Gold-Catalyzed 1,2-Dicarbofunctionalization of Alkynes

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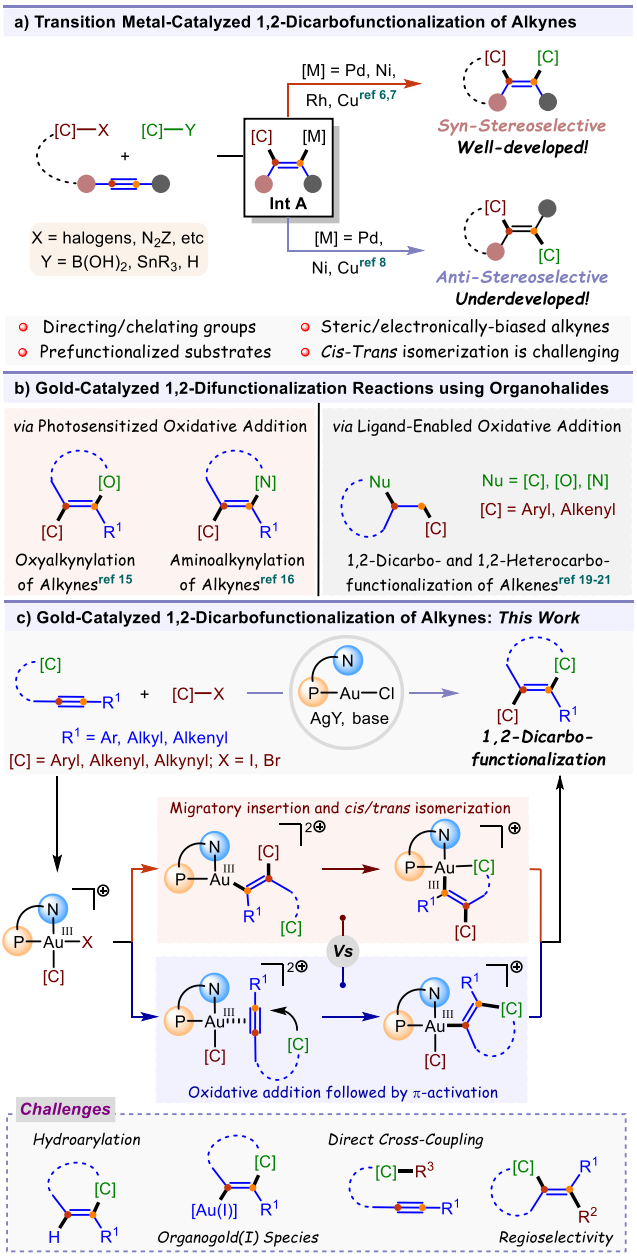
ABSTRACT: Herein, we report the first gold-catalyzed 1,2-dicarbofunctionalization of alkynes using organohalides as non-prefunctionalized coupling partners. The mechanism of the reaction involves an oxidative addition/π-activation mechanism in contrast to the migratory insertion/*cis-trans* isomerization pathway that is predominantly observed with other transition metals yielding products with *anti*-selectivity. Mechanistic insights include several control experiments, NMR studies, HR-MSMS analyses, and DFT calculations that strongly support the proposed mechanism.

Over the past two decades, the development of 1,2-dicarbofunctionalization of C-C multiple bonds has emerged as a hot topic of interest.[1] In this regard, late transition metals, mainly Pd, Cu and Ni have garnered immense attention due to their ability to easily undergo the fundamental organometallic steps.[2] The 1,2-dicarbofunctionalization of alkynes, in comparison to alkenes,[2] is considered to be significantly challenging due to various difficulties such as facile hydrofunctionalization (and double-hydrofunctionalization);[3] poor regio- and stereoselectivity;[4] and the formation of stable σ-complexes or vinyl metallacycles, that lead to the catalyst sequestration.[5] Consequently, the strategic use of directing groups and sterically/electronically-biased alkynes along with pre-functionalized coupling partners has become imperative for the successful realization of a general 1,2-dicarbofunctionalization of alkynes (**Scheme 1a**).[6] Mechanistically, these reactions follow a carbometallation/migratory insertion pathway to sponsor a *syn*-vinyl-metal intermediate (**Int A**) which after cross-coupling with respective coupling partner affords the 1,2-dicarbofunctionalization products. While this mechanistic pathway has remarkably advanced the development of highly general *syn*-selective 1,2-dicarbofunctionalization,[6,7] reports on *anti*-selective 1,2-dicarbofunctionalization of internal alkynes still remain highly sporadic.[8] This is mainly due to the need of bulky ligands, *ortho*-substituted iodoarenes or specialized substrates that are necessary to enable the *cis-trans* isomerization[9] of the **Int A**, prior to the cross-coupling step. Thus, the development of new mechanistic paradigms that do not involve this limiting *cis-trans* isomerization step remain highly desired.

In the past decade, gold catalysis has emerged as an excellent tool for the functionalization of alkynes.[10] Interestingly, in contrast to the prevalent inner sphere mechanisms observed in Pd, Ni or Cu catalysis,[6,7] gold complexes preferably follow an oxidation/π-activation mechanism which has indeed emerged as an attractive alternative for the development of *anti*-selective 1,2-difunctionalization of alkynes.[11] However, the arduous oxidative addition of Au(I)-center to various carbon-halogen bonds[12] and the facile rate of Au(I)-catalyzed hydrofunctionalization reactions of alkynes,[13] has for long forbidden the use of organohalides for the development of 1,2-difunctionalization of alkynes.[14] In order to overcome these shortcomings and enable the use of organohalides in the field of gold catalysis, Mouriès-Mansuy, Ollivier, Fensterbank and co-workers employed photosensitization technique to facilitate the oxidative addition of Au(I) in iodoalkynes, thereby realizing the first oxyalkynylation[15] and later aminoalkynylation[16] of alkynes (**Scheme 1b**). Likewise, Amgoune/Bourissou disclosed the ligand-enabled oxidative addition of Au(I) in iodoarenes and iodoalkenes to enable C-C cross coupling reactions.[17] This ligand-enabled oxidative addition strategy was also

Scheme 1. Background and Synopsis of Current Work

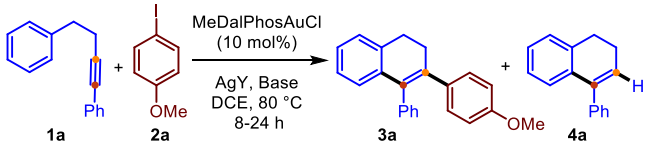


applied to bromoalkynes by Hammond/Lu,[18] thereby realizing C-S/Se cross coupling reactions. Using this strategy, our group,[19]

and groups of Amgoune/Bourissou,[20] and Shi,[21] developed a range of 1,2-difunctionalization reactions of alkenes (**Scheme 1c**).Recently, Bower/Russell also employed this strategy to demonstrate the feasibility of CO migratory insertion in a stoichiometric manner.[22] Subsequently, Gandon/Patil disclosed a gold-catalyzed Heck reaction of alkenes using iodoarenes as coupling partners.[23] Notably, despite such significant developments, there exist no report on 1,2-dicarbofunctionalization of alkynes using organohalides.[24] This could be attributed to various challenges like facile Au(I)-[13,25] and Ag-catalyzed[26] hydroarylation, stable vinyl-Au(I) species formation, direct cross-coupling[27] and regioselectivity issues. Notably, the successful implementation of this reaction paradigm could act as an important step towards the development various gold-catalyzed 1,2-difunctionalization reactions of alkynes using organohalides. Thus, we initiated our endeavour towards the development of the gold-catalyzed 1,2-dicarbofunctionalization of alkynes using organohalides as non-prefunctionalized coupling partners.

To establish the proof-of-concept stoichiometric experiments were performed,[28] wherein we observed the desired 1,2-diarylation product **3a** in 73% yield along with 16% hydroarylation product **4a**. Encouraged by these results we moved towards the development of a catalytic version of this reaction. We began our optimization by using 1 equiv of but-1-yne-1,4-diyldibenzene **1a**, 1 equiv of 4-iodoanisole **2a**, 1 equiv $AgSbF_6$, DCE (0.1 M) and 80 ˚C temperature (**Table 1**). Disappointingly, we observed the formation of **4a** as major product (76%) along with <10% of **3a** (entry 1). While the introduction of of base had significantly suppressed the **4a** formation (entry 2-3), further screening of silver salts (entry 4-6) and increasing the equivalence of **1a** did not have any positive effect on the outcome of the reaction.[28] Pleasingly, increasing the equivalence of **2a** had a positive impact on the outcome of the reaction (entry 7-9). Further, screening of various bases and their equivalence (entry 10-14), led us to the optimized condition to afford **3a** in 86% yield along with **4a** in 10% yield (entry 13).

Table 1. Optimization of Reaction Conditions[a,b]



Entry No.	2a, m equiv	AgY, (n equiv)	Base, (x equiv)	% Yield 3a	% Yield 4a
1	1	$AgSbF_6$ (1.1)	-	<10	76
2	1	$AgSbF_6$ (1.1)	K_3PO_4 (1)	<10	47
3	1	$AgSbF_6$ (1.1)	K_3PO_4 (2)	15	30
4	1	$AgOTf_2$ (1.1)	K_3PO_4 (2)	11	29
5	1	$AgPF_2$ (1.1)	K_3PO_4 (2)	<10	16
6	1	$AgBF_4$ (1.1)	K_3PO_4 (2)	<10	12
7	1.5	$AgSbF_6$ (1.6)	K_3PO_4 (2)	20	45
8	2	$AgSbF_6$ (2.1)	K_3PO_4 (2)	25	27
9	3	$AgSbF_6$ (3.1)	K_3PO_4 (2)	24	32
10	2	$AgSbF_6$ (2.1)	K_2CO_3 (2)	58	15
11	2	$AgSbF_6$ (2.1)	DTBP (2)	<10	12
12	2	$AgSbF_6$ (2.1)	Cs_2CO_3 (2)	35	25
13	**2**	**$AgSbF_6$ (2.1)**	**K_2CO_3 (2.5)**	**86**	**10**
14	2	$AgSbF_6$ (2.1)	K_2CO_3 (3)	70	13

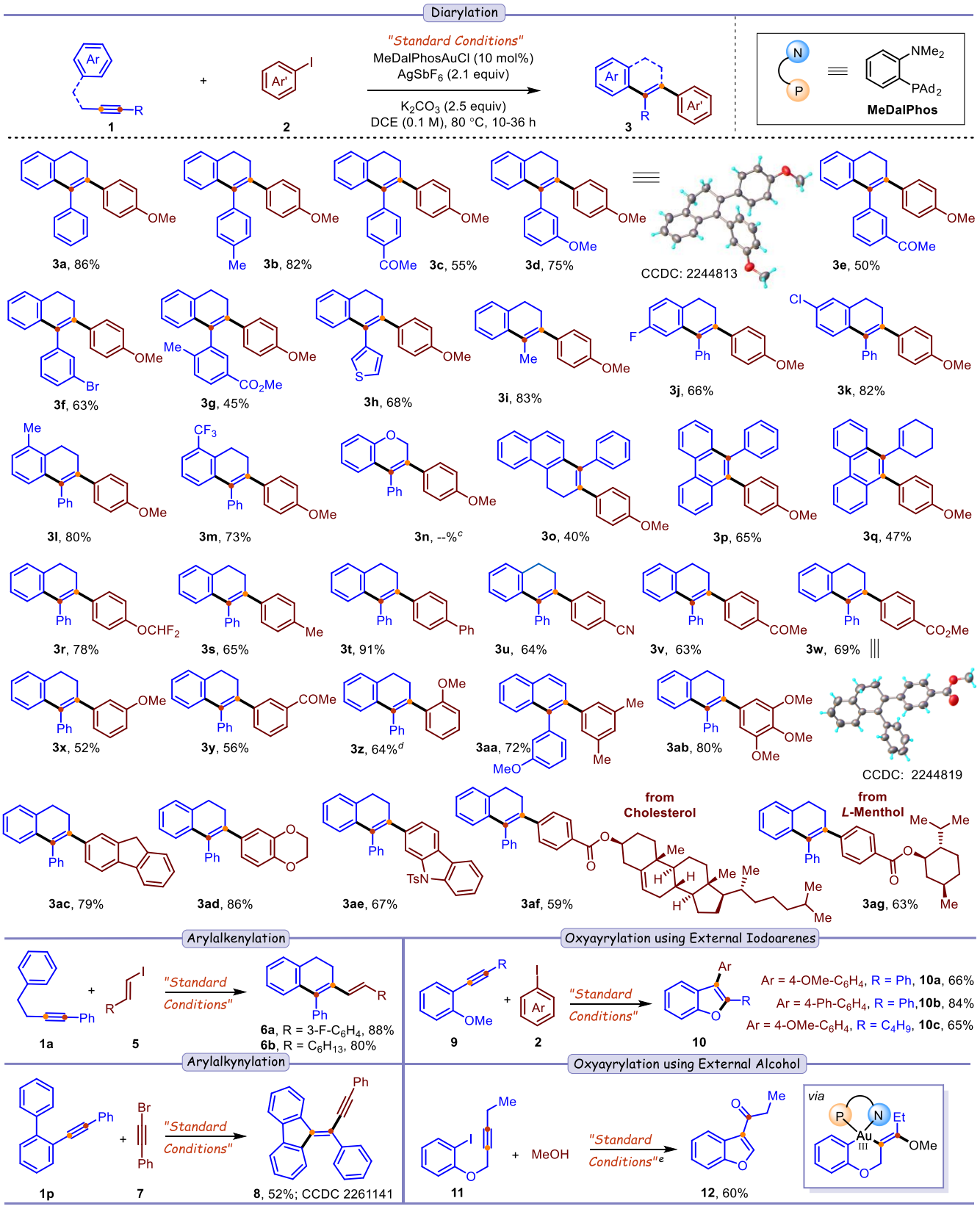
[a]Reaction conditions: 0.15 mmol **1a**, m mmol **2a**, 10 mol% MeDalPhosAuCl, n equiv AgY, x equiv base, DCE (0.1 M), 80 ˚C, 8-24 h. [b]Isolated yields.

With the best reaction conditions identified, we investigated the substrate scope of 1,2-diarylation reaction by treating a variety of internal alkynes **1** with 4-iodoanisole **2a** (**Figure 1**). In this regard, alkynes with various arenes (bearing electron-donating, neutral, withdrawing, and halogen substituents at various position), heteroarenes, and even alkyl substituents were tolerated to afford corresponding diarylation products **3b-3i** in 45-83% yields. Next, substrates with various substitution on the nucleophilic arene rings were well tolerated as well (**3j-3m,** 66-82%). Similarly, other alkyne cores also afforded the corresponding diarylation products in moderate to good yields (**3o-3q,** 40-65%). Of note, the current method did not afford the corresponding arylated 2*H*-chromene **3n**.[29] Next, the scope of iodoarenes for this reaction was investigated. To our delight, iodoarenes bearing electron-donating, -neutral, and halogen substituents at *para*, *meta* and *ortho* positions worked well to afford the diarylation products **3r-3z** in moderate to excellent yields (52-91%). Furthermore, various multi-substituted as well as heterocyclic iodoarenes were also tolerated to afford the corresponding products **3aa-3ae** in 67-86% yields. Next, iodoarenes derived from complex biomolecules also furnished corresponding diarylation products **3af-3ag** in 59-63% yields. With the scope of diarylation established, we questioned if an *anti*-selective arylalkenylation of alkynes could be achieved under the standard reaction conditions by using respective alkenyliodides **5**. This was indeed the case, as both aryl as well as alkyl substituted alkenyliodides worked well to afford corresponding arylalkenylation products **6a** and **6b** in 88 and 80% yield. Interestingly, we could also employ bromoalkyne **7** under the standard reaction conditions to access arylalkynylation product **8** with *exo*-selectivity in 52% yield. With the generality of 1,2-dicarbofunctionalization of alkynes established, we further questioned if we could apply this strategy to various oxyarylation reactions of alkynes. Pleasingly, we could obtain various 2,3-disubstituted benzofurans (**10a-10c**, 65-84% yield), as a result of oxyarylation reaction of substituted 1-ethynyl-2-methoxybenzene **9** with external iodoarenes **2**. Further, the feasibility of an oxyarylation reaction using iodoalkynes **11** and methanol as external nucleophile was also demonstrated to afford 1-(benzofuran-3-yl)propan-1-one **12** in 60% yield. These results clearly warrant the wide applicability of this reaction across other elusive *anti*-selective 1,2-difunctionalization reactions of alkynes.

After exploring the reaction scope, we moved our attention towards the mechanistic investigations (**Figure 2**). To gain insights on whether the strong affinity of Au(I) catalyst towards alkynes could hamper the rate of oxidative addition step, a series of NMR experiments were performed (**Figure 2a**). In this study, we monitored the oxidative addition of 4-iodoanisole with MeDalPhosAuCl in presence of different alkynes. As observed, it took ~30 and ~40 minutes for complete oxidative addition to occur, when a diaryl substituted (R^1, R^2 = Ph) and aryl-alkyl substituted alkynes (R^1 = Ph, R^2 = ^{n}Bu) were used. Strikingly, in the case of dialkyl alkynes (R^1, R^2 = ^{n}Pr), the oxidative addition step was found to be significantly slower and it took about 24 hours for complete conversion. These results clearly suggest that the alkynes and their substituents have a prominent role in hampering the rate of oxidative addition.

Next, in light of the hydroarylation product **4a** obtained, we performed a few control experiments to understand whether the observed hydroarylation reaction was occurring *via* Au(I)- or Au(III)-catalyzed reaction (**Figure 2b**). While we observed the

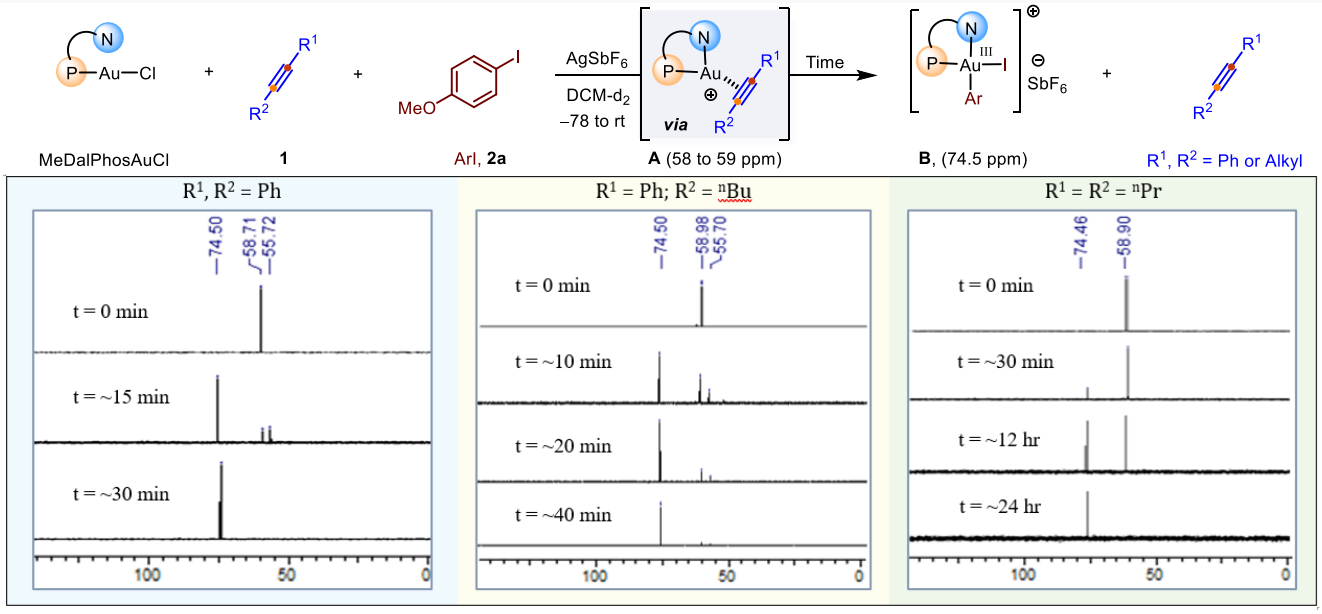
Figure 1. Substrate Scope for 1,2-Dicarbofunctionalization and 1,2-Oxyarylation Reaction of Alkynes.[a,b]



[a]Standard conditions: 0.15 mmol **1**, 0.3 mmol **2**, 0.015 mmol MeDalPhosAuCl, 0.315 mmol $AgSbF_6$, 0.375 equiv K_2CO_3, DCE (0.1 M), 80 ˚C, 10-24 h. [b]Isolated Yields. [c]Hydroarylation product obtained in quantitative yield. [d]Reaction stirred at 120 ˚C with DCB as solvent for 48 h. [e]0.5 equiv K_3PO_4 and 1.1 equiv $AgSbF_6$ used.

Figure 2. Mechanistic Investigations

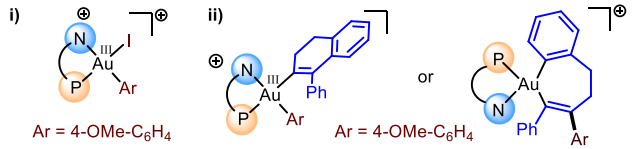
a) NMR studies: Effect of alkyne and its substituents on oxidative addition:



b) Control experiments:

Entry No.	Deviation from standard conditions	% Yields 3a	% Yields 4a
1	-	86	10
2	In absence of **2a**	-	-
3	0.5 equiv K_2CO_3	36	47

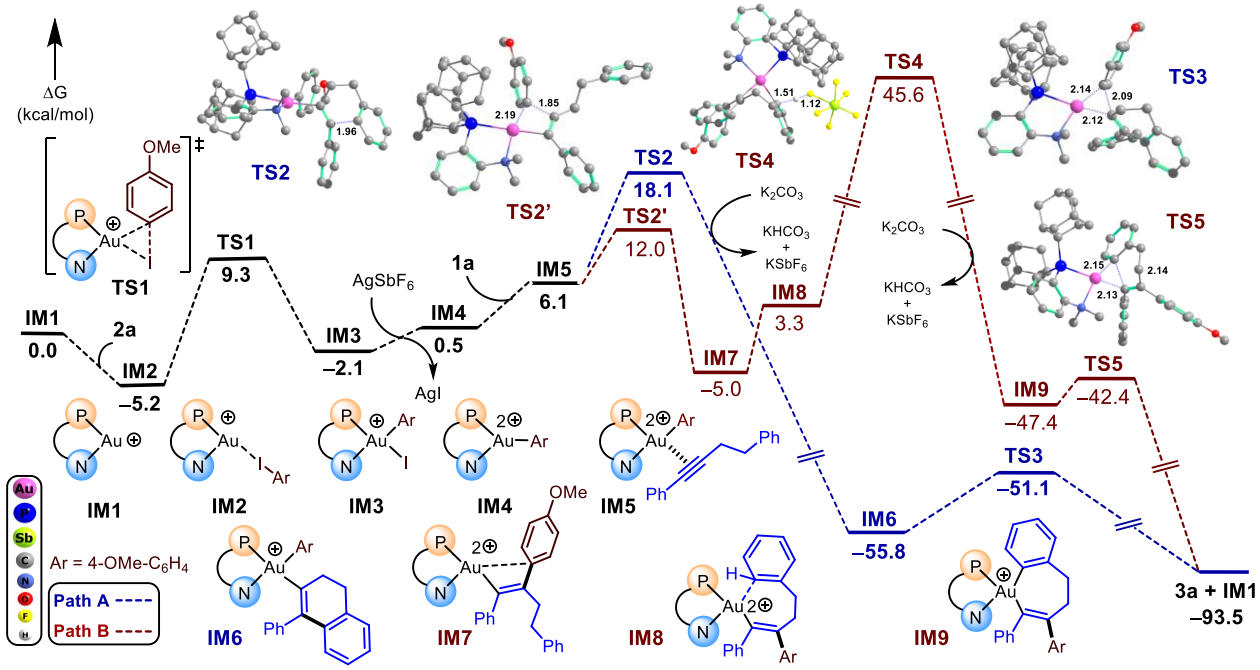
c) Tandem mass spectrometry studies:



***cald m/z* = 852.2100**
***found m/z* = 852.2079**

***cald m/z* = 930.4073**
***found m/z* = 930.4071**

d) DFT studies: Oxidative addition/π-activation vs migratory insertion/*cis-trans* isomerization pathway
(Free energy values are at the M06(SMD-DCE)/SDD(Au,Ag,Sb,I)/def2-TZVP(C,H,O,N,F)//BP86/SDD(Au,Sb,I)/def2-SVP(C,H,O,N,F) level of theory. SbF_6 counterions have been omitted for clarity; selected bond lengths have been mentioned in angstrom.)



formation of 10% hydroarylation product **4a** under the standard reaction conditions (entry 1), **4a** was not observed at all in absence of iodoarene **2a**. These results suggest that cationic Au(I) or $AgSbF_6$ is not capable of catalyzing the hydroarylation reaction and the Aryl-Au(III) species is imperative to facilitate the formation of **4a** (entry 2). Furthermore, when 0.5 equiv K_2CO_3 was used an increase in **4a** and decrease in **3a** formation was observed (47% and 36%, entry 3). These results underscore the importance of base in suppressing the Aryl-Au(III)-catalyzed hydroarylation reaction.[28] Next, with the help of tandem-mass spectrometry, we could successfully detect the two crucial intermediates proposed in the mechanism (**Figure 2c**).

Considering the recently revealed reactivity on the feasible migratory insertion of C-C multiple bonds in Au(III)-C bond as reported by the groups of Patil[23] and Xie,[30] the carbometallation/migratory insertion pathway needs due consideration. Thus, to gain further insights on the energetics of the two possible mechanisms, we performed DFT studies using **1a** and **2a** as model substrates (Figure **1d**). The catalytic cycle begins with a ligand-enabled oxidative addition of cationic Au(I) complex **IM1** to 4-iodoanisole **2a** through a 3-membered transition state **TS1** to afford aryl-Au(III)-I intermediate **IM3** (-2.1 kcal/mol) with an energy barrier of 14.5 kcal/mol. Next, iodide is abstracted by $AgSbF_6$ to liberate silver iodide along with the generation of cationic intermediate **IM4** (0.5 kcal/mol), which upon π-coordination with alkyne **1a** delivers an Au(III)-Ar π-complex **IM5** that is unstable by 5.6 kcal/mol in comparison to **IM4**. Now this intermediate **IM5** can then lead to the formation of desired product **3a** from two different mechanistic pathways. Along path A, the π-activation of C-C triple bond triggers a nucleophilic attack from the pendant arene to afford a significantly stable Ar-Au(III)-vinyl intermediate **IM6** (-55.8 kcal/mol) *via* six-membered transition state **TS2**. This step is associated with an overall barrier of 23.3 kcal/mol relative to **IM2**, and involves a counterion-assisted deprotonation step to generate $HSbF_6$ which can be neutralized by K_2CO_3 in a barrierless fashion. Finally, the reductive elimination from **IM6** *via* transition state **TS3** involving an activation barrier of 4.7 kcal/mol, furnishes the desired product **3a** and regenerates the active catalyst **IM1**. On the other hand, in path B, a migratory insertion of alkyne to Au-C bond affords intermediate **IM7** *via* transition state **TS2'** with a free energy barrier of 17.2 kcal/mol. The transition state **TS2'** is 6.1 kcal/mol more favourable than the **TS2**. In the next step, a *cis-trans* isomerization occurs to furnish intermediate **IM8** which requires a free energy of 8.3 kcal/mol. Subsequently, **IM8** undergoes C-H auration *via* **TS4** involving counterion-assisted deprotonation to produce a highly exergonic intermediate **IM9** (-47.4 kcal/mol). Finally, reductive elimination from **IM9** affords desired product **3a** *via* transition state **TS5** with a free energy barrier of 5 kcal/mol relative to **IM9**. Comparison of the energy profile associated with the π-activation *vs* migratory insertion pathways suggest that **TS2** is associated with barrier of 23.3 and **TS4** is associated with barrier of 50.8 kcal/mol relative to **IM2**. Similarly, in the reductive elimination step, transition state **TS5** is associated with a barrier of 5 kcal/mol relative to **IM9**, the effective barrier height is estimated to be 13.4 kcal/mol relative to **IM6**. These results strongly support that an oxidative addition/π-activation pathway is preferred over the complementary migratory insertion/*cis-trans* isomerisation mechanism.

In summary, the first 1,2-dicarbofunctionalization reaction of alkynes using organohalides was achieved in the realm of gold catalysis. This method has also been applied for the oxyarylation of alkynes. The mechanism of the reaction is investigated using control experiments, mass, NMR and DFT studies suggesting that oxidative addition/π-activation pathway is preferred over the migratory insertion/*cis-trans* isomerization pathway which is commonly observed with other transition metals. We believe that this work is of great significance to the underdeveloped area of transition metal-catalyzed *anti*-selective 1,2-difunctionalization of alkynes. Considering the vast reactivity profile of alkynes in gold catalysis,[10] the successful realization of this mechanistic paradigm is expected to open up new avenues of alkyne functionalizations using organohalides as non-prefunctionalized coupling partners.

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