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Letter

Dual Palladium/Copper-Catalyzed *anti*-Selective Intermolecular Allenylsilylation of Terminal Alkynes: Entry to (*E*)-Silyl Enallenes

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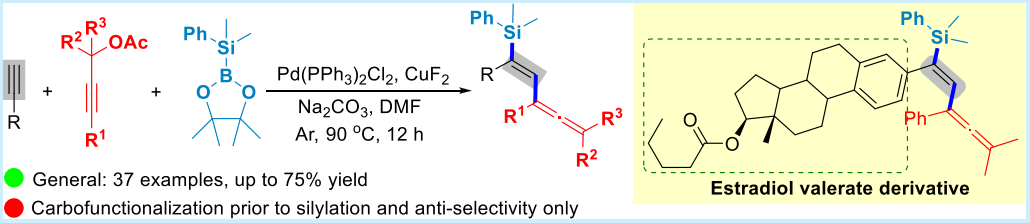
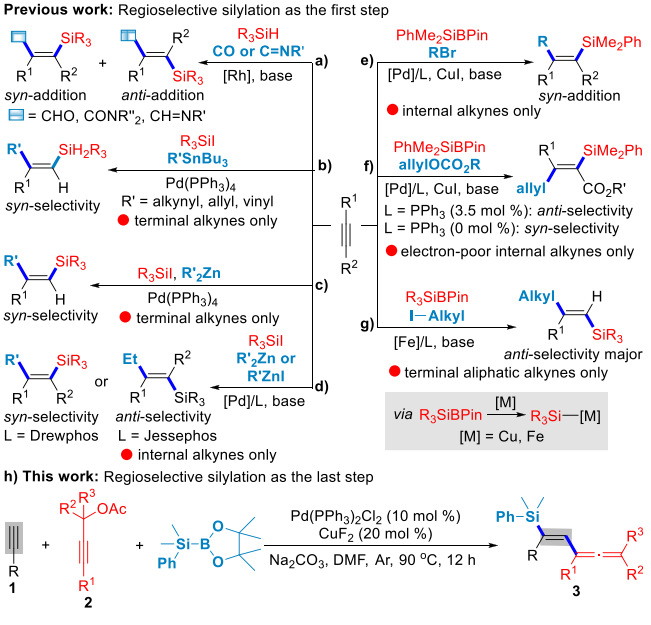


ABSTRACT: A palladium-/copper-cocatalyzed three-component *trans*-allenylsilylation of terminal alkynes with propargyl acetates and $PhMe_2SiBpin$ is described, which is driven by the regioselective allenylation of the alkyne with propargyl acetates and then silylation. This method allows the simultaneous incorporation of an allene and silicon across the C≡C bond and provides a highly chemo-, regio-, and stereoselective alkyne difunctionalization route to the synthesis of valuable (*E*)-silyl enallenes. The utility of this method is highlighted by late-stage derivatization of bioactive compounds.

The alkene difunctionalization reaction is among the most powerful methodologies to economically and rapidly synthesize complex alkene-based structures from readily available feedstocks in synthesis.[1,2] Particularly, those reactions that execute intermolecular difunctionalization of alkynes have additional important values because they can bond the seams of three components together in the desired combinations to create C=C bond networks and exquisitely control the stereo-, regio-, and chemoselectivity.[1,2] Typically, the selective silyl-carbofunctionalization of alkynes that consists of silylation of alkynes with organosilicon reagents followed by carbofunctionalization with carbon donor reagents is attractive and can offer an innovative solution to access versatile vin-2-ylsilane scaffolds, thereby providing the potential to further orient derivatization and increase structural diversity.[2−5] Since Pastor pioneered a $Rh_4(CO)_{12}$-catalyzed silylformylation of alkynes with Me_2PhSiH and CO (10−30 kg/cm^2) in 1989,[3a] transition-metal-catalyzed carbosilylation of alkynes with trisubstituted silanes and carbon donors (such as high-pressure CO and alkyl isocyanides) has been well investigated for constructing various functionalized vinylsilanes, mainly through initially manipulating the regioselective silylation of alkynes and then carbofunctionalization (Scheme 1a).[2,3] However, these approaches suffer from unsatisfactory stereoselectivity with a mixture of *Z* and *E* isomers and narrow carbon donors. To achieve high stereoselectivity, Murai and co-workers have developed a $Pd(PPh_3)_4$ catalysis that uses a combination of trisubstituted silyl iodide electrophiles and organometallic nucleophiles (such as organotin and organozinc reagents) to accomplish the *syn*-selective silyl-carbofunctionalization of terminal alkynes (Scheme 1b,c).[4a,b] Very recently,

Scheme 1. Carbosilylation of Alkynes



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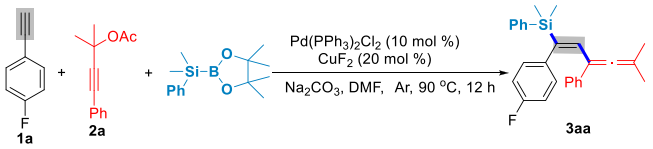
Watson and co-workers found that the ligand effect could control the stereoselectivity of palladium-catalyzed carbosilylation of internal symmetrical alkynes with trisubstituted silyl iodides and primary alkyl zinc iodides. While the use of $(3,5\text{-}^{t}Bu_2C_6H_3)_3P$ (DrewPhos) led to *syn* selectivity, $(3,5\text{-}^{t}Bu_2C_6H_3)_2P(^{t}Bu)$ (JessePhos) gave rise to *anti* selectivity (Scheme 1d).[4c] Similarly, *syn*-selective carbosilylation of internal alkynes has been achieved via palladium-/copper-cocatalyzed tandem silylboration/Suzuki reactions with a new silane donor nucleophile ($PhMe_2SiBPin$) and aryl bromide electrophiles using the PCy_3 ligand, wherein the $PhMe_2Si$-[Cu] intermediates are first formed and then directly added *syn* across the C≡C bonds (Scheme 1e).[5a] In contrast, when a similar Pd/Cu cooperative catalysis is used, the presence of PPh_3 enables the *anti*-selective silylallylation of electron-poor internal alkynes with silyl boronic esters and allylcarbonates, whereas omission of the ligand led to the *syn*-selective version (Scheme 1f).[5b] Iron-catalyzed *anti*-selective silylalkylation of terminal aliphatic alkynes with silyl boronic esters and alkyl iodides occurred through direct addition of the *in situ* generated R_3Si-[Fe] intermediates across the C≡C bond (Scheme 1g).[5c] Nevertheless, all existing approaches have been limited to alkyne silyl-carbofucntionalization and only two papers to date allowed the formation of functionalized *anti*-alkenes from electron-deficient internal alkynes and terminal aliphatic alkynes. A precise regioselective sequence control between the silylation and carbofunctionalization processes to realize carbosilylation of alkynes, especially including non-symmetric terminal and internal alkynes, still remains unprecedented.

We hypothesized that if more highly reactive carbon donors were used as the electrophiles and the nucleophilicity of the *in situ* generated $PhMe_2Si$-[Cu] intermediates were tuned, the palladium-catalyzed addition of the more highly reactive carbon donors across the C≡C bond would take precedence over the direct addition of the *in situ* generated $PhMe_2Si$-[Cu] intermediates, thus enabling exquisite control over both regioselectivity and stereoselectivity to create new methods. Herein, we report a new, general dual palladium-/copper-catalyzed intermolecular *trans*-allenyl silylation of terminal alkynes with propargyl acetates and $PhMe_2SiBpin$ to produce (*E*)-silyl enallenes (Scheme 1h). The method allows propargyl acetates as highly reactive allene precursors[6] to enable allenylation with alkynes prior to silylation and provides a conceptually novel alkyne carbosilylation route to forge new, valuable, functionalized vinyl silane scaffolds[7] with excellent regio-/stereoselectivity and functional group tolerance.

Initial investigations on the allenylsilylation of 1-ethynyl-4-fluorobenzene (**1a**) with 2-methyl-4-phenyl-but-3-yn-2-yl acetate (**2a**) and $Me_2(Ph)SiBPin$ were performed (Table 1 and Table S1 in the Supporting Information). Allenylsilylation of alkyne **1a** with propargyl acetate **2a**, $Me_2PhSiBPin$ (**3a**), 10 mol % of $Pd(PPh_3)_2Cl_2$, 20 mol % of CuF_2, and Na_2CO_3 in DMF was executed smoothly, producing the desired product (*E*)-**3aa** with a 72% yield (entry 1). It should be noted that these parameters, including $Pd(PPh_3)_2Cl_2$, CuF_2, Na_2CO_3, and phosphorus ligands (such as Ph_3P, dppp, and dppf), are all equally crucial for the success of the reaction, since omission of each of them led to no isolation of **3aa** (entries 2 and 3). While using $PdCl_2$ (entry 3) or $Pd(PPh_3)_4$ (entry 7) delivered a trace amount of **3aa**, other Pd catalysts, including $PdCl_2/PPh_3$, $Pd(dppp)Cl_2$, and $Pd(dppf)Cl_2$, were highly reactive (entries 4–6). Other Cu catalysts, such as $Cu(OAc)_2$, CuCl, CuI, and

Table 1. Screening of Optimal Reaction Conditions[a]



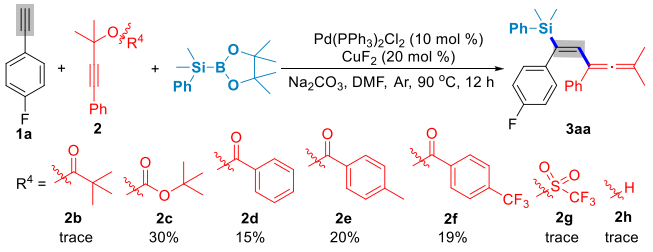
entry	variation from the standard conditions	yield (%)
1	none	72
2	without $Pd(PPh_3)_2Cl_2$, CuF_2, or Na_2CO_3	0
3	$PdCl_2$ instead of $Pd(PPh_3)_2Cl_2$	trace
4	$PdCl_2/PPh_3$ instead of $Pd(PPh_3)_2Cl_2$	60
5	$Pd(dppp)Cl_2$ instead of $Pd(PPh_3)_2Cl_2$	59
6	$Pd(dppf)Cl_2$ instead of $Pd(PPh_3)_2Cl_2$	10
7	$Pd(PPh_3)_4$ instead of $Pd(PPh_3)_2Cl_2$	trace
8	$Cu(OAc)_2$ instead of CuF_2	<5
9	CuCl instead of CuF_2	40
10	CuI instead of CuF_2	25
11	$CuCl_2$ instead of CuF_2	41
12[b]	$CuCl_2$ instead of CuF_2	69
13[c]	none	67

[a]Standard reaction conditions unless specified otherwise: **1a** (0.4 mmol), **2a** (0.2 mmol), $Me_2(Ph)SiBPin$ (0.4 mmol), $Pd(PPh_3)_2Cl_2$ (10 mol %), CuF_2 (20 mol %), Na_2CO_3 (0.6 mmol), DMF (2 mL), argon, 90 °C, 12 h. Only the *E* isomer was obtained, which was determined by a ^1H NMR and/or GC-MS analysis of the crude product. [b]NaF (40 mol %). [c]**2a** (1 mmol), DMF (4 mL), 20 h.

$CuCl_2$, exhibited reactivity, but they were less efficient than CuF_2 (entries 8–11). Interestingly, using $CuCl_2$ combined with NaF gave results identical with those of CuF_2 (entry 12), suggesting that fluoride ions may promote Si–B bond cleavage.[7,8] Screening the effect of the CuF_2 amount, bases (such as Na_2CO_3, $NaHCO_3$, K_2CO_3, and NEt_3) and temperatures (entries 1 and 13–18 in Table S1 in the Supporting Information) proved that the reaction with 20 mol % of CuF_2 and Na_2CO_3 at 90 °C was the best option (entry 1). Intriguingly, the conditions were applicable to a 1 mmol scale of **2a**, giving **3aa** in 67% yield (entry 13).

With the optimized conditions in hand, we next explored the reliable leaving groups in propargyl acetates **2** for the alkyne allenylsilylation protocol (Scheme 2). A wide range of acyl

Scheme 2. Optimization of the Reliable Leaving Groups in the Propargyl Acetates 2



groups, including Boc (**2c**), PhCO (**2d**), $4\text{-}MeC_6H_4CO$ (**2e**), and $4\text{-}CF_3C_6H_4CO$ (**2f**), were suitable to furnish **3aa**, although they had lower reactivity. However, using either bulky $^{t}BuCO$ (**2b**) or CF_3SO_2 (**2g**) led to no conversion of **2**. Likewise, 2-methyl-4-phenylbut-3-yn-2-ol (**2h**) was inert.

Encouraged by these results, we investigated the substrate scope (Scheme 3). This alkyne allenylsilylation was applicable to various substituents, such as F, Cl, Br, CF_3, MeO, Ph, and

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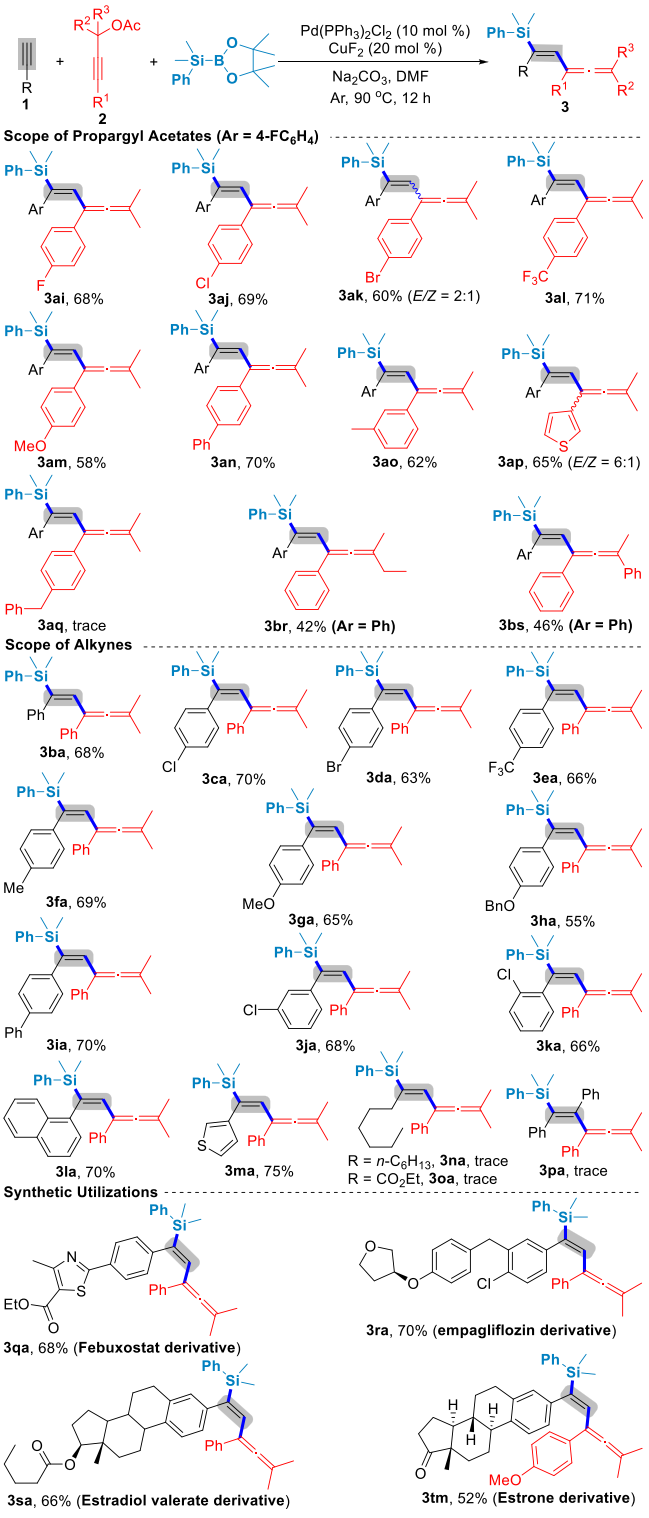
Scheme 3. Scope of the Alkynes 1 and Propargyl Acetates 2[a]



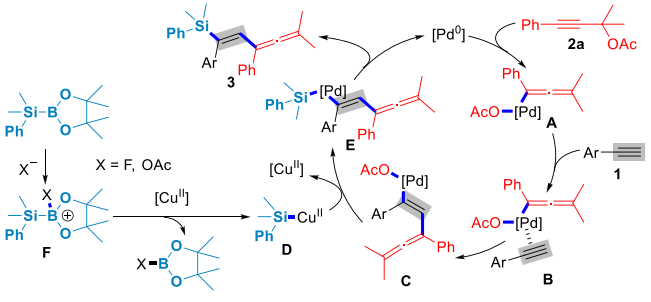
[a]Reaction conditions: **1** (0.4 mmol), **2** (0.2 mmol), $Me_2(Ph)SiBPin$ (0.4 mmol), $Pd(PPh_3)_2Cl_2$ (10 mol %), CuF_2 (20 mol %), Na_2CO_3 (0.6 mmol), DMF (2 mL), argon, 90 °C, 12 h.

Me, on the aryl ring at the terminal alkyne in propargyl acetates **2i**–**o** (products **3ai**–**ao**), and the electronic/steric hindrance effect had an influence on the reaction. Notably, halogen atoms, including F, Cl, and Br, were well tolerated, hence providing the potential for further derivatization of the halo positions (**3ai**–**ak**). While propargyl acetate **2l** bearing an electron-withdrawing *p*-CF_3 group was efficiently converted to **3al** with a 71% yield, propargyl acetate **2m** with an electron-donating *p*-MeO group delivered **3am** in a diminished yield. For propargyl acetates **2n**,**o** with a *p*-Ph or an *m*-Me group the reaction efficiently proceeded to give **3an**,**ao**. In particular, the thiophen-2-yl-substituted propargyl acetate **2p** was well accommodated (**3ap**). However, the alkyl-substituted propargyl acetate **2q** was inert. Using 3-methyl-1-phenyl-pent-1-yn-3-yl acetate (**2r**) and 2,4-diphenylbut-3-yn-2-yl acetate (**2s**), both smoothly underwent allenylsilylation to produce **3br**,**s** in moderate yields.

The allenylsilylation protocol was compatible with a wide array of terminal aryl alkynes (**3ba**–**ma**), but attempts to allenylsilylate terminal alkyl alkyne, electron-poor alkynes and internal alkynes failed (**3na**–**pa**). Phenylacetylene (**1b**) was successfully treated with propargyl acetate **2a**, $Me_2(Ph)SiBPin$, $Pd(PPh_3)_2Cl_2$, and CuF_2, giving **3ba** in 68% yield. A range of aryl substituents at the alkyne terminus, including 4-ClC_6H_4, 4-BrC_6H_4, 4-$CF_3C_6H_4$, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$BnOC_6H_4$, 4-PhC_6H_4, 3-ClC_6H_4, and 2-ClC_6H_4, were perfectly tolerated and produced **3ca**–**3ka** in good yields. Moreover, neither the electronic nature nor the positions of these substituents interfered with our target reaction. Aryl alkynes **1c**,**j**,**k**, bearing a Cl group at *para*, *meta*, or *ortho* positions on the aryl ring, respectively, were all viable substrates (**3ca**,**ja**,**ka**). The reaction could be applied to both strongly electron-withdrawing CF_3-substituted aryl alkynes and strongly electron-donating alkyloxy (such as MeO and BnO)-substituted aryl alkynes (**3ea**,**ga**,**ha**). Most importantly, halogen atoms (such as Cl and Br) remain intact for further elaborations (**3ca**,**da**,**ja**,**ka**). Notably, naphthalen-1-yl and thiophen-2-yl alkynes **1l**,**m** were transformed to **3la**,**ma**, respectively, in good yields. The resulting multisubstituted alkenes are fundamental motifs in natural products, pharmaceuticals, and functional materials, inspiring us to use such alkenes as the embedded functionality of the known bioactive molecules to make them synthetically useful. As expected, this allenylsilylation successfully forged medicinally relevant motif-based alkenes,[8] including febuxostat derivative **3qa**, empagliflozin derivative **3ra**, estradiol valerate derivative **3sa**, and estrone derivative **3tm**.

Consequently, a possible mechanism was proposed (Scheme 4).[2−9] Oxidative addition of propargyl acetate **2a** with the

Scheme 4. Possible Reaction Mechanisms



active Pd(0) species affords the allenyl-PdOAc intermediate **A** due to its activation by the *gem*-aryl electronic effect.[6] This is the reason that alkyl-substituted propargyl acetates have no reactivity during the reaction. Subsequently, the intermediate **B**, which is formed by the coordination of intermediate **A** with alkyne **1a**, undergoes a *trans* addition across the C≡C bond to

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deliver the vinyl-Pd intermediate **C**. Transmetalation between the intermediate **C** and the Cu−Si intermediate **D**, which is generated via the reaction of $Me_2(Ph)SiBPin$ and the active Cu^{II} species,[5,8] leads to the formation of the vinyl-Pd-Si intermediate **E**. Reductive elimination of the intermediate **E** affords the desired product (*E*)-**3** and regenerates the active Pd(0) species. Anions, especially the fluoride anion with a strong negative charge property, might react with the B unit and thus promote the Si−B bond cleavage.

In summary, we have developed the first regio- and stereoselective intermolecular *anti*-allenylsilylation of terminal alkynes with propargyl acetates and $Me_2PhSiBPin$ using dual palladium/copper cooperative catalysis for the synthesis of (*E*)-silyl enallenes. The efficient allenyl-Pd intermediates generated from highly reactive allene precursors, such as propargyl acetates, are crucial to the success of this method, wherein the cooperative $Pd(PPh_3)_2Cl_2$ and CuF_2 catalytic system enables the selective formation of allenyl-Pd intermediates and Si-Cu intermediates, allowing exquisitely regioselective access to highly valuable (*E*)-1-silyl-2-allenyl alkenes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02364.

Experimental procedures, characterization of all compounds, NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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