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Gold-Catalyzed Hydrosilyloxylation Driving Tandem Aldol and Mannich Reactions

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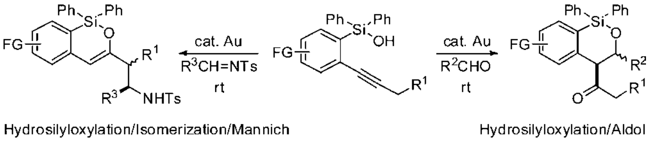
ABSTRACT



The chemoselective formation of an enolate from alkyne in the presence of a carbonyl and imine group was realized, which constructed a variety of structural motifs under exceedingly mild reaction conditions in a tandem process. Reaction driving tandem hydrosilyloxylation/aldol reactions was achieved through the formation of enol silyl ethers catalytically generated in situ from readily available alkynes. These reactions were expanded to obtain β-amino enol silyl ethers in good yields *via* the tandem hydrosilyloxylation/isomerization/Mannich reaction.

The aldol[1] and Mannich reactions[2] are well-recognized as two of the most important carbon–carbon bond-forming reactions in organic synthesis. Most of these processes critically depend on the activation of the aldehydes or ketones by converting them into enolates or their derivatives such as enol silyl ethers. Accordingly, synthetic methods based on this approach have been extensively investigated over the past decades.[3] In general, enolates and enols can be prepared from the corresponding carbonyl compounds by deprotonation with more than stoichiometric amounts of bases.[1]

However, this method is not compatible with sensitive functional groups that are commonly employed in organic synthesis. Therefore, enol silyl ethers and their derivatives must be prepared separately prior to the addition of certain electrophiles having sensitive functional groups in the next step. This indicates that the chemoselective formation of an enolate from one carbonyl group in the presence of another is highly challenging. We thus have long been interested in developing a synthetic method of enol silyl ethers and their derivatives from readily available non-carbonyl precursors without the use of bases.[4] To date, a variety of synthetic methods of enolates from alkynyl

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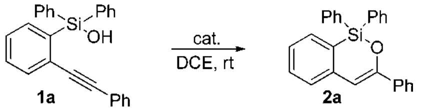
boronic acid,[5] allylic alkoxide,[6] allylic alcohols,[7] and vinyl metals[8] were reported.[9] An addition reaction of silanols to enynes to produce 1,3-silyloxydienes was reported.[10] Recently, Gaunt et al. reported a scandium-catalyzed tandem hydrosilyloxylation/aldol reaction with an activated alkyne.[11] We envisioned that an aldol or a Mannich reaction upon the catalytic formation of enol silyl ethers from alkynes would be an attractive tandem process[12] to give a variety of structural motifs. To the best of our knowledge, no example of a hydrosilyloxylation/aldol and hydrosilyloxylation/Mannich tandem process has been described, and encouraged by recent advances in tandem processes we decided to explore such a sequence. Herein, we report the Au-catalyzed[13] tandem hydrosilyloxylation/aldol and hydrosilyloxylation/Mannich reaction starting from readily available alkynes in one pot under extremely mild conditions.

To find out the most effective catalyst for the cyclization, an initial study was carried out with **1a** in DCE (Table 1) and a wide range of gold catalysts along with silver salts and protic acids were examined. A gold catalyst system of $(C_6F_5)_3PAuCl/AgOTf$ (1 mol % each) turned out to be the most effective to selectively provide an 6-*endo* addition product **2a** in 86% yield in DCE (0.25 M) at room temperature within 30 min without detection of a 5-*exo* addition product (entry 10). It is noteworthy that high dilution conditions are not necessary in the present intramolecular cyclization.[10,14] AgOTf and triflic acid (5 mol % each) were totally ineffective (entries 11 and 12). In addition, the effects of disubstituents tethered to silicon on cyclization were next examined. Under the optimized reaction conditions, the alkynyl silanol **1b** having a dimethyl group on the silicon atom was converted to an enol silyl ether **2b** in 58% yield along with disiloxane in 26% yield (eq 1). When an alkynyl silanol **1c** bearing a sterically bulky diisopropyl group on silicon was treated with the gold catalyst, the corresponding disiloxane was not observed as anticipated while the cyclization (**2c**, 60% yield) was not complete (eq 2).

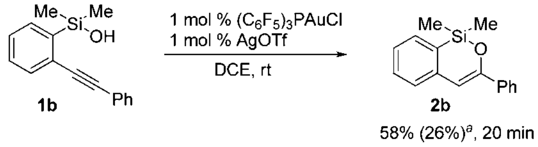
With this newly developed protocol in hand, we subsequently examined a variety of alkynyl silanols for the

Table 1. Optimization of Intramolecular Hydrosilyloxylation[a]

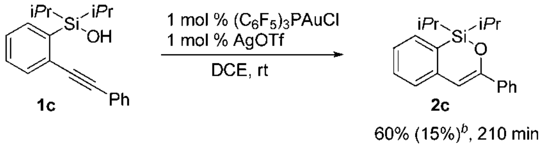


entry	cat. (mol %)	time (h)	yield (%)
1	$AuCl_3/AgOTf$	12	23[b]
2	$Ph_3PAuCl/AgOTf$	0.6	40
3	$Ph_3PAuCl/AgPF_6$	1	39
4	$Ph_3PAuCl/AgAsF_6$	0.3	36
5	$Ph_3PAuCl/AgSbF_6$	12	14 (66)[c]
6	$Ph_3PAuCl/AgBF_4$	12	13 (64)[c]
7	$Ph_3PAuCl/AgNTf_2$	2	57
8	$(C_6F_5)_3PAuCl/AgNTf_2$	0.5	43
9	$(C_6F_5)_3PAuCl/AgOTf$	0.17	88
10	$(C_6F_5)_3PAuCl/AgOTf$	0.5	86[d]
11	AgOTf	3	0[e]
12	TfOH	24	0[e]

[a] Au and Ag catalyst (5 mol % each) was used unless otherwise noted. [b] AgOTf (15 mol %) was used. [c] Recovery yield of **1a**. [d] $(C_6F_5)_3PAuCl$ (1 mol %) and AgOTf (1 mol %) were used. [e] AgOTf and TfOH (5 mol %) were used.



(1)



(2)

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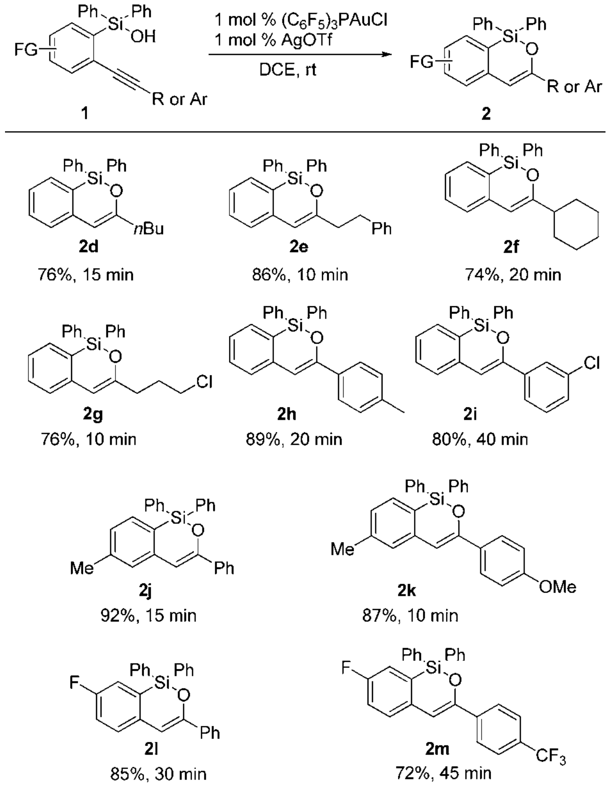
(14) In ref 10, an addition reaction of silanol to enyne was carried out under high dilution (0.05 M in fluorobenzene) conditions.

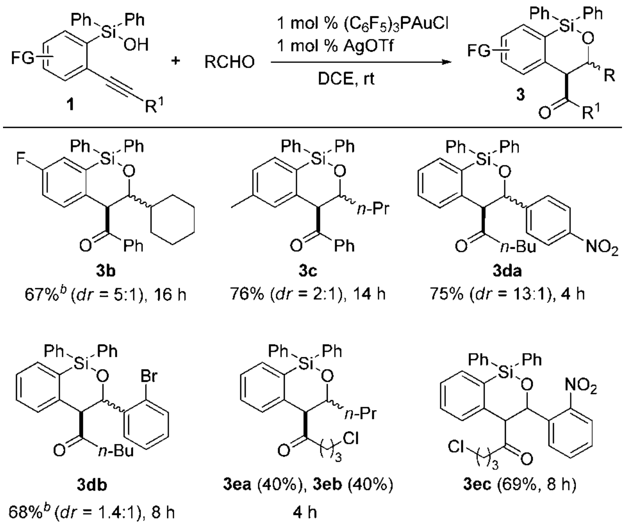
Scheme 1. Au-Catalyzed Intramolecular Hydrosilyloxylation



intramolecular hydrosilyloxylation (Scheme 1). Treatment of alkynyl silanols (**1d**, **1e**, **1f**, and **1g**) having various substituents such as butyl, phenethyl, cyclohexyl, and chloropropyl on *sp*-hybridized carbon with $(C_6F_5)_3$PAuCl/AgOTf (1 mol % each) provided the desired enol silyl ethers (74−86% yields) at room temperature within 20 min. 4-Methylphenyl and 3-chlorophenyl-substituted alkynyl silanols (**1h** and **1i**) were efficiently cyclized to afford enol silyl ethers (**2h** and **2i**) in 89% and 80% yields, respectively. Electronic variation (methyl and fluoride groups) on the phenyl ring possessing diphenylhydroxysilyl and alkynyl groups did not much influence the cyclization efficiency although a fluoride-substituted silanol (**1l** and **1m**) required a slightly longer reaction time.

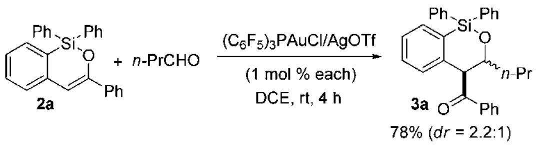
We first examined the gold-catalyzed aldol reaction of enol silyl ether with aldehyde to find reaction conditions that tolerate both the catalytic generation of enol silyl ether and the subsequent aldol reaction. When enol silyl ether **2a** was treated with butyraldehyde under the optimized reaction conditions, the corresponding aldol product **3a** was produced in 78% yield (*dr* = 2.2:1) in DCE at room temperature after 4 h (eq 3).[15] Encouraged by this result, a one-pot tandem hydrosilyloxylation and aldol reaction from alkyne and aldehyde was carefully investigated. Gratifyingly, treatment of alkynyl silanol **1a** and

Scheme 2. Au-Catalyzed Intramolecular Hydrosilyloxylation/Aldol Reaction[a]



[a] RCHO (2 equiv) was used. [b] $(C_6F_5)_3$PAuCl and AgOTf (5 mol % each) was used.

butyraldehyde with $(C_6F_5)_3$PAuCl/AgOTf (1 mol % each) in DCE (25 °C, 4 h) gave the aldol product **3a** in 76% yield (*dr* = 2.2:1) (eq 4). This indicates that the enolate was catalytically generated in situ from alkyne in the presence of aldehyde.



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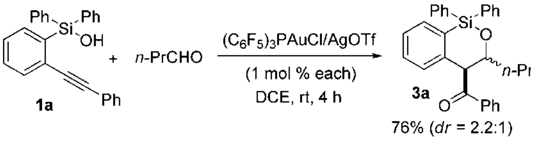

(4)

Next, we explored the gold-catalyzed tandem intramolecular hydrosilyloxylation and aldol reaction with a wide range of alkynes and aldehydes in one pot (Scheme 2). Fluorophenyl and methylphenyl silanol **1l** and **1j** having a phenylethynyl group underwent the tandem hydrosilyloxylation and aldol reaction to provide aldol products **3b** (67%, *dr* = 5:1) and **3c** (76%, *dr* = 2:1), respectively. Although a tandem reaction of silanol **1d** bearing hexyn-1-yl with 2-bromobenzaldehyde gave **3db** in 68% yield with moderate diastereoselectivity (*dr* = 1.4:1), 4-nitrobenzaldehyde gave **3da** in 75% yield with high diastereoselectivity (*dr* = 13:1). Under the optimized reaction conditions, 5-chloropentyn-1-yl-substituted silanol **1g** was also successfully subjected to the tandem intramolecular hydrosilyloxylation and aldol reaction with butyraldehyde, affording the desired aldol product **3ea** and **3eb** in 40% yields, respectively. When a tandem reaction was carried out with **1g** and 2-nitrobenzaldehyde, the desired aldol

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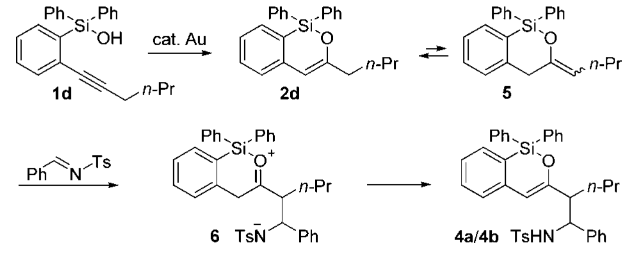
(15) Reaction of **2a** with butanal did not produce aldol product **3a** without a gold catalyst. Reaction of **2a** with butanal in the presence of AgOTf (10 mol %) and (separately) TfOH (10 mol %) did not proceed.

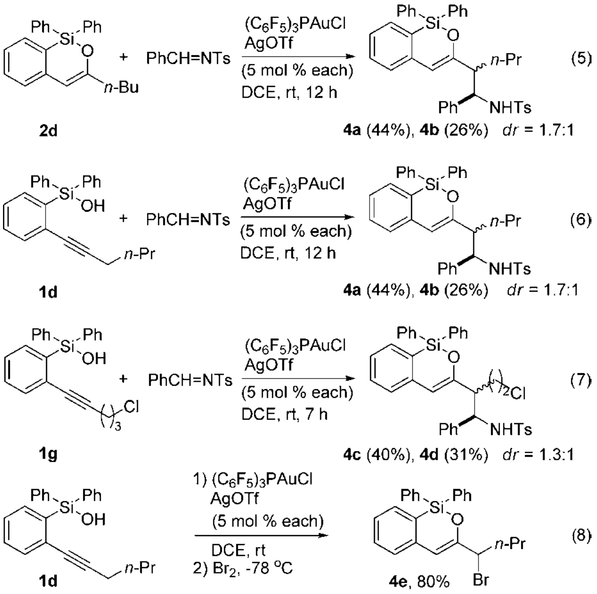
compound **3ec** was isolated in 69% yield as a single diastereomer.

Encouraged by these tandem hydrosilyloxylation/aldol reactions, we investigated a gold-catalyzed tandem intramolecular hydrosilyloxylation/Mannich reaction starting from alkynes and imines. Reaction of **1d** with (*E*)-*N*-benzylidene-4-methyl benzenesulfonamide (1.2 equiv) in DCE at room temperature afforded unexpectedly **4a** and **4b**, which are enol silyl ether forms of the Mannich product, in 44% and 26% yields (*dr* = 1.7:1), respectively, albeit requiring $(C_6F_5)_3PAuCl$ and AgOTf (5 mol %, each) (eq 6).[16] In addition, a silyl enol ether **2d** was reacted with imine to give the same result (eq 5).[17] The structure of diastereomer **4b** was unambiguously determined by spectroscopy and X-ray crystallography (Supporting Information). The serendipitous introduction of an imine moiety at the *exo* position indicates that isomerization of a double bond of enol silyl ether occurred during the tandem reaction.[4a,18] A plausible reaction mechanism is shown in Scheme 3. After initially generated **2d** from **1d** was isomerized to **5** by the present conditions, **5** was sequentially reacted with imine to afford **6** and then deprotonation finally furnished **4a** and **4b**. The selective introduction of an imine moiety to the *exo* position could be explained by the steric effect. These results might be supported by the fact that nonisomerizable **2a** generated in situ from **1a** did not react with imine under the optimized reaction conditions. Alkynyl silanol **1g** underwent a smooth gold-catalyzed tandem hydrosilyloxylation/isomerization/Mannich reaction in one pot to provide **4c** and **4d** in 40% and 31% yields (*dr* = 1.3:1), respectively (eq 7). Enol silyl ether generated in situ from the treatment of **1d** with a gold catalyst was sequentially subjected to bromine (1 equiv) at −78 °C to furnish **4e** in 80% yield *via* tandem hydrosilyloxylation/isomerization/bromination (eq 8).

In conclusion, we have developed an extremely mild tandem Au-catalyzed hydrosilyloxylation/aldol reaction and hydrosilyloxylation/isomerization/Mannich reaction through the formation of enol silyl ether catalytically generated in situ from readily available alkynes in one pot. When enol silyl ethers were treated with imine and bromine, these moieties were selectively introduced at the *exo* position *via* isomerization of a double bond of enol silyl ether. Key to the success of these tandem reactions is the chemoselective formation of an enol silyl ether from alkyne in the presence of a carbonyl and imine group, which opens new opportunities for the invention of related transition metal and Lewis acid catalyzed processes.

Scheme 3. Plausible Mechanism of the Tandem Hydrosilyloxylation/Isomerization/Mannich Reaction





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Supporting Information Available. Experimental procedure, X-ray crystallographic data for **4b** (CIF) and spectral data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Alkynyl silanol **1d** did not react with imine without a gold catalyst. The use of $(C_6F_5)_3PAuCl$ and AgOTf (1 mol % each) gave **4a** and **4b** in 50% yield.

(17) Reaction of **2d** with imine in the presence of AgOTf (10 mol %) did not proceed. Treatment of **2d** with imine in the presence of TfOH (10 mol %) gave the desired product **4a** (43%) and **4b** (43%), indicating that a gold(I) catalyst is essential for intramolecular hydrosilyloxylation and TfOH can assist sequential Mannich reaction.

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The authors declare no competing financial interest.