OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Gold-Catalyzed Silyl-Migrative Cyclization of Homopropargylic Alcohols Enabled by Bifunctional Biphenyl-2-ylphosphine and DFT Studies

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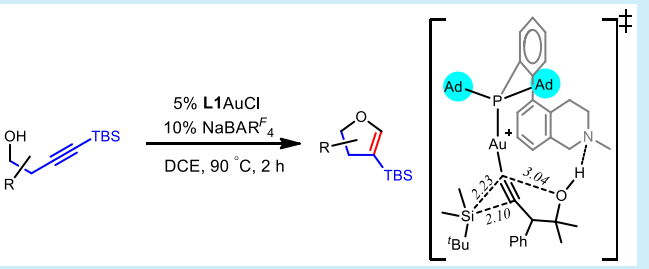
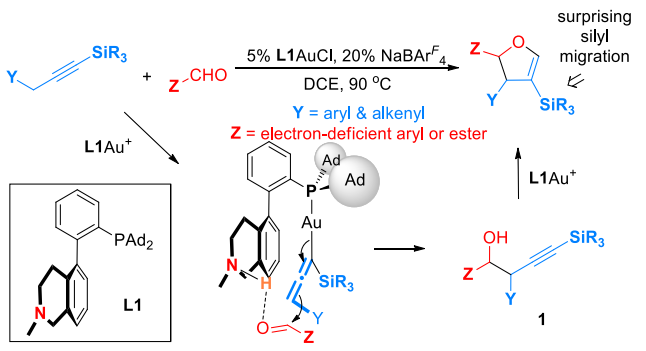
Supporting Information

ABSTRACT: The development of novel ligands specifically tailored for homogeneous gold catalysis permits the development of new gold catalysis. In this work, we report that a remotely functionalized biphenyl-2-ylphosphine ligand enables gold-catalyzed cyclization of homopropargylic alcohols accompanied by an unusual silyl migration, which provides efficient access to 3-silyl-4,5-dihydrofurans. DFT studies of the mechanism of this novel transformation suggest the synergy between the steric bulk of the ligand and its properly positioned remote tertiary amino group in facilitating a concerted silyl migration and cyclative C−O bond formation step.



Recently, we reported the development of designed biphenyl-2-ylphosphine ligands[1] featuring a remote basic functional group for homogeneous gold catalysis.[2] These ligands possessing an amide,[1b,e,f] an aniline,[1d] or a tertiary amine[1a,c] can dramatically accelerate gold catalysis or enable reactions that could not be achieved in the presence of typical phosphine or NHC ligands. A recent study of ours[1g] details the in situ generation of σ-allenylgold species[3] and their nucleophilic reactions with activated aldehydes (Scheme 1).[1g] This reaction could not be achieved with other gold ligands and represents for the first time the catalytic deprotonative generation of nucleophilic σ-allenylmetal species. The anticipated homopropargylic alcohol products further undergo cyclization to deliver 4,5-dihydrofuran products. To our surprise, there is an apparent silyl migration[4] in the cyclization step that has limited precedents.[5] It is important to understand the underpinning mechanism and, moreover, the role, if any, of the bifunctional phosphine ligand in such an unusual migration. In this work, we report a much broader scope of this cyclization by directly employing silylated homopropargylic alcohol substrates and reveal via DFT calculations the essential roles of the steric bulk and the properly positioned remote tertiary amino group of the bifunctional phosphine ligand in facilitating a concerted silyl migration and cyclative C−O bond formation step.

Scheme 1. Our Previous Work on the Reaction of Catalytically Generated σ-Allenylgold Intermediates



The scope of the homopropargylic alcohol **1** in our previous work is limited by the prerequisite of its in situ generation, i.e., the gold-catalyzed propargylation of aldehyde, which has to be activated by the presence of an electron-deficient aryl or an ester group and the alkyne propargylic position must be substituted with a π system (Scheme 1). Moreover, these alcohol intermediates were generated with low to moderate *syn*/*anti* selectivities, which in turn led to mixtures of product diastereomers. With homopropargylic alcohols generated from conventional methods and their *syn*/*anti* isomers potentially separable, we could probe the generality of this surprising silyl-migrating cyclization and develop a general approach to 3-silylated 4,5-dihydrofurans with excellent stereochemistry

Received: August 3, 2019

DOI: 10.1021/acs.orglett.9b02735
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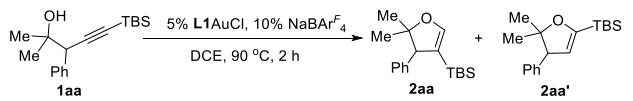
control. This type of dihydrofurans, however, has only been accessed via the reaction of allenylsilanes in a limited scope.[6,7]

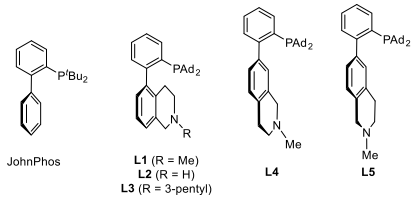
Initially, we examined the reaction by using **1aa** as the substrate. It could not be generated using our previously reported σ-allenylgold chemistry but was prepared in 90% yield from deprotonated TBS-terminated 3-phenylprop-1-yne and acetone.[8] The optimal conditions of the cyclization entail **L1**AuCl (5 mol %), $NaBAr^F_4$ (10 mol %), DCE as the solvent, 90 °C, and 2 h. Under these conditions, the desired silyl-migrated 4,5-dihydrofuran product **2aa** was formed in 92% isolated yield while the nonmigrated counterpart **2aa′** was barely detectable (Table 1, entry 1). Not to our surprise, in the

Table 1. Conditions Optimization[a]



entry	deviation from the optimized conditions	conversion[b] (%)	2aa yield (2aa/2aa′)[b]
1	none	>99	92 (>50/1)[c]
2	JohnPhos as Au ligand	0	0
3	JohnPhos as Au ligand, 10% Et_3N	<20	15 (0/1)
4	**L2** as Au ligand	>99	55% (<1/10)
5	**L3** as Au ligand	30	20% (>50/1)
6	**L4** as Au ligand	<10	<5
7	**L5** as Au ligand	<10	<5
8	$AgNTf_2$ instead of $NaBAr^F_4$	<5	<5
9	AgOTf instead of $NaBAr^F_4$	<5	<5
10	20 °C and 48 h	85	72 (>50/1)
11	$PhCF_3$ as solvent	62	52 (>50/1)
12	THF as solvent	57	50 (>50/1)

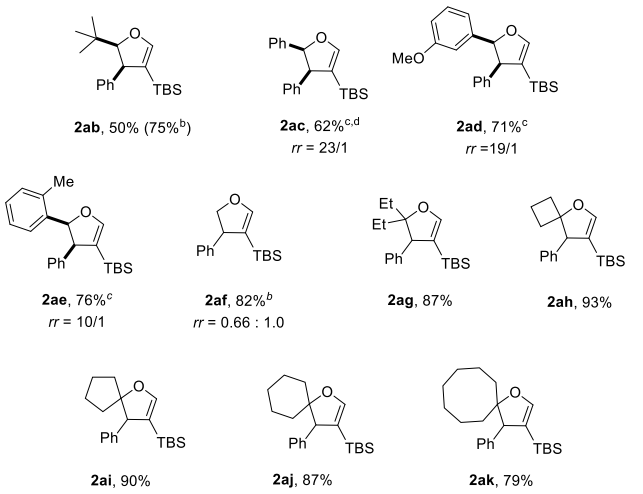
[a]All reactions were run in sealed vials with the initial [**1a**] = 0.1 M. DCE = 1,2-dichloroethane. [b]Isolated yield. [c]Determined by ^1H NMR.



absence of the ligand remote amino group, the related biphenyl-2-ylphosphine JohnPhos led to no reaction, while 15% yield of the nonmigrated **2aa′**[5] was formed when 10 mol % of Et_3N was added (entries 2 and 3). The congener of **L1** featuring a sterically smaller secondary amine, i.e., **L2**, that could facilitate the cyclization to completion and with moderate efficiency (entry 4), but surprisingly, **2aa′** was favored by >10:1 over the silyl-migrated product **2aa**. The much bulkier congener **L3** with a 3-pentyl group at the remote nitrogen[1a] led to a much slower reaction, although the silyl group regioselectivity was similar to that of **L1** (entry 5). These results reveal the role of ligand steric bulk in promoting the silyl migration. Other bifunctional ligands[1a] with the tertiary amino moiety positioned differently from **L1**, such as **L4** (entry 6) and **L5** (entry 7), were mostly ineffective, reflecting the critical importance of a properly positioned ligand remote basic group in this catalysis. Further studies indicated that $NaBAR^F_4$ is essential as the chloride abstractor. With $AgNTf_2$ or AgOTf instead, only trace product could be observed (entries 8 and 9). It was also found that a slower reaction could be observed when it was performed at room temperature (entry 10). The solvent DCE was optimal for the transformation as $PhCF_3$, and THF led to much slower reactions (entries 11 and 12).

With the optimized conditions in hand, we next examined the reaction scope. First, the substrates prepared from *tert*-butyldimethyl(3-phenylprop-1-yn-1-yl)silane and various aldehydes were studied. As shown in Scheme 2, the dihydrofuran

Scheme 2. Reaction Scope with Substrates Derived from *tert*-Butyldimethyl(3-phenylprop-1-yn-1-yl)silane[a]



[a]Reactions run in vials; the substrate initial concentration was 0.1 M; isolated yields are reported. The ratio of the silyl-migrated product vs the silyl-unmigrated product is mostly >50:1 unless otherwise noted as the rr (regioisomeric ratio) value. [b]Yield based on the portion of the *syn*-substrate used (67%). [c]*Syn*-substrate used. [d]The reaction was performed at 60 °C for 4 h.

products **2ab**−**2af** were formed smoothly in moderate to good yields. It is worth noting that low silyl regioselectivity was observed in the case of **2af**, where the substrate is a primary alcohol. In the cases of **2ac**−**2ae**, the *syn*-homopropargylic alcohol substrates were readily prepared pure. Consequently, the *cis*-products were obtained. The substrates derived from various ketones reacted with high efficiencies, affording **2ah**−**2ak** in mostly >80% yields.

Next, the scope of the substrates prepared from various silylated alkynes was examined. As shown in Scheme 3, dihydrofuran products **2ba**−**2ga** with various substituted phenyl groups at C4 were isolated in moderate to good yields. Other π-systems such as 2-naphthyl (**2ha**), 2-thiophene-yl (**2ia**), and alkenyl (**2ja** and **2ka**) are readily allowed at the 4-position. To substantially expand the scope, we also examined reactions employing substrates prepared from aliphatic alkynes. The products **2la** and **2ma** possessing a nonfunctionalized and an oxygenated alkyl group at the 4-position, respectively, were formed in good yields. Moreover, the 4,5-dihydrofurans without such a substitution such as **2o** and **2p** were accessed without event. Unlike the other cases where the silyl regioselectivities are >50:1, the selectivities are 10/1 in the case of **2o** and an even worse 4:1 in the case of **2p**. The poor regioselectivities in these cases and that of **2af** revealed a positive correlation between substrate steric congestion and the preference for silyl migration. The reaction can also be run on a 2 mmol scale without event. As shown in eq 1, **2aa** was isolated in 495 mg and 86% yield.

DOI: 10.1021/acs.orglett.9b02735
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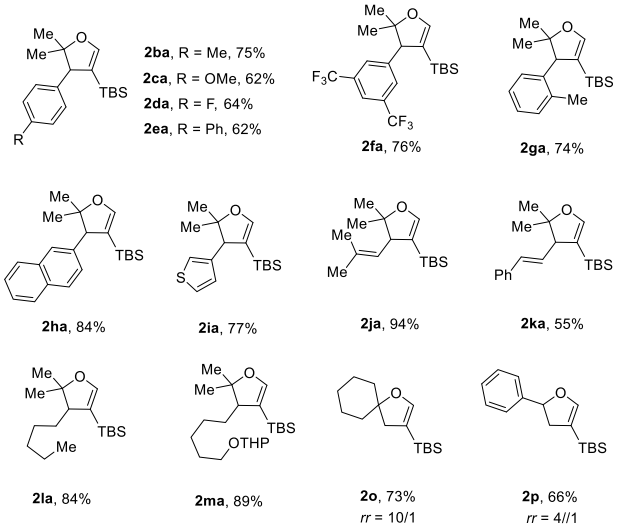
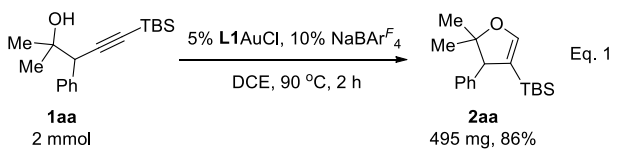
Scheme 3. Reaction Scope with Substrates Prepared from Various Silylated Alkynes[a]



[a]Reactions run in vials; [1] = 0.1 M; isolated yields are reported; the ratio of the silyl-migrated product vs the silyl-unmigrated product is mostly >50:1 unless otherwise noted.



To understand the unexpected 1,2-silyl migration in this cyclization reaction and to elucidate the impact of substrate steric bulk on product regioselectivity and the essential role of the ligand **L1** in the reaction, DFT calculations were performed, and the energy profiles are shown in Figure 1. Initially, the substrate **1aa** and the catalyst **L1**Au$^+$ form a complex with two conformations, i.e., **INT1** and **INT1′**, via the coordination of the C≡C of **1aa** with Au(I) in two different orientations. For **INT1**, an H-bonding interaction between the hydroxyl group of **1aa** and the amino moiety of **L1** ligand (O−H···N) is formed to stabilize the complex. Remarkably, the Si−C1−C2 angle of 137° in **INT1** significantly deviates from linearity in **1aa** due to the pronounced steric congestion between one of the bulky Ad groups of **L1** and the TBS group of **1aa**. For **INT1′**, such steric crowdedness is less significant, which is reflected is less significant, which is reflected by the less distorted angle of the Si−C1−C2 angle of **1aa** (163°); on the other hand, the stabilizing O−H···N H-bond interaction is absent in this complex. Computational results show that **INT1** and **INT1′** are very close in energy, suggesting that both of these conformers are possible. From **INT1**, driven by the steric repulsive interaction between the Ad group and the TBS group, a transition state (i.e., **TS1**) was located for the concerted cyclization, 1,2-silyl migration, and proton transfer to N of **L1**, in which the Si···C1 and Si···C2 distances are 2.23 and 2.10 Å, respectively, and the O···C1 distance is 3.04 Å. The predicted free energy barrier is 10.4 kcal/mol relative to **INT1**. This step affords the cyclized intermediate **INT5**. The involvement of a water molecule in the 1,2-silyl migration process (**TS2**) was also considered but unlikely as the energy barrier is 7 kcal/mol higher than that of **TS1**. Afterward, the protodeauration step via internal proton transfer (**TS3**) could occur to furnish the final product **2aa**. Alternatively, the Au(I)-catalyzed *5-endo* cyclization from **INT1′** was also considered, which leads to the formation of **2aa′**. The optimized TS was shown as **TS4**, in which the O···C1 distance is shortened to 2.03 Å. The Au(I)-

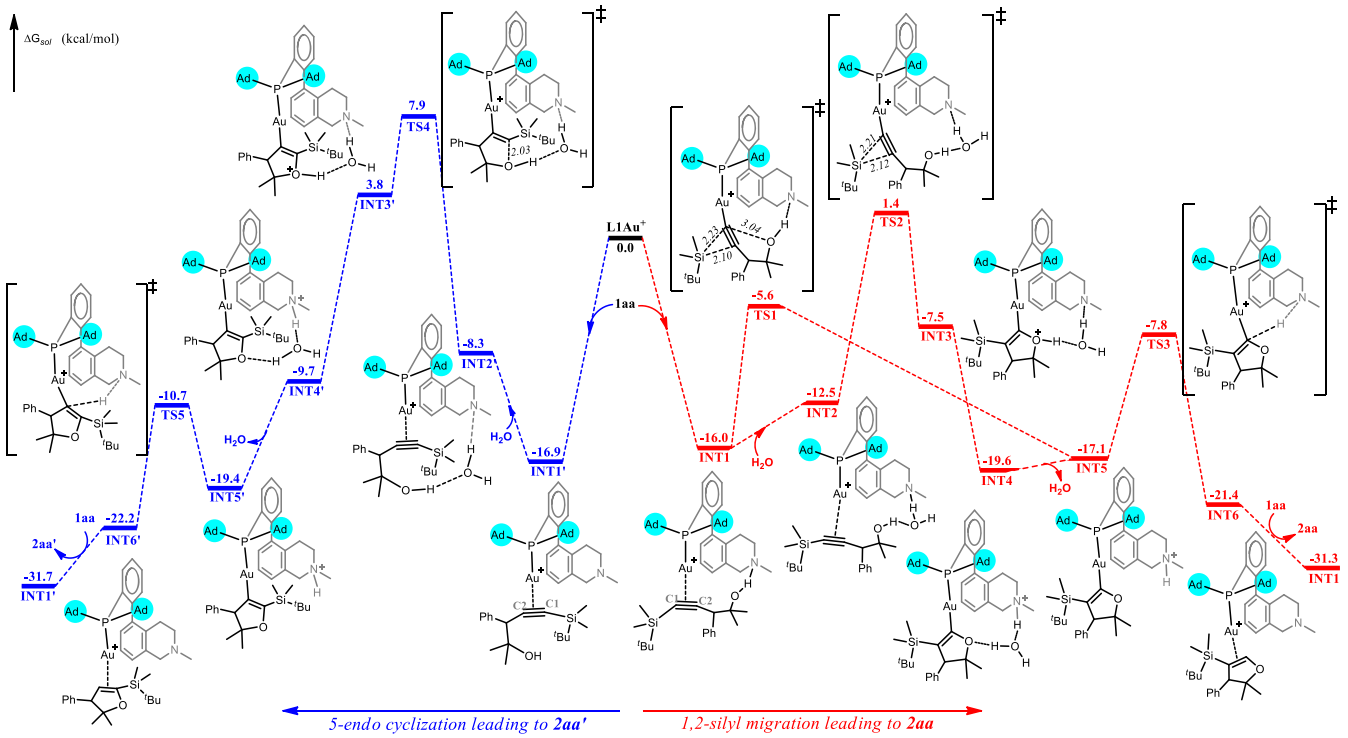


Figure 1. Energy profiles for the pathways of Au(I)-catalyzed 1,2-silyl group migration and *5-endo* cyclization of **1aa** leading to **2aa** and **2aa′**, respectively. Bond distances are shown in Å.

DOI: 10.1021/acs.orglett.9b02735
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catalyzed *5-endo* cyclization step is facilitated by a water molecule, which acts as a proton shuttle to assist proton transfer. The predicted energy barrier for this pathway is ca. 25 kcal/mol relative to **INT1′** and a separate water molecule, which is much higher than that of the 1,2-silyl migration pathway. Therefore, the computational results suggest that it is more favorable for **1aa** to undergo the 1,2-silyl migration to yield **2aa** driven in the presence of the **L1A**$^+$ catalyst. Both the bulky Ad group and the properly positioned tertiary amino moiety in **L1** appear to be essential for achieving **TS1** en route to this unusual Au(I)-catalyzed silyl-migrative cyclization. The substrate steric bulk likely exacerbates the steric clash between the Ad group and the TBS group in **INT1** and thus raises its energy level, thereby facilitating the 1,2-silyl migration.

In conclusion, we demonstrated in this work an expedient construction of 3-silyl-4,5-dihydrofurans from readily available homopropargylic alcohols with an unusual silyl migration. This transformation is enabled by a bifunctional phosphine ligand featuring a properly positioned remote tertiary amino group and a bulky diadamantylphosphinyl moiety. The 4,5-dihydrofuran products are formed typically in good to excellent yields and with mostly high selectivity toward the silyl migration products. The influence of substrate steric bulk on the 1,2-silyl migration is computationally revealed. DFT calculations suggest a novel concerted 1,2-silyl migration and *5-endo-dig* cyclization process that hinges on the synergy of the remote basic amino group and the steric bulk of the designed ligand for achieving a transition state of a moderate energy barrier.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02735.

Experimental procedures, characterization data for all products, NMR spectra, and DFT-optimized Cartesian coordinates and energies (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank NSF CHE 1800525 for financial support and NIH shared instrument grant S10OD012077 for the purchase of a 400 MHz NMR spectrometer. T.L. acknowledges financial support from the NSFC (21602120).

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(8) For details, see the Supporting Information.

DOI: 10.1021/acs.orglett.9b02735
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