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Copper-Catalyzed Oxidative *ipso*-Annulation of Activated Alkynes with Silanes: An Approach to 3-Silyl Azaspiro[4,5]trienones

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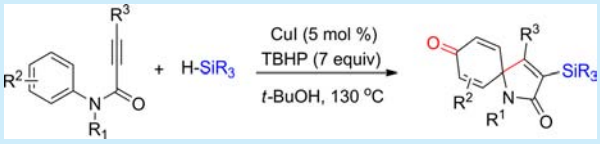
Supporting Information

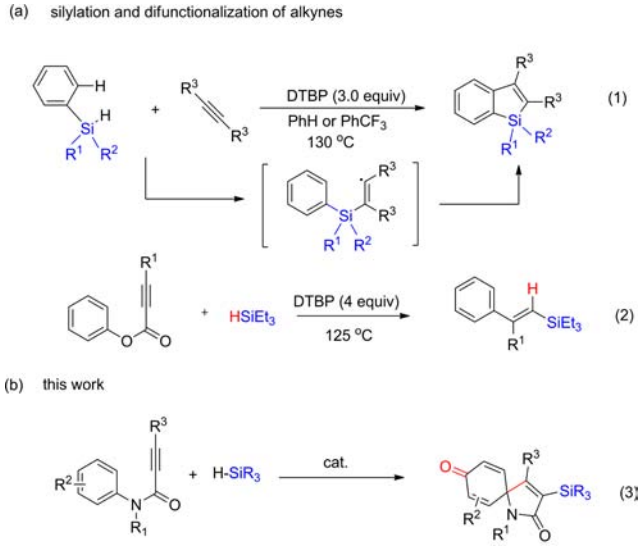
ABSTRACT: A novel strategy of silylation and dearomatization of activated alkynes with silanes to synthesize azaspiro[4,5]trienones is developed, which could be facilely achieved through a tandem difunctionalization of alkyne, dearomatization, and oxidation and provided a facile approach to produce useful 3-silyl azaspiro[4,5]-trienones in an efficient manner.



Vinylsilanes compounds have been widely utilized as versatile synthetic building blocks in organic chemistry and materials science due to their nontoxicity, ease of handling, and ability to undergo a variety of transformations.[1] As a consequence, the exploitation of efficient methods to construct vinylsilanes has become one of the hot-topic areas in modern organic synthesis.[2] Recently, some atom-economical and waste-minimizing strategies to construct a C_{vinyl}–Si bond have been developed, including the silyl-Heck reaction, direct dehydrogenative silylation of alkenes, and alkynes hydrosilylation.[3−5] For example, Flack's group reported the iridium-catalyzed trialkyl silylation of terminal olefins via silyl-Heck transformation.[3a] Dehydrogenative silylation of alkenes with $(TMSO)_2MeSiH$ was described by Hartwig's group.[4d] The hydrosilylation of alkynes with silanes could be achieved by using ruthenium, cobalt, or another transition metal as the catalyst as well.[5] Most of the reported reactions suffer from drawbacks, including poor reaction selectivity, noble transition-metal catalyst, and a special ligand. Most importantly, the synthesis of tetrasubstituted vinylsilanes is much more difficult than that of diverse di- or trisubstituted vinylsilanes. Thus, the more efficient and versatile strategy to afford tetrasubstituted vinylsilanes is still highly desirable.

Cascade radical reactions have attracted considerable attention and emerged as powerful synthetic methods for their advantages of mild reaction conditions, efficient conversion, and economy.[6] Among them, rapid progress has been made in difunctionalization of alkynes to construct multisubstituted alkenes.[7] Although considerable development has been achieved in silicon-radical chemistry in recent decades, novel silicon involved reactions are still attractive topics.[8,9] In 2015, Li's group reported a silyl radical-based strategy for silaindene with 1,2-disubstituted acetylene as substrates through a highly reactive alkenyl radical intermediate (Scheme 1, eq 1).[9d] In 2016, a metal-free cascade reaction of aryl alkynoates via Si–H activation was achieved by Liu and co-workers, providing trisubstituted vinylsilanes in moderate yields (Scheme 1, eq 2).[9g] Those two reports and our continued interest in the difunctionalization of alkynes[7c,d] prompted us to verify whether the reactive alkenyl radical could undergo spirocyclization to give 3-silyl azaspiro[4,5]trienones derivates (Scheme 1, eq 3).[10] Therefore, a novel method for difunctionalization and dearomatization of arylalkynes to construct a series of synthetically useful 3-silyl azaspiro[4,5]-trienones with silanes is successfully achieved in the present contribution. The C–Si, C–C, and C═O bonds were sequentially constructed in the process. Notably, diverse transformations from the 3-silyl azaspiro[4,5]trienones could give a variety of core structures in many natural products and pharmaceuticals.[11]

Scheme 1. Difunctionalization of Alkynes Constructs Multisubstituted Vinylsilanes



Our exploration commenced with the reaction of *N*-methyl-*N*,3-diphenylpropiolamide (**1a**) with triphenylsilane (**2**), TBAI,

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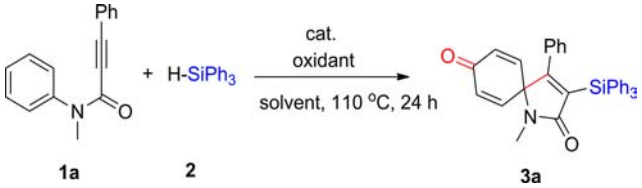
and TBHP (*tert*-butyl hydroperoxide, 70% in aqueous solution) in $PhCF_3$ at 110 °C under an air atmosphere. To our delight, the silylation and dearomatization product **3a** was isolated in 17% yield (Table 1, entry 1), whose structure was determined

Table 1. Optimization of the Reaction Conditions[a]



1a 2 3a

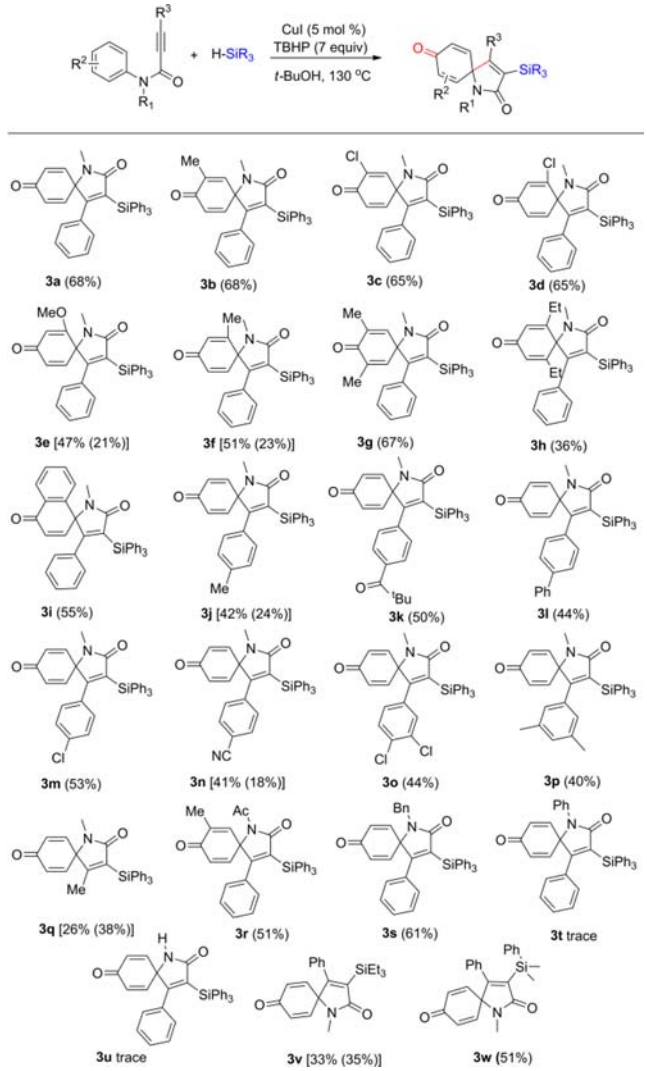
entry	cat.	peroxide[b]	solvent	yield (%)[c]
1	TBAI	TBHP	$PhCF_3$	17
2	TBAI	TBHP	benzene	26
3	TBAI	TBHP	DCE	32
4	TBAI	TBHP	*t*-BuOH	40
5	TBAB	TBHP	*t*-BuOH	trace
6	CuI	TBHP	*t*-BuOH	52
7	CuTc	TBHP	*t*-BuOH	48
8	CuCl	TBHP	*t*-BuOH	50
9	$CuCl_2$	TBHP	*t*-BuOH	47
10[d]	CuI	TBHP	*t*-BuOH	56
11[e]	CuI	TBHP	*t*-BuOH	68
12[e,f]	CuI	TBHP	*t*-BuOH	55
13[e]	no	TBHP	*t*-BuOH	54
14[e,g]	CuI	TBHP	*t*-BuOH	55
15[e]	CuI	DTBP	*t*-BuOH	trace
16[e]	CuI	DCP	*t*-BuOH	trace
17[e,h]	CuI	TBHP	*t*-BuOH	63
18[e,i]	CuI	TBHP	*t*-BuOH	67

[a]Reaction conditions: **1a** (0.1 mmol), triphenylsilane (5 equiv, 0.5 mmol), catalyst (5 mol %), peroxide (7 equiv, 0.7 mmol) in solvent (1.0 mL) were stirred at 110 °C for 24 h under air. [b]TBHP (in water). [c]Isolated yield. [d]The reaction was stirred at 120 °C. [e]The reaction was stirred at 130 °C. [f]Triphenylsilane (4 equiv, 0.4 mmol) was used. [g]TBHP (5.5 M in decane). [h]*t*-BuOH (0.5 mL) was used. [i]*t*-BuOH (2.0 mL) was used.

by X-ray crystallographic analysis (see the Supporting Information).[12] By screening different solvents for this cyclic transformation, *t*-BuOH was demonstrated to be more effective than others such as benzene and DCE (Table 1, entries 2−4). Among all the investigated catalysts including TBAB, CuI, CuTc, CuCl, and $CuCl_2$ (Table 1, entries 5−9), CuI proved to be the most efficient catalyst for this transformation (Table 1, entry 6). A higher yield was obtained in the reaction conducted at 130 °C (Table 1, entry 11) compared to 120 °C (Table 1, entry 10). Reducing the silanes loading led to a 55% yield (Table 1, entry 12). In addition, the reaction efficiency was reduced in the absence of CuI as the catalyst (Table 1, entry 13). Replacing TBHP with other peroxides, such as *tert*-butyl hydroperoxide (TBHP, in decane), dicumyl peroxide (DCP), and di-*tert*-butyl peroxide (DTBP) gave no better yields (Table 1, entries 14−16). Additionally, changing the concentration of the substrate also failed to promote the transformation (Table 1, entries 17−18).

With the optimized reaction conditions in hand, the scope of the silylation and spirocyclization reaction with various substituted *N*-arylpropiolamides was subsequently explored, and the results are summarized in Scheme 2. First, *N*-arylpropiolamides with various substitution patterns at the

Scheme 2. Free-Radical Cascade Silylation and Dearomatization of *N*-Arylpropiolamides with Silanes[a,b]



[a]The reaction was carried out with **1** (0.1 mmol), silane (5 equiv, 0.5 mmol), CuI (5 mol %), TBHP (7 equiv, 0.7 mmol) in *t*-BuOH (1.0 mL) at 130 °C for 24 h under air. [b]Yields of isolated products and the recovery of the starting material were given in parentheses.

aniline moieties were investigated. Both electron-donating and -withdrawing groups such as Me, OMe, and Cl at the *ortho*- or *meta*-position of the aniline moieties were well tolerated to produce the desired products **3b**−**3f** in moderate to good yields. Substrates with two substituents on the phenyl rings were also screened. It should be noted that the electronic and steric effects of the substituent exhibit a certain influence on the efficiency. For example, **1g** containing two methyls at the *meta*-position of the aniline afforded the 3-silyl azaspiro[4,5]trienone **3g** in 67% yield. In contrast, **1h** with two ethyls at the *ortho*-position showed a lower activity, giving the desired product in only 36% yield. Interestingly, the reaction of a naphthylamine-derived substrate also could take place smoothly to afford a tetrasubstituted vinylsilane **3i** in moderate yield. Subsequently, the substituent effect on the alkynyl moiety was examined. All aryl alkynes were compatible with the optimal conditions, transforming into the desired products **3j**−**3p** in moderate yields. The substrate with a methyl group attached to the triple bond could also be engaged in this protocol to afford the

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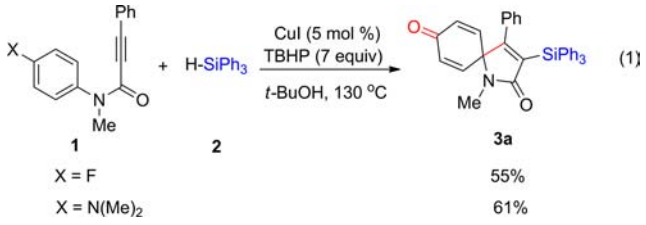
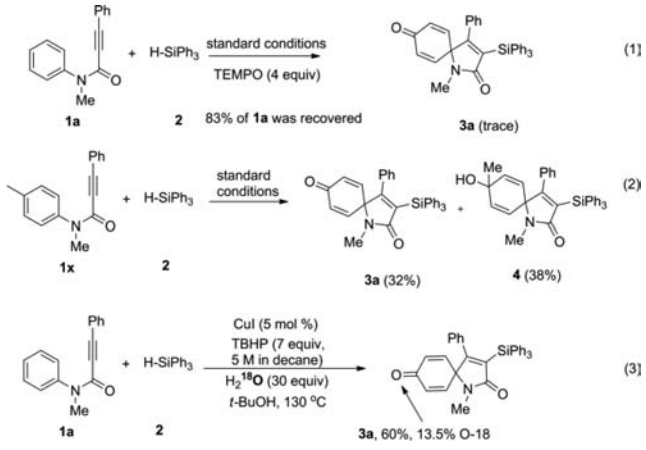
product **3q** in 26% yield. In addition, changing the substrate from the *N*-Me group to the *N*-Ac and *N*-Bn group could also afford the objective products **3r**−**3s** in 51% and 61% yields, respectively. However, the reaction is unsuccessfully preceded by substrates containing an *N*-Ph or *N*-H group, probably due to the electronic effect (**1t**−**1u**). Other silanes such as triethylsilane and dimethylphenylsilane proved to be effective substrates following this protocol (**3v**−**3w**). Remarkably, some *para*-position substituted *N*-arylpropiolamides could also finely undergo the silylation and spirocyclization reactions to give the product **3a** in good yields by releasing the *para*-substituents (*p*-F and *p*-N(Me)$_2$) (Scheme 3).

Scheme 3. Silylation and Spirocyclization of Substrates with *para*-Substituents on the N-Aryl Moiety



Several control experiments were carefully carried out to gain deep insight into the reaction pathway. First, 3-silyl azaspiro-[4,5]trienone (**3a**) was not observed when 4 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as the radical scavenger was added into the reaction system (Scheme 4, eq 1),

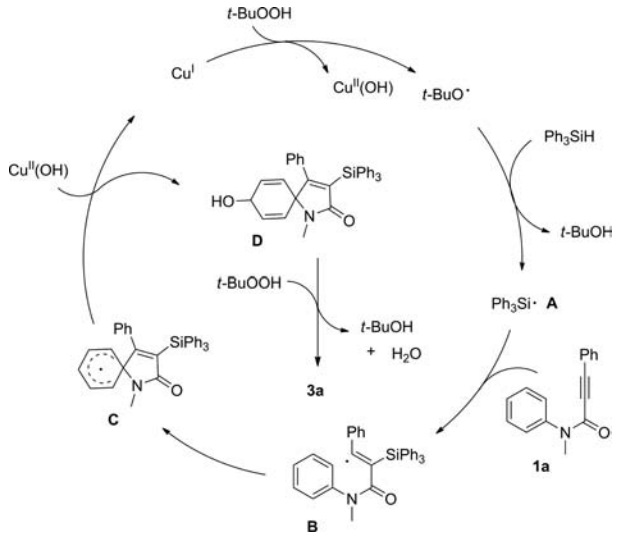
Scheme 4. Control Experiments



which suggests the transformation might be involving a silyl radical. Furthermore, when the *para*-methyl substituted *N*-arylpropiolamide **1x** was used, the product **3a** was obtained in 32% yield, together with the intermediate **4** isolated in 38% yield (Scheme 4, eq 2). The ^{18}O-labeling experiment was also performed to explore the source of the oxygen atom of the newly formed carbonyl group (Scheme 4, eq 3). However, the amount of ^{18}O in **3a** did not increase obviously (for details, see the Supporting Information). This result suggests that the oxygen atom of the newly formed carbonyl group is not mainly from H_2O.

On the basis of the above control experiments and according to previous literature, the possible mechanism was proposed as depicted in Scheme 5.[9,10,13] First, TBHP would generate the *tert*-butoxy radical in the presence of CuI at elevated

Scheme 5. Proposed Mechanism



temperature.[10f] Then, the *tert*-butoxy radical abstracts one proton from silane to give the silyl radical **A**, which would undergo a radical addition reaction toward the alkyne **1a** to afford the radical intermediate **B**.[9d,g] Subsequently, a 5-*ipso* cyclization would arise on the benzene ring and produce the radical intermediate **C**, which would react with Cu^{II}(OH) to yield intermediate **D**, along with the regeneration of Cu(I).[10a,13] Finally, intermediate **D** would be oxidized by TBHP and give the desired product **3a**.[10b,e,f]

In conclusion, a novel copper-catalyzed oxidative *ipso*-annulation of activated alkynes to synthesize 3-silyl azaspiro-[4,5]trienones with silanes through selective activation of the Si−H/C−H bonds has been developed. The reaction proceeds efficiently in a highly regioselective manner to give various 3-silyl azaspiro[4,5]trienones in moderate to good yields. Preliminary mechanistic studies reveals that the C−Si, C−C, and C═O bonds could be successively constructed via a process that includes highly regioselective difunctionalization of alkyne, dearomatization, and oxidation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02781.

General experimental procedures and spectroscopic data (^{1}H and ^{13}C NMR) for the corresponding products (PDF)

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Notes

The authors declare no competing financial interest.

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