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Bifunctional Biphenyl-2-ylphosphine Ligand Enables Tandem Gold-Catalyzed Propargylation of Aldehyde and Unexpected Cycloisomerization

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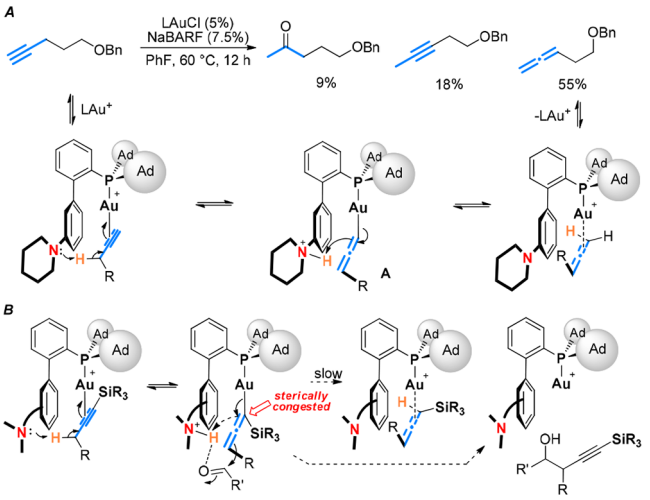
Supporting Information

ABSTRACT: Despite extensive studies in gold catalysis, σ-allenylgold species have not been invoked as catalytic intermediates and their reactivities not studied. This work reports for the first time they are generated in situ and undergo nucleophilic addition to activated aldehydes in a bifunctional phosphine ligand-enabled gold catalysis. This development reveals a broad range of opportunities to achieve propargylic C−H functionalization for the first time under catalytic and mild conditions. The homopropargylic alcohols generated undergo ligand-enabled cycloisomerizations involving an unexpected silyl migration.

The recent exponential development of homogeneous gold catalysis[1] has led to the proposals of a diverse range of organogold species as catalytic reaction intermediates, including alkylgold, alkenylgold, alkynylgold, gold carbene/carbenoid, gold vinylidene, gold alkyne/alkene/allene complexes, and etc., and in special circumstances their isolations and characterizations.[2] σ-Allenylgold species, however, were only recently characterized,[3] and, moreover, their preparations were not catalytically relevant and their reactivities were not studied. To date, this class of potentially versatile organogold species is conspicuously missing in catalysis, except our recent work where they promptly undergo protodeauration (*vide infra*).[4] Studying its completely unexplored reactivities beyond protonation[4] in catalytic settings should dramatically enrich gold catalysis and, moreover, the chemistry of σ-allenylmetals.[5]

Our lab has devoted much effort lately to the development of designed biphenyl-2-ylphosphine ligands[4,6] featuring a remote basic functional group, such as an amide,[6c−f] an aniline,[4a] or a tertiary amine,[4b,6a,b] and the application of them in the discovery of highly efficient or unprecedented gold catalysis. In our early work on soft propargylic deprotonation,[4a] we proposed the isomerization of an alkyne to an allene via an in situ generated σ-allenylgold (i.e., **A**, Scheme 1A). DFT calcuations corrobrate such an intermediate and its subsequent protodeauration step.[7] Nucleophilic σ-allenylmetal species[5] are typically generated or employed in stoichiometric fashion in propargylation reactions. We are not aware of prior studies where such an intermediate is generated and reacted catalytically. Our previous attempts, however, to coerse **A** toward far more interesting reactions with electrophiles other than a proton were all thwarted by the facile internal protonation. Eventually, a related study prompted us to examine terminally silylated alkynes as substrates. As shown in Scheme 1B, the silyl group, despite its steric bulk, should electronically facilitate the propargylic deprotonation, as it could stabilize partial positive charge development at its β-C(sp) (i.e., β-silicon effect); moreover, the corresponding allenylgold intermediate, if generated, should undergo *ipso*-protodeauration much more slowly due to the steric hindrance posed by the bulky silyl group. A competitive reaction with electrophiles such as aldehydes would then be achieved, affording valuable homopargylic alcohol products. This strategy enables catalytic propargylic C−H functionalization, which has been seldom documented.[4] Herein, we disclose a premilinary implementation of this design.

Scheme 1. Our Prior Results and Design



As shown in Table 1, we chose the TBS-terminated 3-phenylprop-1-yne (**1a**) as the substrate and 4-nitrobenzaldehyde (**2a**) as the electrophile for reaction discovery and optimization. Extensive exploration of ligands and reaction conditions revealed that the optimal reaction conditions are **L1**AuCl (5 mol %), $NaBAr^F_4$ (20 mol %), DCE, 18 h, 90 °C. As shown in entry 1, under these reaction conditions, a nearly full conversion of **1a** was achieved, but the desired

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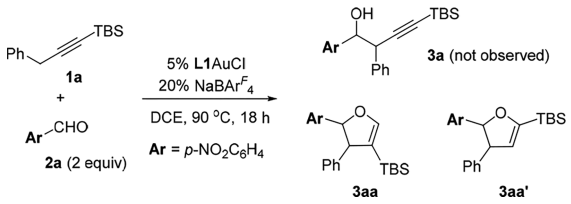
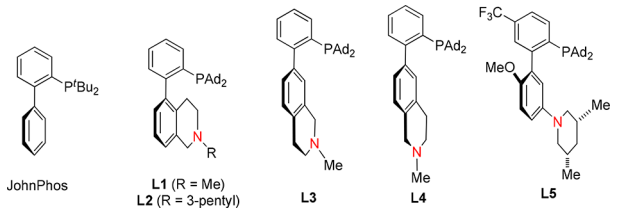
Table 1. Conditions Optimization[a]



entry	deviation from the optimized conditions	conversion[b]	3aa yield (%)[b]
1	–	92	78 (*dr* 3/1)[c,d]
2	JohnPhos as Au ligand	<5	0
3	JohnPhos as Au ligand, 10% Et_3N	<5	<5
4	**L2** as Au ligand	30	15
5	**L3** as Au ligand	<10	<5
6	**L4** as Au ligand	<10	<5
7	**L5** as Au ligand	<5	<5
8	$AgNTf_2$ instead of NaBAr$^F_4$	<5	<5
9	AgOTf instead of NaBAr$^F_4$	<5	<5
10	10 mol % of NaBAr$^F_4$ was used	85	72
11	$PhCF_3$ as solvent	40	12
12	THF as solvent	62	52

[a]The initial [**1a**] = 0.1 M. [b]Determined by ^{1}H NMR. [c]**3aa**/**3aa′** > 30:1. [d]Isolated yield.



homopropargylic alcohol product **3a** was not observed. Instead, the cyclized dihydrofuran **3aa** was formed in 78% yield in a *cis*/*trans* ratio of 3/1. To our surprise, there is an apparent 1,2-silyl migration[8] in **3aa** as the anticipated cyclization product **3aa′** was barely detectable. The structural assignment of **3aa** is corroborated by the X-ray diffraction study of one of its homologues (see Figure 1, *vide infra*).

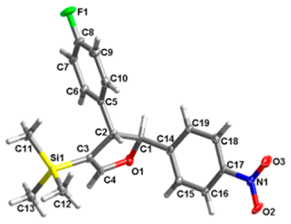


Figure 1. X-ray structure of *trans*-**3ma**.

Subsequent catalyst screenings revealed that the use of the precatalyst JohnPhosAuCl resulted in no product, while only trace **3aa** (<5% yield) was detected in the presence of 10% Et_3N (entries 2–3). Other typical gold catalysts are similarly ineffective. Additional tertiary amine-functionalized ligands[6b] such as **L2** (entry 4), **L3** (entry 5), **L4** (entry 6),[6c] and the aniline-based ligand **L5** (entry 7)[4a] that we previously developed were also examined. It was found that only the bulkier homologue of **L1**, i.e., **L2**, could notably promote the transformation, albeit in a much slower and less efficient manner, resulting in a poor yield. These results highlight the critical importance of an optimally positioned ligand remote basic group in this catalysis. Further studies indicated that NaBAr$^F_4$ is essential as the chloride abstractor. With AgOTf or $AgNTf_2$ instead, only trace product was observed (entries 8–9). A lower 10% of NaBAr$^F_4$ led to a slower reaction (entry 10). It was also found that the solvent DCE was optimal as $PhCF_3$ and THF led to much slower reactions and the former a lower yield based on conversion (entries 11–12).

Other silyl protecting groups were also examined. As shown in Table 2, the much smaller TMS group led to an excellent yield but a low preference for the product with silyl migration (entry 1). As the silyl group possesses increasing steric bulk in entries 2–4, the reaction became slower and less efficient, but in entries 2–3, it became more regioselective. On the other hand, bulky Ph_3Si (entry 5) and TIPS (entry 6) mostly shut down the reaction.

With the optimized reaction conditions in hand, we set out to first investigate the scope of the aldehyde. Our initial probing revealed that benzaldehyde and aliphatic aldehydes did not participate in the reaction due to their moderate electrophilicity. To this end, we turned to benzaldehydes bearing other EWGs besides *p*-NO_2. As summarized in Table 3, less electron-withdrawing SO_2Me, CO_2Me, and even CN at the *para* position worked well to yield the desired dihydrofurans **3ab**, **3ac**, and **3ad** in 79%, 69%, and 66% yields, respectively. Inductively withdrawing CF_3 groups at the *meta*-positions of benzaldehyde also enabled the reaction, and **3ae** was formed in a moderate yield. A NO_2 group at the *ortho*-position was also allowed, but the product regioisomeric ratio is only 3:1. Besides EWG-substituted benzaldehydes, 6-bromopicolinaldehyde and ethyl glyoxylate also reacted smoothly to furnish **3ag** and **3ah** in 95% and 76% yield, respectively.

Next, the scope of the silylated alkynes was examined. As summarized in Table 4, substituents of varying electronic and steric characteristics were generally allowed at the phenyl group of **1a**, leading to products **3ha**–**3qa** in moderate to excellent yields. Notably, the severe steric hindrance posed by an *ortho*-Ph group in the case of **3ra** mostly inhibits the reaction with TBS as the silyl group, but the smaller TMS led to a serviceable 49% yield of **3qa**. In the case of a *para*-fluoro group, the *cis*/*trans* isomers of the TMS-lated product **3ma** were separated, and the minor *trans*-**3ma** is crystalline. Its X-ray diffraction study (Figure 1) confirms the apparent silyl migration and corroborates our general structural assignments. Replacing the phenyl group of **1a** with other heterocycles, including 2-naphthyl (**3sa**) and 3-thienyl (**3ta**), was also successful, but not in the case of an 3-indolyl (**3ua**). To substantially expand the scope, we also examined alkenyl groups in place of the **1a** aryl group. With a cyclohexen-1-yl group, the skipped enyne substrate completely isomerized to its conjugated enyne isomer, and the desired dihydrofuran could not be observed. However, with 2-methylprop-1-en-1-yl and *β*-styryl, such isomerizations are slowed due to steric hindrance and electric delocalization, respectively. As such, the dihydrofuran products **3wa** and **3xa** were formed in fair to good yields. On the other hand, replacing the **1a** phenyl with an alkyl group resulted in no reaction at this point.

To shed light to the reaction mechanism, we performed several studies. First, **1a** was allowed to react with 20 equiv of D_2O under the standard reaction conditions (eq 1). >85% of deuterium labeling was detected at the propargylic methylene, revealing reversible deprotonation/protonation at the site and hence corroborating an allenylgold intermediate. Notably, only

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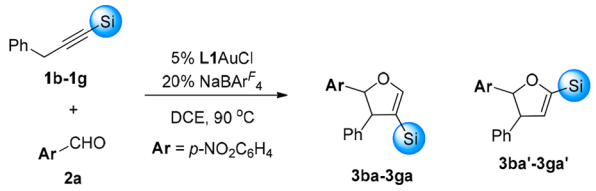
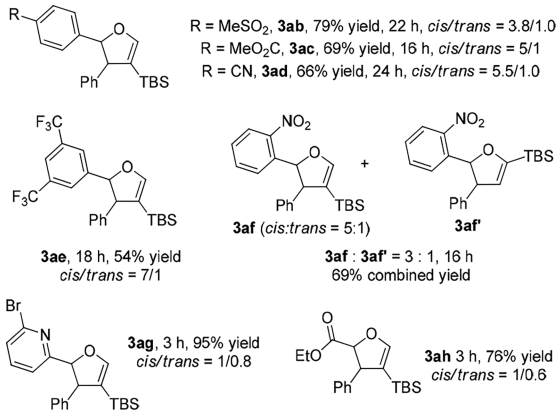
Table 2. Varying the Silyl Group[a]



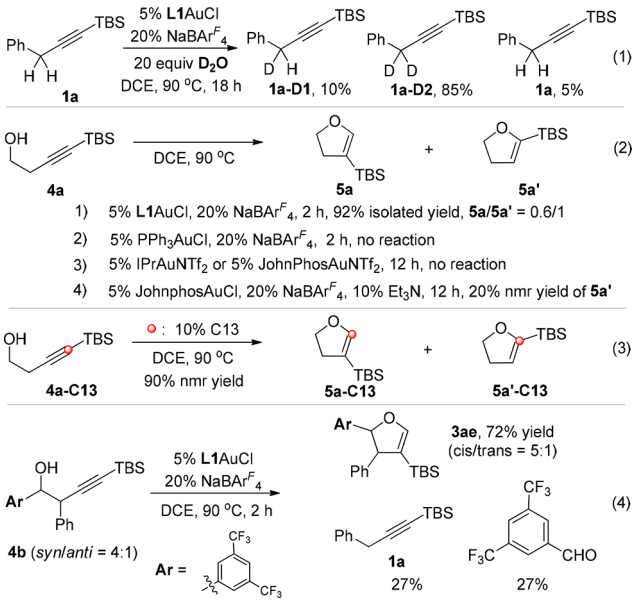
entry	substrate	silyl group	reaction time	NMR yield[b]	regioselectivity[c]	*cis/trans*
1	**1b**	TMS	3 h	92%	5:1	2.5:1
2	**1c**	$PhMe_2Si$	8 h	86%	14:1	2.4:1
3	**1d**	Ph_2MeSi	16 h	76%	20:1	2.2:1
4	**1e**	Et_3Si	12 h	77%	4:1	4.0:1
5	**1f**	Ph_3Si	24 h	<10%	–	
6	**1g**	TIPS	24 h	<10%	–	

[a]The initial [**1a**] = 0.1 M. [b]Of all dihydrofuran products. [c]The ratio of the silyl-migrated product vs the silyl-unmigrated product.

Table 3. Scope of the Aldehyde with 1a as the Alkyne Partner[a]

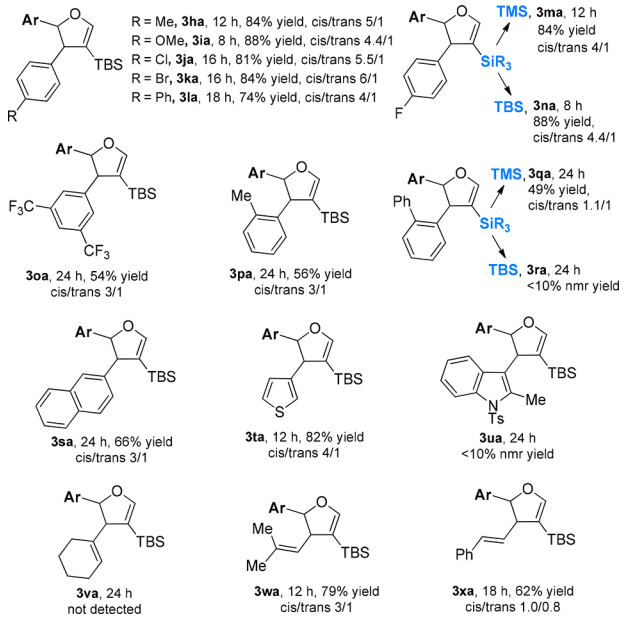


[a]The initial [**1a**] = 0.1 M. The ratio of the silyl-migrated product vs the silyl-unmigrated product is mostly >30:1 unless specified.



7% deuterium labeling occurred with JohnPhos as ligand and in the presence of 10% Et_3N. Second, the TBS-terminated parent homopropargylic alcohol **4a**, which differs from the putative alcoholic reaction intermediate by the absence of any

Table 4. Scope of Silylated Alkynes with 2a as Electrophile (Ar = *p*-Nitrophenyl)[a]



[a]Standard reaction conditions employed. Mostly >30:1 ratio of the silyl-migrated product vs the silyl-unmigrated product.

chain substituent, was subjected to gold catalysis (eq 2). With **L1** as the ligand, the cyclization and, moreover, the apparent silyl migration did occur. In contrast, with Ph_3P, IPr, or JohnPhos as the ligand, there was no reaction, revealing that the remote amino group also plays a critical role in enabling the cyclization step. When 10 mol % of Et_3N was added to the JohnPhos reaction, a 20% yield was observed, but the reaction was sluggish (12 h, ~20% conversion). With C13 labeling of the TBS-substituted C(sp) of **4a**, no carbon skeleton rearrangement was detected (eq 3), which confirms a silyl migration. Lastly, the putative propargylic alcohol intermediate **4b** en route to **3ae** was prepared with a *syn*/*anti* ratio of 4:1 and subjected to the standard reaction conditions (eq 4). Not surprisingly, **3ae** was indeed formed, which corroborates the general intermediacy of homopropargylic alcohols in this chemistry. What surprised us is that at the end of 2 h, **1a** and 3,5-di(trifluoromethyl)benzaldehyde were formed in 27% yield each. This suggests that the nucleophilic attack of allenylgold

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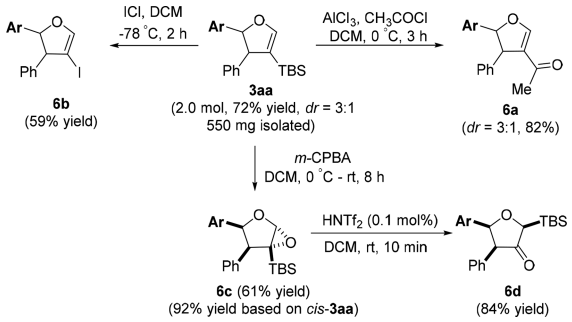
to aldehyde is reversible under gold catalysis. This reasoning is also consistent with the 5:1 *cis*/*trans* ratio of **3ae** observed in this experiment, which falls between the expected ratio of 4:1 if there were no reversion and the 7:1 ratio reported in Table 3.

Based on these studies, the first phase of the reaction resulting in the formation of a homopropargylic alcohol should follow what we initially designed (see Scheme 1B), where the tertiary amine-functionalized phosphine ligand **L1** is essential for the success; moreover, the gold catalysis appears to be reversible. The subsequent cyclization is again enabled by the bifunctional ligand and involves an unexpected silyl migration.[8a,b] Its mechanism is currently examined by DFT calculations and will be disclosed in future. Notably, the cyclization also serves to drive the reaction to completion.

Synthetic transformations of these dihydrofurans were then explored by using **3aa** as the substrate, which was prepared in a 2-mol scale without any issue (Scheme 2). For example, **3aa**

Scheme 2. Synthetic Applications (Ar = *p*-NO_2Ph)



was acylated smoothly with acetyl chloride to produce the cyclic β-alkoxyenone **6a** in 82% yield,[9] and treatment of **3aa** with ICl afforded the 3-iododihydrofuran **6b** in 59% yield.[8a] Interestingly, the reaction of **3aa** with *m*-CPBA allowed clean isolation of the epoxide **6c** as a single diastereomer in 61% yield. The yield was 92% based on the *cis* substrate. As low as 0.1 mol % of triflimide was sufficient to catalyze an efficient isomerization of **6c** to the dihydrofuranone **6d** with exquisite all *cis* relative stereochemistry in 84% yield.[10]

In summary, we have for the first time realized the reactions of in situ generated, catalytic σ-allenylmetal species with nonproton electrophiles. The homopropargylic alcohol thus generated undergoes cycloisomerization to deliver dihydrofurans with unexpected silyl migration. Our designed bifunctional biphenyl-2-ylphosphine ligand featuring a remote tertiary amino group is critical for the success of both processes, as typical ligands are completely incapable or far inferior. This work is of high significance as (a) it opens vast opportunities to achieve unprecedented catalytic propargylic C−H functionalization, (b) the potential of realizing these reactions asymmetrically by using chiral bifunctional ligands would be of exceptional synthetic values, and (c) the reaction of TBS-terminated alkynes should inspire increasing studies of their seldom studied gold chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b12478.

General information, preparation of silylated alkynes, synthesis of dihydrofuran, X-ray of **3ma**, mechanism studies, transformation of the product, NMR spectra (PDF)

Crystallographic data for **3ma** (CIF)

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Notes

The authors declare no competing financial interest.

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