioxide molecule; in all cases, the transition states corresponding to the C−C bond formation do not exhibit any major interaction between the carbon dioxide and the metal.

Although many copper(I)-based catalysts have been employed in the literature, only a handful of silver salts have been tested for the same purpose, and no gold system has been reported yet that efficiently promotes this transformation. In this work, some alternative catalysts have been computationally studied to conclude that silver and gold complexes with phosphine or carbene ligands could also make good catalysts for the carboxylation of terminal alkynes. Some examples of potential candidates to test experimentally could be [Ag(IPr)]$^+$ and [Ag(P^{t}Bu$_3$)]$^+$ in DMSO or the analogous gold systems in DMF.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Cartesian coordinates and absolute free energies of all stationary points reported in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge financial support from the ICIQ Foundation and from MINECO through project CTQ2011-27033 and Severo Ochoa Excellence Accreditation 2014-2018 (SEV-2013-0319). J.J. thanks MINECO for a Juan de la Cierva Fellowship (JCI-2011-10134).

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