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Palladium-Catalyzed Difunctionalization of 1,3-Diene with Amine and Disilane under a Mild Re-oxidation System

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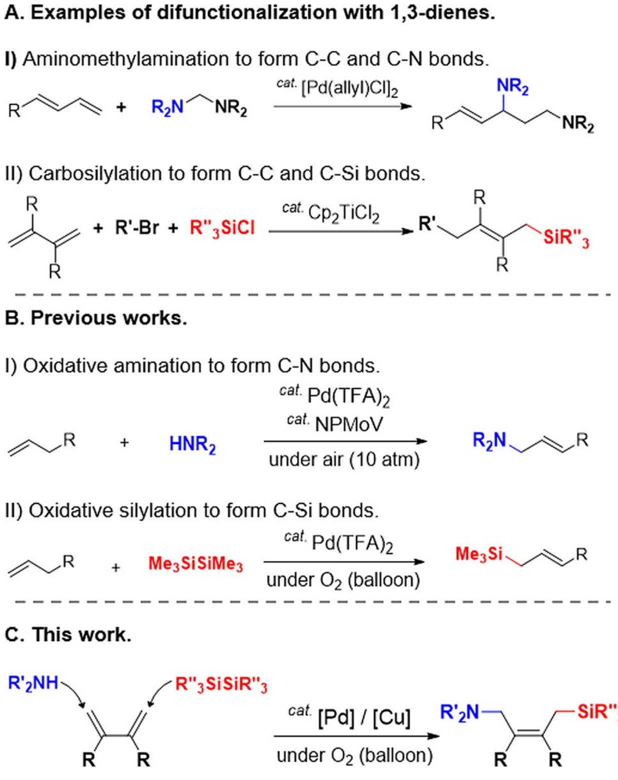
Abstract: A highly regioselective and stereoselective difunctionalization reaction of 1,3-diene with amine and disilane to form C—N and C—Si bonds via a one-step Pd/Cu/O_2 system is disclosed. The difunctionalization reaction affords allylic silanes, including the allylic amine moiety, in up to 92% yield in the absence of any acid, base, or external ligand. The developed synthetic methodology can be scaled to 100 g in high yield with high *Z*-selectivity, which demonstrates the feasibility of the reaction for industrial applications.

Catalytic bond formation reactions have been the subject of a wealth of interdependent research as one of the most useful strategies in the development of organic chemistry, as well as for global industrial growth. Importantly, a wide variety of methods to form C—C bonds, such as classical cross-coupling reactions, have been developed over many decades. These reactions have been designed to produce desired products along with stoichiometric amounts of by-products. In addition, environmentally friendly reactions are desirable to suppress excess energy losses and to reduce waste emissions.



Scheme 1. A) Difunctionalization reaction examples with 1,3-dienes. B) Previous reports. C) Difunctionalization of 1,3-diene to form C—Si and C—N bonds.

Alternatively, difunctionalization reactions with 1,3-dienes have received significant attention over recent decades because 1,3-dienes are regarded as chemical feedstocks, and 1,3-butadiene in particular is produced on a global scale that exceeds 10 million tons per annum.[1–7] These difunctionalization reactions allow 1,3-dienes to form two chemical bonds in one step, which increases the molecular complexity. Thus, difunctionalization reactions of 1,3-dienes are effective methods for organic transformation reactions in terms of atom economy and step economy. Huang and co-workers reported palladium-catalyzed aminomethylamination of 1,3-dienes to form C—C and C—N bonds (Scheme 1 A-I).[8] Terao and Kambe developed a titanium-catalyzed carbosilylation of 1,3-diene using alkyl halides and chlorosilanes to form C—C and C—Si bonds (Scheme 1 A-II).[9] Recently, iron-catalyzed difunctionalization of olefins using hydrosilane and amine to form C—N and C—Si bonds was reported by Song, Li, Luo, and co-workers.[10] However, difunctionalization reactions of 1,3-dienes to form C—N and C—Si bonds, to the best of our knowledge, have not been published.[11] Our group previously reported Pd-catalyzed decarbonylative coupling of 1,3-diene with acyl chloride and disilane to form C—C and C—Si bonds in one step.[12] However, emission of a stoichiometric amount of Me_3SiCl and carbon monoxide remains a significant problem because of the utilization of acylchloride for alkylation into the allyl silane moiety. Furthermore, our group has reported the oxidative amination reaction of simple olefins via a Pd/molybdovanadophosphate salt (NPMoV)/O_2 system for introduction of an amino group (Scheme 1 B-I).[13] Our research has also established oxidative silylation of simple olefins via a Pd/O_2 system for introduction of

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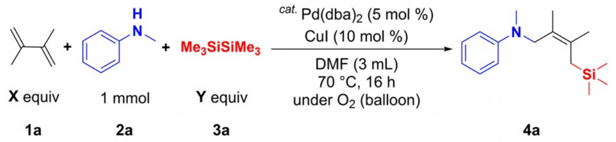
a silyl group (Scheme 1B-II).[14] These reactions proceed under halogen-free conditions using molecular oxygen as the terminal re-oxidant.

Next, our group envisioned a one-step Pd-catalyzed difunctionalization of 1,3-diene with amine and disilane to form C–N and C–Si bonds (Scheme 1C). This reaction provided allylic silane, including the allylic amine framework, in high yield with high chemo-, regio-, and stereoselectivity. Furthermore, the reaction system demonstrates significant advantages as a green reaction procedure and a mild re-oxidation system because a stoichiometric amount of the re-oxidant and halogen reagent are not required.

First, the difunctionalization reaction conditions were optimized (Table 1). The use of 2,3-dimethyl-1,3-butadiene (**1a**), *N*-methylaniline (**2a**), and hexamethyldisilane (**3a**) in the presence of $PdCl_2$ (0.05 mmol, 5 mol%) and CuI (0.1 mmol, 10 mol%) as re-oxidant under an oxygen atmosphere (1 atm, balloon) afforded the desired nitrogen-containing allylic silane **4a** in 36% GC yield (entry 1). $Pd(PPh_3)_4$ was not an effective catalyst in this reaction (entry 2). Compared with these catalysts, $Pd(OAc)_2$ and $Pd(TFA)_2$ exhibited high catalytic activity (entries 3 and 4). Furthermore, the use of $Pd(dba)_2$ gave **4a** in the highest yield (92% GC yield) with high stereoselectivity (92:8, *Z*/*E*) (entry 5).[15] Surprisingly, this reaction proceeded only oxygen atmosphere (entries 5–7). The addition of 1,4-benzoquinone (1 equiv) to the reaction system under Ar gave no reaction (entry 8). These results suggest that molecular oxygen plays a crucial role except in the re-oxidation of the catalytic species. Alternative copper salts were also tested. The use of CuBr improved the yield of **4a** (entry 9). Conversely, CuCl and CuOAc were not efficient re-oxidants (entries 10 and 11) and CuI was superior to any other copper salt. Among the solvents employed in the difunctionalization reaction, amide solvents such as *N*,*N*-dimethylformamide (DMF), *N*,*N*-dimethylacetamide (DMA), and *N*-methylpyrrolidone (NMP) were extremely effective in yielding **4a** (entries 5, 12 and 13). The reaction in the presence of acetonitrile or toluene barely proceeded (entries 14 and 15). The yield of **4a** was also significantly influenced by the substrate ratio (entries 16–18).

Table 1. Optimization of reaction conditions.[a]

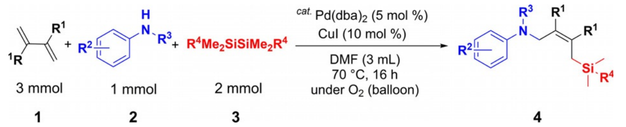


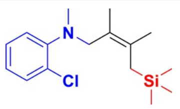
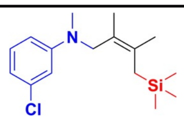
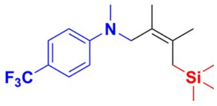
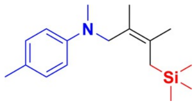
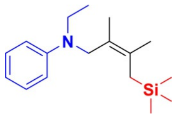
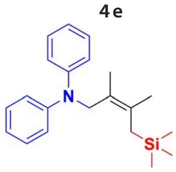
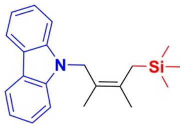
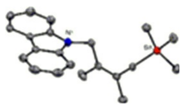
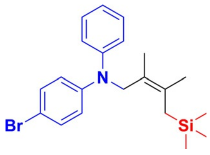
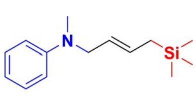
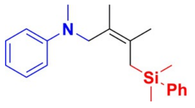
Entry	Pd/Cu	Solvent	X, Y	Yield [%][b]
1	$PdCl_2$/CuI	DMF	3, 2	36(90:10)
2	$Pd(PPh_3)_4$/CuI	DMF	3, 2	34(92:8)
3	$Pd(OAc)_2$/CuI	DMF	3, 2	72(92:8)
4	$Pd(TFA)_2$/CuI	DMF	3, 2	63(94:6)
5	$Pd(dba)_2$/CuI	DMF	3, 2	92[87][c] (92:8)
6[d]	$Pd(dba)_2$/CuI	DMF	3, 2	<1
7[e]	$Pd(dba)_2$/CuI	DMF	3, 2	n.d.[f]
8[g]	$Pd(dba)_2$/CuI	DMF	3, 2	n.d.[f]
9	$Pd(dba)_2$/CuBr	DMF	3, 2	81(91:9)
10	$Pd(dba)_2$/CuCl	DMF	3, 2	28(94:6)
11	$Pd(dba)_2$/CuOAc	DMF	3, 2	34(92:8)
12	$Pd(dba)_2$/CuI	DMA	3, 2	88(92:8)
13	$Pd(dba)_2$/CuI	NMP	3, 2	72(94:6)
14	$Pd(dba)_2$/CuI	MeCN	3, 2	<1
15	$Pd(dba)_2$/CuI	toluene	3, 2	<1
16	$Pd(dba)_2$/CuI	DMF	1, 1	44(94:6)
17	$Pd(dba)_2$/CuI	DMF	3, 1	46(94:6)
18	$Pd(dba)_2$/CuI	DMF	3, 3	93(92:8)

[a] Reaction conditions: **1a** (3 mmol), **2a** (1 mmol), **3a** (2 mmol), Pd catalyst (0.05 mmol, 5 mol%) and additive (0.1 mmol, 10 mol%) were stirred at 70 °C for 16 h under O_2. Yield was determined by GC based on **2a** used (*n*-decane as internal standard). [b] The numbers in parentheses show the *Z*/*E* ratio determined by GC. [c] Number in brackets shows isolated yield. [d] Under air. [e] Under Ar. [f] n.d. = not detected. [g] Benzoquinone (1 equiv) was used under Ar. $Pd(TFA)_2$ = palladium bis(2,2,2-trifluoroacetate); DMF = *N*,*N*-dimethylformamide; DMA = *N*,*N*-dimethylacetamide; NMP = *N*-methyl-2-pyrrolidone.

Thereafter, various amines, dienes, and disilanes were studied for the difunctionalization reaction (Table 2). In the presence of amines, *N*-methylaniline derivatives bearing electron-withdrawing groups such as –Cl or $-CF_3$ were applicable to this reaction and gave corresponding products in good to excellent yields with high *Z*-selectivity (**4b**–**4e**). The reaction with

Table 2. Variation of amines, dienes, and disilanes.[a]



		
69% (88:12) **4b**	85% (87:14) **4c**	83% (84:16) **4d**
		
69% (90:10) **4e**	79% (93:7) **4f**	85% (86:14) **4g**
		
77% (92:8) **4h**	60% (>99:-)[b,c] **4j**	CCDC 2044491[18]
		
92% (94:6)[b] **4i**	51% (11:89)[c,d] **4k**	65% (95:5)[e] **4l**

[a] Reaction conditions: **1** (3 mmol), **2** (1 mmol), **3** (2 mmol), $Pd(dba)_2$ (0.05 mmol, 5 mol%) and CuI (0.1 mmol, 10 mol%) were stirred at 70 °C for 16 h under O_2. The numbers in parentheses show *Z*/*E* ratio determined by GC. [b] Reaction time was 48 h. [c] Disilane (5 mmol) and CuI (0.3 mmol, 30 mol%) were used. [d] DMF (8 mL) was used. [e] CuI (0.3 mmol, 30 mol%) was used.

o-, *m*-, and *p*-chloro-*N*-methylaniline proceeded with yields of 69%–85% (**4b**–**4d**). The use of *N*-methylaniline substituted with an electron-donating group (–CH_3) yielded **4f** in excellent yields. The reaction in the presence of sterically hindered amines, *N*-ethylaniline and diphenylamine, yielded **4g** and **4h** in excellent yields. The highest yield was obtained in the presence of the diphenylamine derivative (**4i**). Significantly, the heterocyclic amine, carbazole, also participated in this reaction and a conformation of **4j** was determined by X-ray crystallographic analysis. However, the reaction with *N*-methylbenzylamine or aniline did not afford the corresponding product under these conditions. Next, the scope of dienes and disilanes was investigated. The reaction with 1,3-butadiene proceeded by employing 8 mL of DMF, and, because of the low boiling point of 1,3-butadiene, the reaction furnished **4k** in moderate yield. In this case, the *E*-isomer was principally obtained because of the smaller steric hindrance compared with **1a**. The reaction to generate **4k** was sluggish under typical reaction conditions. The reaction with 2,3-diphenyl-1,3-butadiene or 1,3-cyclohexadiene was sluggish under these conditions. Other 1,3-dienes such as isoprene or myrcene were tolerable to this reaction; however, the generation of regioisomers increased the difficulty of purifying the reaction mixture. The use of $PhMe_2SiSiMe_2Ph$ as the disilane reagent was successful and gave **4l** in good yield. Unfortunately, other disilanes such as $Ph_2MeSiSiMePh_2$ and $Ph_3SiSiPh_3$ were not suitable in this reaction as a result of their poor solubility in DMF.

To evaluate the utility and scalability of this protocol, scale-up experiments for the synthesis of **4a** were performed (Figure 1 A).[16]

The use of **1a** (29.8 mmol), **2a** (9.9 mmol), and **3a** (19.8 mmol) in the presence of $Pd(dba)_2$ (0.5 mmol, 5 mol%) and CuI (1.0 mmol, 10 mol%) under an oxygen atmosphere (1 atm, balloon) afforded **4a** in a satisfactory yield (87%) with excellent regioselectivity (94:6, *Z*/*E*). Next, the difunctionalization reaction was scaled to 10 g in the presence of 1 mol% (0.5 mmol) of $Pd(dba)_2$ and 2 mol% of Cu (1.0 mmol) using **1a** (151 mmol), **2a** (49 mmol), and **3a** (99 mmol). Product **4a** was obtained in excellent yield (89%) and with high *Z*-selectivity (94:6, *Z*/*E*). Further scale-up achieved the synthesis of more than 150 g of **4a** with excellent *Z*-selectivity based on the reaction of 2.22 mol of **1a**, 0.74 mol of **2a**, and 1.50 mol of **3a** in the presence of $Pd(dba)_2$ (7.5 mmol, 1 mol%) and CuI (15 mmol, 2 mol%). These results demonstrate the feasibility of this reaction strategy for industrial application.

We envisioned four plausible reaction pathways (A–D) (Scheme S1). In path A, 1,3-dienes reacted with amine via oxidative amination, followed by silylation with disilane. Path B

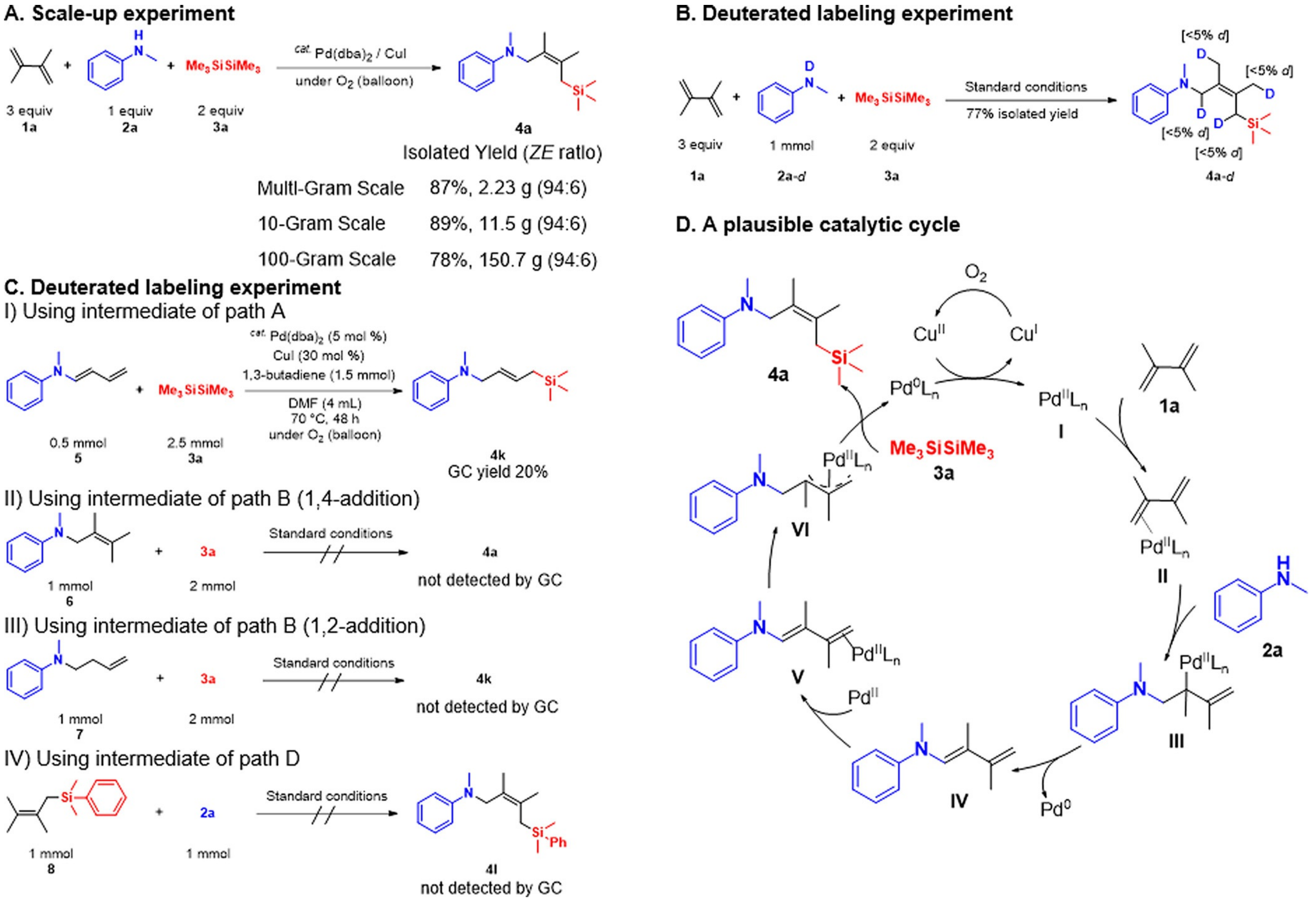


Figure 1. A) Scale-up experiment for multi-gram, 10 g, and 100 g scale synthesis of **4a**. B) Deuterated labeling experiment using **2a**-*d*. C) Mechanistic studies. (D) A plausible catalytic cycle for the difunctionalization reaction.

sees hydroamination of 1,3-diene via 1,2- or 1,4-addition and then silylation occurs. In the third possible mechanism described as path C, a silyl group is introduced to 1,3-diene before the oxidative amination process. Alternatively, oxidative amination takes place after introduction of the silyl group to 1,3-diene in path D. To gain insight into the reaction mechanism, a deuterated labeling experiment was performed substituting **2a** with **2a**-*d* under standard conditions (Figure 1B). Deuterated **4a** was not observed from this experiment, which rules out the hydroamination path (Path B and C). Further investigation was performed by using possible reaction intermediates (Figure 1C).[16] The oxidative amination product **5**, which is the intermediate of path A was reacted with hexamethyldisilane in the presence of Pd(dba)$_2$ and CuI in DMF at 70 °C for 48 h, furnishing the desired product **4k** in 20% yield as determined by GC (Figure 1C-I). Compound **5** was not formed when the reaction was performed without disilane. When intermediates of hydroamination of 1,3-diene (**6** and **7**) reacted with **3a** under standard conditions, desired product **4a** was not observed (Figure 1C-II and III). An intermediate of silylation of 1,3-diene **8** of path D did not react with **2a** (Figure 1C-IV). These results suggest that **5** is the intermediate of this difunctionalization reaction via oxidative amination followed by silylation.

From the results of mechanistic studies and previous reports, a plausible catalytic cycle for the difunctionalization reaction is shown in Figure 1D.[14,17] First, Pd^{II} (**I**) coordinates with 1,3-diene (**1a**) to afford intermediate **II**. Thereafter, nucleophilic amine (**2a**) undergoes an intermolecular nucleophilic attack to form intermediate **III**. β-hydride elimination of intermediate **III** leads to intermediates **IV**, followed by the production of intermediate **V** by coordination of Pd^{II}. Finally, π-allyl intermediate **VI** is formed from **V** and reacts with disilane (**3a**) to give desired product (**4a**) along with metallic Pd, which is oxidized to Pd^{II} by Cu and O$_2$. Previously, our group reported that Pd/π-allyl intermediate could react with disilanes.[14] Therefore, the mechanism involves oxidative amination, leading to Pd/π-allyl formation, followed by silane functionalization and reoxidation.

In conclusion, a highly regioselective and stereoselective difunctionalization reaction of 1,3-dienes with amine and disilane was developed using molecular oxygen as the terminal re-oxidant. The reaction produces allylic silanes, including the allylic amine moiety, in up to 92% yield and scale-up has been demonstrated for more than 150 g. Further investigations of the detailed reaction mechanism and applications of this methodology in medicinal or biological chemistry are in progress.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: difunctionalization · molecular oxygen · oxidative amination · palladium · regio- and stereoselective

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[15] We conducted computational calculations of the Gibbs free energy (kcal mol^{-1}) between *Z* and *E* isomers of **4a** at the M06-2X/6–311+G(d,p)//B3LYP/6–31+G(d,p) level of theory with Gaussian 16. All calculated data involve Gibbs energy using thermal corrections at 343 K with

CPCM model (DMF solvent). The results showed that *Z* isomer is thermodynamically more stable than *E* isomer (see the Supporting Information).

[16] For detailed reaction conditions, see the Supporting Information.

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[18] Deposition Number 2044491 contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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