

Palladium-Catalyzed Three-Component Silylalkoxylation of 1,3-Diene with Alcohol and Disilane via Oxidative Coupling

Kazuyuki Torii, Kazuki Tabaru, and Yasushi Obora*



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ABSTRACT: A regioselective and Z-selective three-component silylalkoxylation of 1,3-diene using various alcohols, disilane, and a catalytic Pd/Cu/1,4-benzoquinone/O₂ system is established in this Letter. The reaction generates tetra-substituted allyl silanes containing allyl ether moieties in up to 80% isolated yield and on a 1–10 mmol scale via oxidative coupling. A wide variety of substrates, including benzyl alcohol derivatives, aliphatic alcohols, and bioactive compounds such as cholesterol, are suitable for use in the developed reaction system.



The development of efficient, environmentally benign synthetic methods that use chemical feedstocks to generate fine chemicals represents a challenging target in modern chemistry. Oxidative coupling reactions that employ transition-metal catalysts comprise one of the most promising and straightforward approaches to reaching this objective.¹ This type of reaction methodology has emerged in catalytic organic chemistry as a green, atom-economical process, compared with traditional cross-coupling reactions and classical C–C bond formations, because prefunctionalized substrates, such as halogenated reagents or organometallic materials, are not required (Figure 1A). These advantages have recently inspired enthusiastic chemical research in this field.

Several inter- and intramolecular oxidative coupling reactions using unsaturated compounds to form C–C or C–(heteroatom) bonds have been reported.^{2–4} Our group has also described methods for introducing an amino group to an olefin or 1,3-diene through an oxidative coupling mechanism.⁵ Although many groups have investigated oxidative amination reactions to form C–N bonds, studies involving oxidative alkoxylation reactions to form C–O bonds are rare. Bäckvall and coworkers carried out the palladium-catalyzed oxidative 1,4-dialkoxylation of conjugated dienes using benzoquinones (BQs) as a catalyst reoxidant and a catalytic amount of methanesulfonic acid (Figure 1B (I); OAc = acetate).⁶ White and coworkers detailed the palladium-catalyzed intramolecular oxidative alkoxylation of terminal olefins using two equivalents of 1,4-BQ as a catalyst reoxidant and used this method to successfully synthesize oxygen-containing heterocycles (Figure 1B (II)).⁷ Monguchi and Sajiki developed a method for the intermolecular oxidative alkoxylation of α,β -unsaturated carbonyl compounds using a palladium catalyst with more than two equivalents of AgOAc as the reoxidant (Figure 1B (III)).⁸

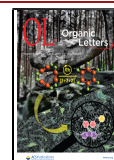
In this work, we have designed a system that achieves the palladium-catalyzed three-component silylalkoxylation of 1,3-diene with alcohol and disilane through an oxidative

alkoxylation mechanism (Figure 1C). The silylalkoxylation reaction proceeded with exclusive Z selectivity in the Pd/Cu/1,4-BQ/O₂ system and achieved a high yield using commercially available reagents. Moreover, the reaction afforded a tetra-substituted Z-allyl silane containing an allyl ether moiety, which is difficult to synthesize. Such multi-substituted compounds cannot be accessed simply using alternative methods for olefin synthesis, such as olefin metathesis or Wittig reactions.⁹

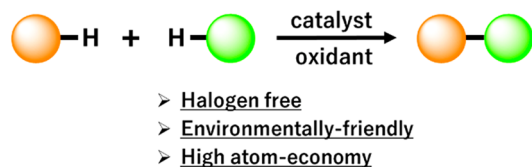
First, it was necessary to optimize the silylalkoxylation reaction conditions (Table 1). The reaction between 2,3-dimethyl-1,3-butadiene (**1a**), benzyl alcohol (**2a**), and hexamethyldisilane (**3a**) in the presence of Pd(dba)₂ (0.05 mmol, 5 mol %; dba = (*E,E*)-dibenzylideneacetone), CuBr₂ (0.1 mmol, 10 mol %), and 1,4-BQ (0.4 mmol, 40 mol %) under an oxygen atmosphere (1 atm, balloon) gave the desired Z-allyl silane (**4a**) in 88% yield based on gas chromatography (GC; entry 1). The stereostructure of the desired product was determined by the DPGSE 1D-NOE measurement. (See the Supporting Information (SI) for spectral data.) The use of Pd(OAc)₂ and Pd(TFA)₂ as the catalyst also afforded **4a** in good yield (entries 2 and 3), but Pd(PPh₃)₄ was an inert catalyst under these conditions (entry 4). Potential alternative copper salts included CuCl₂, CuBr, or CuI. The reaction with CuCl₂ proceeded effectively (entry 5), but CuBr and CuI were not suitable additives (entries 6 and 7). Switching from DMF to other amide solvents, such as DMA or NMP, did not improve the yield of **4a** (entries 8 and 9). In addition, the desired product was not produced when MeCN or toluene was

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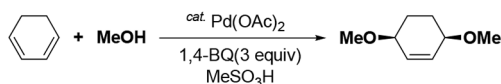


A. Oxidative coupling reactions

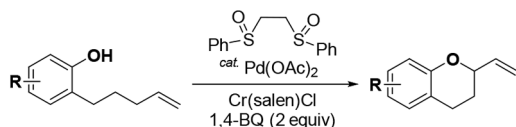


B. Pd-catalyzed alkoxylation via oxidative coupling

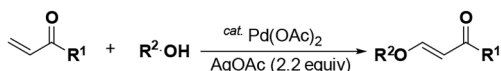
(I) Oxidative 1,4-dialkoxylation of conjugated dienes



(II) Intramolecular oxidative alkoxylation of olefin



(III) Intermolecular oxidative alkoxylation of olefin



C. This work

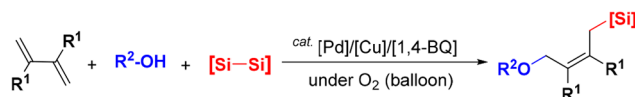


Figure 1. (A) Oxidative coupling reactions and their advantages in organic chemistry. (B) Previous reports for alkoxylation of olefin through the intramolecular and intermolecular oxidative coupling mechanism. (C) Three-component silylalkoxylation with 1,3-diene, alcohol, and disilane via oxidative coupling

used as the solvent (entries 10 and 11). Interestingly, the reaction under air or Ar did not afford **4a** (entries 12 and 13), thus indicating that molecular oxygen was necessary for the reaction. Next, the substrate ratio was optimized. The experimental data suggested that the stoichiometric ratio of **1a** and **3a** to **2a** significantly impacted the reaction yield (entries 1 and 14–16) and that the highest yield was obtained with (**1a/2a/3a** 3:1:4). Finally, control experiments were carried out in the absence of Pd, copper salt, or 1,4-BQ. The desired product **4a** was not obtained without Pd or copper (entries 17 and 18). The results in entries 13 and 18 indicated that 1,4-BQ did not serve as the reoxidant of the catalytic species. Notably, when the reaction was performed in the absence of 1,4-BQ, **4a** was produced in good yield (entry 19).

Second, we investigated the substrate scope of the silylalkoxylation reaction (Scheme 1). The reaction with *o*-, *m*-, and *p*-methyl benzyl alcohol afforded the corresponding products in 74–76% yield (**4b–4d**), and the yields were in a similar range. The use of *p*-*tert*-butyl benzyl alcohol afforded the desired product (**4e**) in 75% yield, and *p*-methoxy benzyl alcohol gave the desired product (**4f**) in 80% yield. The silylalkoxylation with *p*-Cl benzyl alcohol also proceeded smoothly to produce **4g**, and the reaction with *p*-CF₃ benzyl alcohol afforded **4h** in 56% yield. Secondary alcohols were also suitable for this reaction (**4i**). With *E*-cinnamyl alcohol, the corresponding product (**4j**) was obtained in 62% yield. Interestingly, the cinnamyl alcohol-derived C=C moiety

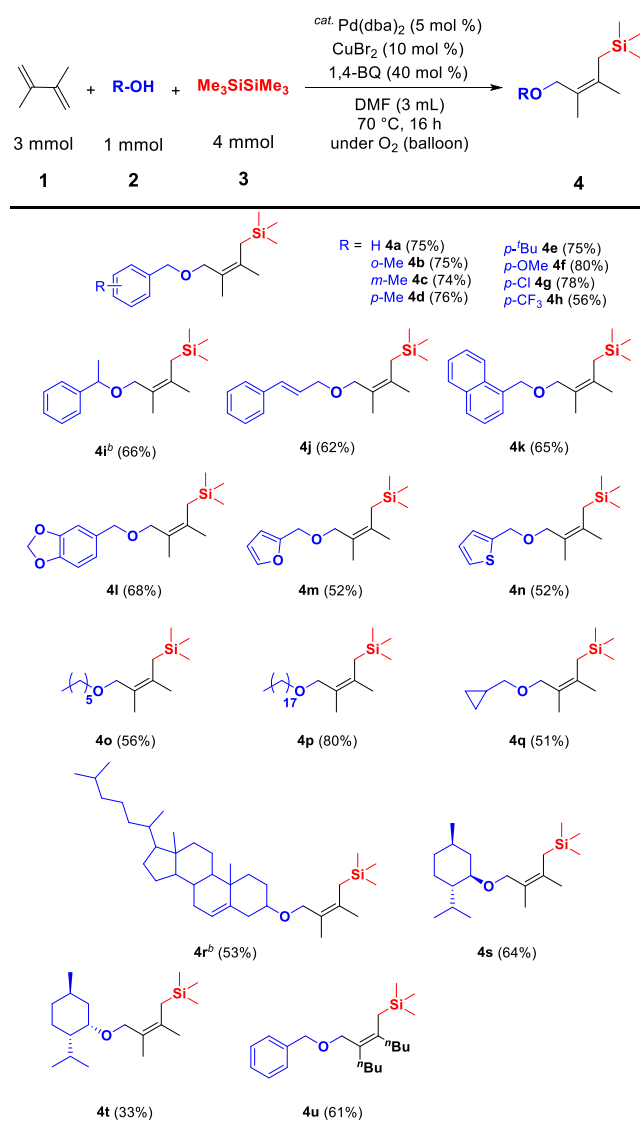
Table 1. Optimization of the Reaction Conditions^a

entry	Pd/Cu	solvent	X, Y	yield (%) ^b
1	Pd(dba) ₂ /CuBr ₂	DMF	3, 4	88 (75) ^b
2	Pd(OAc) ₂ /CuBr ₂	DMF	3, 4	71
3	Pd(TFA) ₂ /CuBr ₂	DMF	3, 4	77
4	Pd(PPh ₃) ₄ /CuBr ₂	DMF	3, 4	nd
5	Pd(dba) ₂ /CuCl ₂	DMF	3, 4	70
6	Pd(dba) ₂ /CuBr	DMF	3, 4	nd
7	Pd(dba) ₂ /CuI	DMF	3, 4	12
8	Pd(dba) ₂ /CuBr ₂	DMA	3, 4	44
9	Pd(dba) ₂ /CuBr ₂	NMP	3, 4	17
10	Pd(dba) ₂ /CuBr ₂	MeCN	3, 4	nd
11	Pd(dba) ₂ /CuBr ₂	toluene	3, 4	nd
12 ^c	Pd(dba) ₂ /CuBr ₂	DMF	3, 4	nd
13 ^d	Pd(dba) ₂ /CuBr ₂	DMF	3, 4	nd
14	Pd(dba) ₂ /CuBr ₂	DMF	1, 1	29
15	Pd(dba) ₂ /CuBr ₂	DMF	3, 1	18
16	Pd(dba) ₂ /CuBr ₂	DMF	3, 2	59
17	CuBr ₂ (no Pd)	DMF	3, 4	nd
18	Pd(dba) ₂ (no Cu)	DMF	3, 4	nd
19 ^e	Pd(dba) ₂ /CuBr ₂ (no 1,4-BQ)	DMF	3, 4	68

^aReaction conditions: **1a** (1–3 mmol), **2a** (1 mmol), **3a** (1–4 mmol), Pd catalyst (0.05 mmol, 5 mol %), Cu salt (0.1 mmol, 10 mol %), and 1,4-BQ (0.4 mmol, 40 mol %) were stirred at 70 °C (oil bath temperature) for 16 h under O₂ (balloon). Yield was determined by GC based on the amount of **2a** (*n*-decane was used as an internal standard). ^bNumber in parentheses is the isolated yield. ^cUnder air. ^dReaction performed with 1,4-BQ (1.2 equiv) under Ar. ^eReaction performed in the absence of 1,4-BQ. Pd(TFA)₂ = palladium bis(2,2,2-trifluoroacetate); 1,4-BQ = 1,4-benzoquinone; DMF = *N,N*-dimethylformamide; DMA = *N,N*-dimethylacetamide; NMP; *N*-methyl-2-pyrrolidone. nd = not detected.

retained its conformation. A sterically hindered alcohol (1-naphthalene methanol) was also applicable (affording **4k**). Heterocyclic alcohols were also tested with this catalytic system. Oxygen-containing heterocyclic alcohols (e.g., piperonyl alcohol and furfuryl alcohol) successfully afforded the corresponding products in good yield (**4l** and **4m**, respectively). Surprisingly, 2-thiophene methanol, which is often poisonous for Pd species, was tolerated by this silylalkoxylation (**4n**). However, no desired product was detected in the presence of 2-pyridine methanol because the high basicity of the pyridyl group rendered the catalytic species inert. Further investigations concerning the scope of aliphatic alcohol and 1,3-diene reagents were performed. With simple aliphatic alcohols, such as 1-hexanol, the reaction achieved 56% yield (**4o**), and the longer-chain 1-octadecanol delivered its corresponding product (**4p**) in 80% yield.

Importantly, a cyclopropyl ring, which has been integrated in preclinical or clinical drugs, could be introduced (**4q**).¹⁰ In addition, a bioactive compound, such as cholesterol, was compatible with the silylalkoxylation and furnished the desired product (**4r**). Moreover, configurational defined secondary alcohols were used for the reaction to give the stereochemical information on the chiral carbon center. (–)-Menthyl provided the product (**4s**) in 64% yield, whereas (+)-neo-

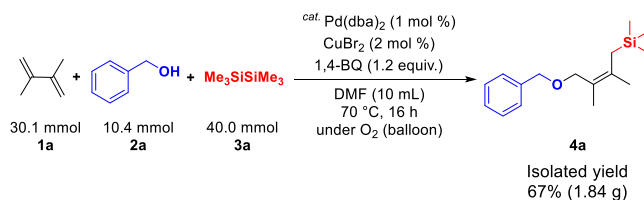
Scheme 1. Palladium-Catalyzed Silylalkoxylation with Benzyl Alcohol Derivatives^a

^aReaction conditions: **1a** (3 mmol), **2a** (1 mmol), **3a** (4 mmol), Pd(dba)_2 (0.05 mmol, 5 mol %), CuBr_2 (0.1 mmol, 10 mol %), and 1,4-BQ (0.4 mmol, 40 mol %) were stirred at 70 °C (oil bath temperature) for 16 h under O_2 . ^bAbsolute configuration is not determined.

menthol, which is the epimer of menthol, gave the product (**4t**) in 33% yield. The epimerization of the products was not observed in these reactions, and the steric hindrance of isopropyl group on the axial position to hydroxy group would significantly affect the yields of the products. *t*-BuOH did not give the corresponding product. The reaction with 2,3-dibutyl-1,3-butadiene proceeded smoothly to afford a good yield (**4u**). However, 2,3-diphenyl-1,3-butadiene did not give the corresponding product. Unfortunately, the use of isoprene as an unsymmetric diene gave a mixture of intractable products. The reactions with cyclic dienes such as 1,3-

cyclohexadiene and phellandrene were sluggish under these conditions.

The feasibility and utility of this transformation were demonstrated by the gram-scale synthesis of **4a** (Scheme 2).

Scheme 2. 1 g scale synthesis of **4a**.

Specifically, **1a** (30.1 mmol), **2a** (10.4 mmol), and **3a** (40.0 mmol) were mixed in the presence of Pd(dba)_2 (0.1 mmol, 1 mol %), CuBr_2 (0.2 mmol, 2 mol %), and 1,4-BQ (1.2 equiv) in DMF (10 mL), which afforded **4a** in good yield (1.84 g) with exclusive *Z* selectivity. This result supports the scalability of the process and DMF compared with typical methods.

To better understand the detailed reaction mechanism, a deuterium labeling experiment was performed using deuterated alcohol (**2a-d₁**) under the optimized conditions (see the SI), but the deuterated **4a** product was not observed. This result implied that the reaction proceeded via oxidative alkoxylation, not hydroalkoxylation. Moreover, deuterated benzyl alcohol (**2a-d₇**) gave the corresponding product (**4a-d₇**). (See the SI.)

To elucidate the role of 1,4-BQ, the reaction with Pd(dba)_2 (0.05 mmol, 5 mol %) and CuBr_2 (0.1 mmol, 10 mol %) was performed with and without 1,4-BQ (0.4 mmol, 40 mol %) in the presence of **1a** (3 mmol), **2a** (1 mmol), and **3a** (4 mmol), and the yield of **4a** was monitored (Figure S3). The yield with no 1,4-BQ rapidly increased during the initial stage of the reaction and then leveled off. In contrast, when 1,4-BQ was present, the reaction proceeded slowly at first, but the yield of **4a** continuously increased. These experimental results suggested that 1,4-BQ stabilizes catalytic active species.¹¹

On the basis of previous reports and the experimental results presented herein, a plausible catalytic cycle for the silylalkoxylation reaction was proposed, and it is illustrated in Figure 2.^{4g,12} First, complex **II** is generated by the coordination of 1,3-diene (**1a**) to Pd(II) . Then, the alcohol (**2a**) performs a nucleophilic attack on **II**, which is followed by the formation of 4-alkoxy-(π -allyl)palladium complex **III**.^{6a} It is reported that the 1,4-difunctionalization of 1,3-diene *via* the π -allyl metal

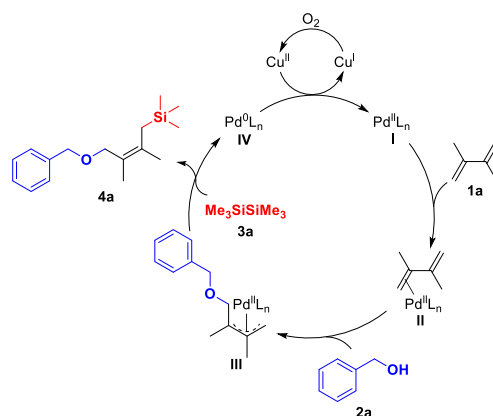


Figure 2. Plausible reaction mechanism.

complex exhibited Z selectivity, which would be due to the coordination of the complex with the nucleophile.¹³ Finally, **III** reacts with disilane (**3a**) to afford the desired product (**4a**) along with Pd(0), which is reoxidized to Pd(II) by Cu and O₂. Activation of the Si–Si bond with palladium to form Si–Pd–Si would be involved,¹⁴ and the details of this step in this catalytic cycle cannot be elucidated in this stage.

In summary, we achieved regioselective and Z-selective three-component silylalkoxylation with commercially available diene, alcohol, and disilane reagents. This approach enabled the synthesis of ally silanes containing an allyl ether moiety via oxidative coupling to alcohol and 1,3-diene by the Pd/Cu/1,4-BQ/O₂ system. This reaction system exhibited a broad substrate scope and scalability to the gram scale. Further studies applying this reaction system to other organic transformations and detailed mechanistic investigations are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.1c01648>.

Experimental procedures, characterization of compounds, and mechanistic experiments (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Yasushi Obora – Department of Chemistry and Materials Engineering, Faculty of Chemistry, Materials and Bioengineering, Kansai University, Suita, Osaka 564-8680, Japan; orcid.org/0000-0003-3702-9969; Email: obora@kansai-u.ac.jp

Authors

Kazuyuki Torii – Department of Chemistry and Materials Engineering, Faculty of Chemistry, Materials and Bioengineering, Kansai University, Suita, Osaka 564-8680, Japan

Kazuki Tabaru – Department of Chemistry and Materials Engineering, Faculty of Chemistry, Materials and Bioengineering, Kansai University, Suita, Osaka 564-8680, Japan

Complete contact information is available at: <https://pubs.acs.org/doi/10.1021/acs.orglett.1c01648>

Notes

The authors declare no competing financial interest.

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