Gold-Catalyzed Stereoselective Synthesis of Di- or Trisubstituted Olefins Possessing a 1,4-Diene Framework via Intramolecular Allylation of Alkynes

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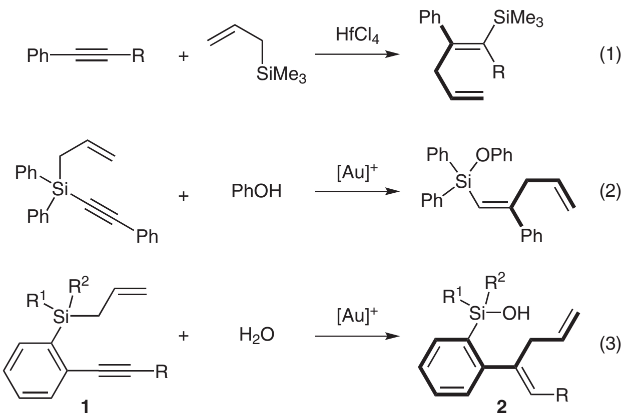
Abstract: The cationic gold(I)-catalyzed reaction of 1-alkynyl-2-allylsilylbenzenes with water results in intramolecular allylation of the alkynes via 7-*exo*-dig cyclization to give 1,4-dienes in good yield with excellent stereoselectivities.

Key words: catalysis, 1,4-dienes, allylation, allylsilanes, gold

The efficient regio- and stereoselective synthesis of trisubstituted olefins possessing a 1,4-diene framework, which constitutes an important structural assembly in many molecules of biological importance,[1] is a particular challenge in organic synthesis.[2] The addition of active allylmetal reagents to nonactivated alkynes is a well-recognized and straightforward method for this purpose.[3,4] However, although a number of transition-metal-catalyzed allylmetalations of alkynes have been reported, some of which allow for the regio- and stereoselective construction of trisubstituted olefins possessing a 1,4-diene framework, the allyl group is usually introduced in a position vicinal to the aryl group due to steric or electronic effects.

In contrast, little attention has been paid to the transition-metal-catalyzed allylsilylation of alkynes due to the relative stability of allylsilanes.[4–6] Thus, Yamamoto and Asao reported the aluminium- or hafnium-catalyzed *trans*-allylsilylation of nonactivated alkynes (Scheme 1, equation 1).[4b–4f] These methods allow the use of allylsilanes as the nucleophile and lead to the corresponding 1,4-diene efficiently in a different manner from the allylmetalation of alkynes with other active allylmetal reagents, where the allyl group is introduced at the geminal position to the aryl group. Furthermore, the recently developed acetylenic sila-Cope rearrangement[7] catalyzed by cationic gold complexes, which have emerged as powerful π-acids that are capable of promoting a diverse range of unsaturated carbon–carbon bonds,[8] has been also used to synthesize geometrically pure trisubstituted olefins possessing a 1,4-diene framework (Scheme 1, equation 2). However, the former reaction has several limitations as regards the introduction of functional groups, and stereoselectivity can be problematic with some substrates in the latter case.



Scheme 1

In light of the reported acetylenic sila-Cope rearrangement of alkynylallylsilane, we envisioned that a cationic gold(I) complex induced 7-*exo*-dig cyclization of 1-alkynyl-2-allylsilylbenzenes **1** would initiate a related allylation and provide a method for the stereoselective synthesis of trisubstituted *E*-olefins **2** possessing a 1,4-diene framework, where the allyl group is installed at the geminal position to the aryl group (Scheme 1, equation 3). To this end, we initially examined the intramolecular allylation of alkynes using 1-(1-hexynyl)-2-allyldimethylsilylbenzene (**1a**) in the presence of catalytic amounts of $(PPh_3)AuNTf_2$ and two equivalents of water in nitromethane as a solvent (Table 1, entry 1).[9,10] The reaction proceeded smoothly to give the desired 1,4-diene **2a**, which possesses a silanol functional group, in 20% isolated yield along with a significant amount of dimer **3**. Although changing the dimethylsilyl group of **1a** to a more sterically bulky group such as methyl(phenyl)silyl and diphenylsilyl group caused a noticeable elongation of reaction time,[11] dimerization of the resulting silanol was eliminated, and the desired products **2b** and **2c** were isolated in high yields, respectively (entries 2 and 3).[12] It was found that the use of nitromethane, which is known to be a cation stabilizing and Lewis acid activating solvent, was suitable for the present reaction (entries 3 and 4).[13] Among the several ligands tested, triphenylphosphine showed the best catalytic activity (entries 3–6). The use of $AgSbF_6$ as the silver reagent exhibited similar results to $AgNTf_2$ (entry 7), whereas changing the silver additive from $AgNTf_2$ to $AgBF_4$ resulted in prolonged reaction time and diminished yield of **2c** (entry 8). The use of other transition-

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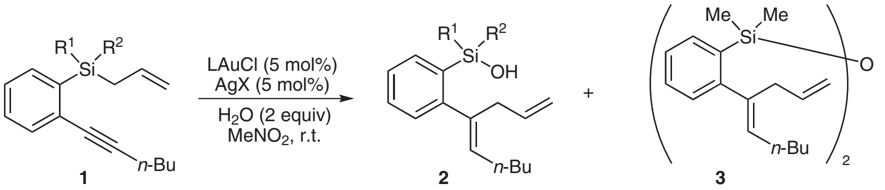
Table 1 Optimization of Reaction Conditions



Entry	L	X	**1**	R^1	R^2	Time	Yield of **2** (%)	Yield of **3** (%)
1	Ph_3P	NTf_2	**1a**	Me	Me	10 min	**2a** 20	69
2	Ph_3P	NTf_2	**1b**	Ph	Me	30 min	**2b** 71	
3	Ph_3P	NTf_2	**1c**	Ph	Ph	1 h	**2c** 88	
4[a]	Ph_3P	NTf_2	**1c**	Ph	Ph	10 h	**2c** trace	
5	t-Bu_3P	NTf_2	**1c**	Ph	Ph	1 h	**2c** 70	
6[b]	IPr[c]	NTf_2	**1c**	Ph	Ph	3 h	**2c** 63	
7	Ph_3P	SbF_6	**1c**	Ph	Ph	1 h	**2c** 81	
8	Ph_3P	BF_4	**1c**	Ph	Ph	10 h	**2c** 70	

[a] MeCN was used as a solvent.

[b] Run at 60 °C.

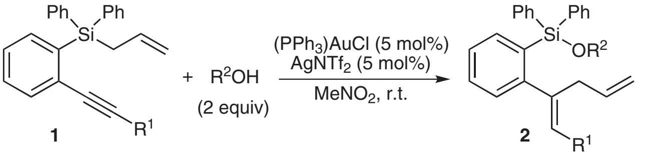
[c] IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.

metal catalysts proved unsuccessful.[14] In all cases, the stereochemistry of **2a**–**c** was determined to be *E* by NOE experiments.

Next, the substrate scope for this gold(I)-catalyzed intramolecular allylation of alkynes was examined (Table 2). We are pleased to find that the reaction is general for a variety of substituent R^1 on the acetylenic moiety of **1**, thus providing opportunities for further elaboration of the 1,4-diene **2**. Among them, the gold(I)-catalyzed allylation of alkynes possessing electron-withdrawing groups produced the desired 1,4-dienes **2** in better yield than when using terminal or alkyl-substituted alkynes as the electorophile (entries 1–5). It should be noted that homoallyl-substituted **1g**, which possesses a 1,5-enyne skeleton, gave selective formation of the desired 1,4-diene **2g** rather than the product of the competing 1,5-enyne cycloisomerization (entry 4).[15] As for the scope of the aryl containing substrate, both electron-donating and electron-withdrawing groups are also supported (entries 6–10). Furthermore, bromoalkyne moieties could be installed in the substituent to produce **2n** in moderate yield (entry 11).

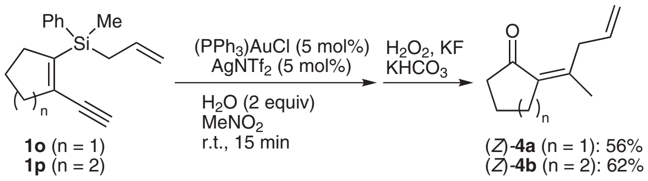
The aryl group on the molecular backbone is not essential for this reaction. For instance, switching the backbone from an aromatic skeleton to an aliphatic one does not affect the reaction notably. Indeed, treatment of **1o** and **1p** afforded the desired α-alkylidene cyclic ketones **4a** and **4b**, respectively, as a single isomer after treatment under Tamao–Fleming oxidation conditions (Scheme 2).[16] The stereochemistry of **4a** and **4b** was determined to be *Z* by NOE experiments.

Table 2 Gold-Catalyzed Intramolecular Allylation of Alkynes **1**



Entry	**1**	R^1	R^2	Time	Yield of **2** (%)
1	**1d**	H	H	1 h	**2d** 83
2	**1e**	Me	H	30 min	**2e** 76
3	**1f**	All	H	3 h	**2f** 75
4	**1g**	3-butenyl	H	3 h	**2g** 75
5	**1h**	CO_2Me	H	3 h	**2h** 93
6	**1i**	Ph	H	5 h	**2i** 70
7	**1j**	4-$MeO_2CC_6H_4$	H	30 min	**2j** 95
8[a]	**1k**	4-BrC_6H_4	H	3 h	**2k** 69
9	**1l**	2-BrC_6H_4	H	3 h	**2l** 70
10[a]	**1m**	2-$MeOC_6H_4$	H	1 h	**2m** 84
11	**1n**	Br	Me	3 h	**2n** 42

[a] Run at 60 °C.

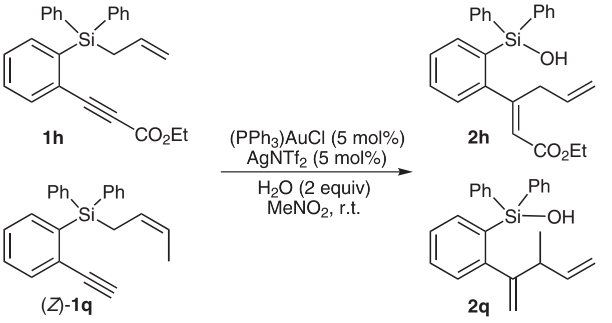


Scheme 2

A deuterium labeling study was performed with **1c** to confirm the reaction mechanism (Scheme 3). Under the conditions shown above, the gold(I)-catalyzed reaction of **1c** with D_2O (2 equiv) afforded (*E*)-**2c**-*d* in 83% isolated yield, which strongly supported the existence of vinylgold intermediate.[17]

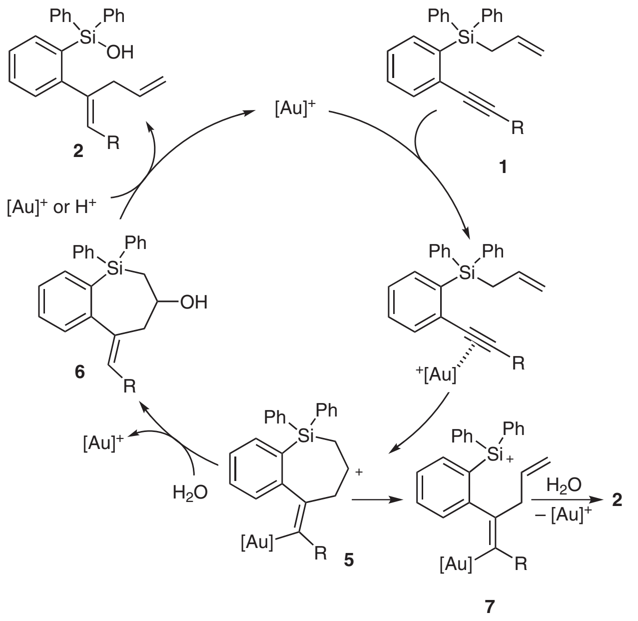
Scheme 3

Furthermore, no crossover products were detected by ^1H NMR spectroscopy in a crossover experiment performed under standard conditions with a 1:1 mixture of **1h** and (*Z*)**-1q** (Scheme 4), whereas the concerted products **2h** and **2q** were obtained in 60% and 61% isolated yield, respectively. This result strongly suggests that the present reaction proceeds intramolecularly.



Scheme 4

A mechanism proposed on the basis of these experiments is outlined in Scheme 5. Initial complexation of the cationic gold(I) complex to the alkyne moiety induces a 7-*exo*-dig intramolecular cyclization to form vinyl gold intermediate **5**, which undergoes either S_E2'-type reaction or Peterson olefination reaction via **6** to produce **2**. As one of the experimental evidence to support this hypothesis, the reaction of alternative intermediate of **6**, whose hydroxy group was replaced with methoxy group, in the presence of 5% of either Tf_2NH or $(PPh_3)AuNTf_2$ gave the corresponding desired product **2**.[18,19]



Scheme 5 Proposed catalytic cycle

In conclusion, we have developed a cationic gold(I)-catalyzed intramolecular allylation of alkynes for the stereoselective synthesis of di- or trisubstituted olefins possessing a 1,4-diene framework. Moreover, contrast to other methods, the present reaction enables the introduction of an allyl group at the position geminal to the aryl group in a regioselective manner. Further studies of this methodology in organic synthesis are under way.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(18) For details, see Supporting Information.

(19) Another interesting alternative mechanism for the formation of **2**, as suggested by one referee, involves initial formation of 3-allyl-1-silaindenes and their subsequent hydrolysis. Indeed, we have observed the formation of **2** from isolated 3-allyl-1-silaindenes under our reaction conditions. However, we were unable to detect such intermediates when monitoring the reaction of **1** by ^{1}H NMR spectroscopy (see Supporting Information for further details). Nevertheless, we would like to thank the referee for this suggestion.