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Pd-Catalyzed Modifiable Silanol-Directed Aromatic C–H Oxygenation

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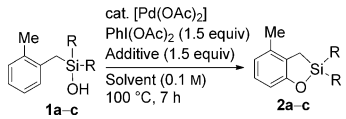
Transition-metal-catalyzed C–H functionalizations have emerged as a powerful tool for the synthetic community.[1] One common strategy involves the use of directing groups to achieve high reactivity and selectivity.[1d–g] As a broad spectrum of C–H functionalizations becomes a toolkit of choice, the expansion of substrate scope is therefore in a high demand. Recently, the employment of removable and/or modifiable directing groups has allowed an orthogonal diversification of C–H functionalized products.[2] This strategy illuminates an avenue for a quick functionalization of products obtained by C–H functionalization. Along the line of our development on silicon-tethered removable/modifiable directing groups,[3] we have shown that silanol[4] acts as a traceless directing group for the synthesis of catechols from phenols.[4a] Herein, we report the Pd-catalyzed, modifiable benzylsilanol-directed aromatic C–H oxygenation towards oxasilacycles—versatile intermediates for organic synthesis (vide infra).

Carbon-based silicon tethers have been shown to exhibit a high degree of diversification.[3,5] Thus, we started by searching a suitable carbon-based organosilanol for our method design. Given the similarity between silanol and alcohol and the generality of hydroxyl-directed C–H oxygenation[6] reaction developed by Yu and co-workers,[7] three benzyl-bound silanols[8] were tested under Yu's oxidative C–O cyclization conditions (Table 1). Dimethylsilanol **1a**, an established nucleophilic component in Hiyama–Denmark cross-coupling reaction,[9] was tested first. However, the reaction with $PhI(OAc)_2$ and Li_2CO_3 in the presence of 10 mol% $[Pd(OAc)_2]$ in dichloroethane (DCE) at 100 °C led to decomposition of starting material, providing only trace amounts of cyclized product **2a** (Table 1, entry 1). Likewise, diphenylsilanol **1b**[10] also decomposed under these conditions (Table 1, entry 2). However, bulkier diisopropyl benzylsilanol **1c**, which was previously reported in an oxidative Heck reaction,[4c] was stable yet reactive enough under the C–O cyclization conditions to produce five-membered oxasilacycle **2c** in 35% GC yield (Table 1, entry 3). The reactions under base-free conditions usually afforded higher yields of **2c** (Table 1, entries 3–6). Performing the reaction in $PhCF_3$ resulted in an increased yield (Table 1, entry 7). The catalyst loading was reduced to 5 mol% without loss of efficiency (Table 1, entry 9). Employment of $[Pd(OPiv)_2]$, which was previously found superior for phenoxysilanol-directed catechol synthesis,[4a] resulted in a reduced yield (Table 1, entry 10).[11]

Table 1. Optimization of reaction conditions.



	Substrate	Pd [mol%]	Additive	Solvent	Yield [%][a]
1	**1a** (R=Me)	10	Li_2CO_3	DCE	trace
2	**1b** (R=Ph)	10	Li_2CO_3	DCE	0
3	**1c** (R=*i*Pr)	10	Li_2CO_3	DCE	35
4	**1c**	10	none	DCE	46
5	**1c**	10	Li_2CO_3	PhMe	42
6	**1c**	10	none	PhMe	54
7	**1c**	10	none	$PhCF_3$	73
8[b]	**1c**	10	none	PhMe	49
9	**1c**	5	none	$PhCF_3$	73
10[c]	**1c**	5	none	$PhCF_3$	60

[a] GC yields. [b] The reaction concentration was 0.05 M. [c] $[Pd(OPiv)_2]$ (5 mol%) was used as the catalyst.

Next, the generality of this transformation was examined (Table 2). It was found that both alkyl and aryl groups can be tolerated at *ortho*-, *meta*-, and *para*-positions of aromatic rings (Table 2, entries 1–7). For *meta*-substituted substrates **1i–j**, the oxygenation selectively goes to the less hindered C–H site. Besides, silanols **1m** and **1n** substituted at the benzylic position were also competent reactants in this transformation (Table 2, entries 8–9). Moreover, naphthalene-based silanol **1o** smoothly underwent oxidative cyclization to produce tricyclic product in 70% yield. Remarkably, tetralin- (**1p**), chroman- (**1q**), and benzosuberan (**1r**)-derived silanols were efficiently transformed into their corresponding tricyclic products in good-to-high yields (Table 2, entries 11–13). It deserves mentioning that the reaction can be easily scaled up to gram scale with comparable yields (Table 2, entry 7).

To verify whether this transformation, similarly to the previously developed silanol-directed oxygenation reaction [Eq. (1)],[4a] proceeds via an acetoxylated intermediate of type **B**, a GC monitoring of the oxygenation reaction of **1c** was performed. Surprisingly, the reaction profile showed no formation of substantial amounts of acetoxylated intermedi-

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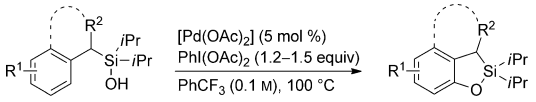
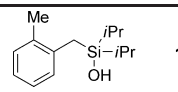
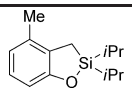
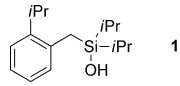
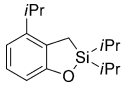
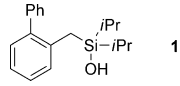
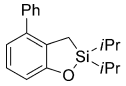
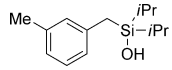
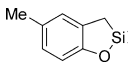
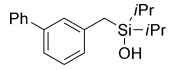
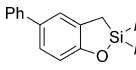
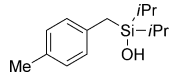
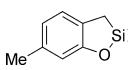
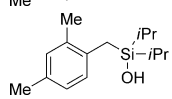
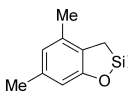
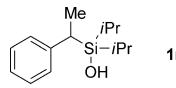
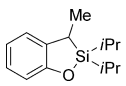
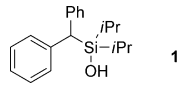
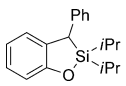
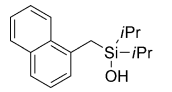
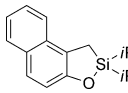
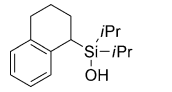
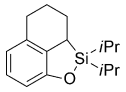
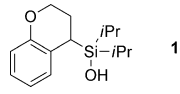
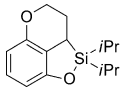
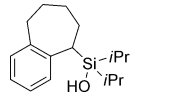
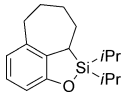
Table 2. Reaction scope of silanol-directed C–H oxygenation.



1 2

	Substrate		Product		Yield [%][a]
1		1c		2c	72
2		1g		2g	87
3		1h		2h	74
4		1i		2i	50[b,c] (72)
5		1j		2j	(71)[c]
6		1k		2k	(66)
7		1l		2l	68 (85) 83[b,d]
8		1m		2m	69[b] (80)
9		1n		2n	58 (76)
10		1o		2o	70
11		1p		2p	77
12		1q		2q	58
13		1r		2r	90

[a] Isolated by column chromatography on Florisil®. ^{1}H NMR yields are provided in the parentheses. [b] Isolated by Kugelrohr distillation. [c] Regioselectivity is >20:1. [d] Gram scale (5 mmol), isolated with 92% purity.

ate **3c** (<3%) during the reaction course (Figure 1). Next, ^{18}O-labeled silanol **4** was subjected to the reaction under the standard conditions. It was found that, accompanied by the formation of **2g**, cyclized product **5** with ^{18}O label was indeed formed. Moreover, the amount of ^{18}O label in the cyclized products was lower than that of **4** and gradually decreased as the reaction proceeded. The test experiments indicated no ^{16}O/^{18}O scrambling in the starting silanol **4** throughout the reaction course occurred (Figure 2). Likewise, prolong (overnight) heating of the completed reaction did not change ^{18}O-label incorporation in the cyclized products. We envisioned that the in situ generation and accumulation of HOAc[13] during the reaction could be responsible for the observed downhill trend of ^{18}O-label incorporation in the products. To verify the role of HOAc, additional experiments with exogenous HOAc were performed in the presence of base (Li_2CO_3). As expected, the abundance of ^{18}O label in the products was substantially lower under acidic conditions, but higher under the basic media compared to that under the additive-free reaction conditions (Figure 2).

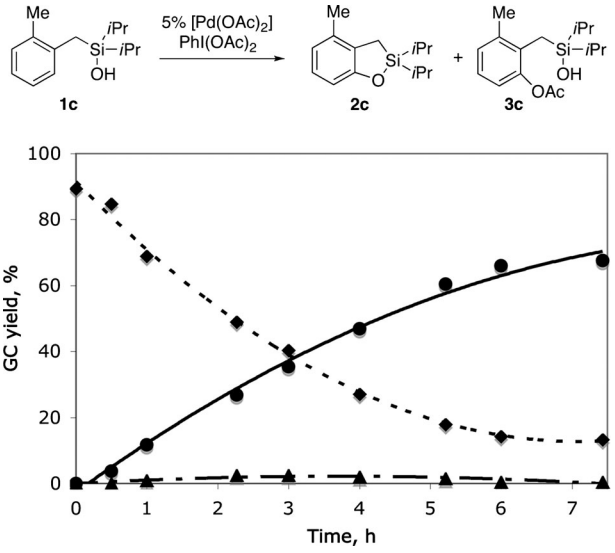
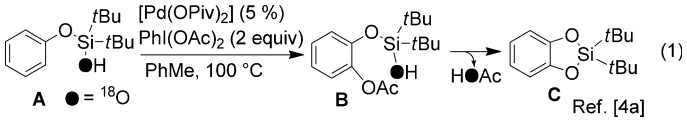


Figure 1. Reaction profile.[12] The reaction was monitored by GC/MS with tetradecane as the internal standard. ◆=**1c**; ●=**2c**; ▲=**3c**.



(1)

Although the mechanistic details of this transformation are still unclear, the above observations indicate on two possible general pathways (Scheme 1). According to the first path, the partial loss of ^{18}O label in the products suggests the possibility of the previously proposed reaction route, featuring an acetoxylation/cyclization sequence (path **A**).[4a] Alternatively, the formation of ^{18}O-enriched product **5** implies the possibility of a direct reductive C–O cyclization[7a] (path **B**).[14]

To test the feasibility of this oxygenation reaction on sp^3 C–H systems, silanols **D** and **E** were subjected to the standard oxygenation reaction conditions. However, instead of benzylic C–H activation reaction toward silacycles **D′** and **E′**, an *ipso*-acetoxydesilylation occurred, producing acyloxy benzenes **D″** and **E″** in 83 and 67% yield, respectively

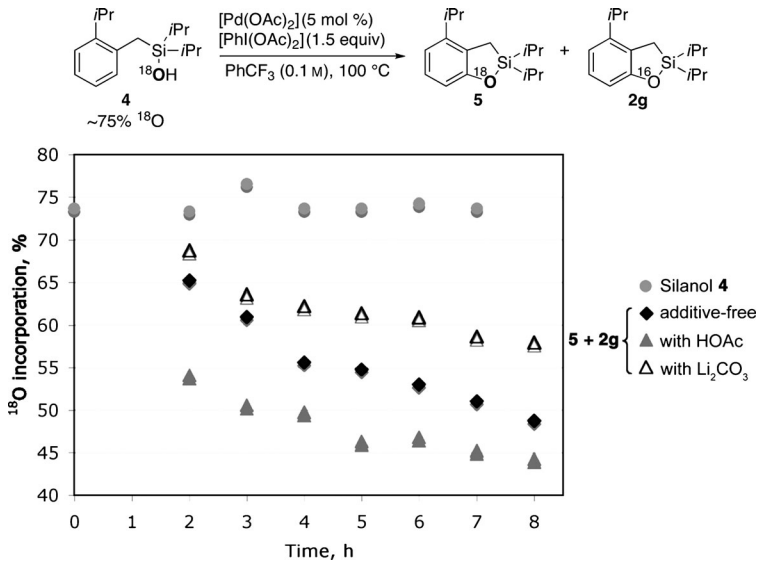
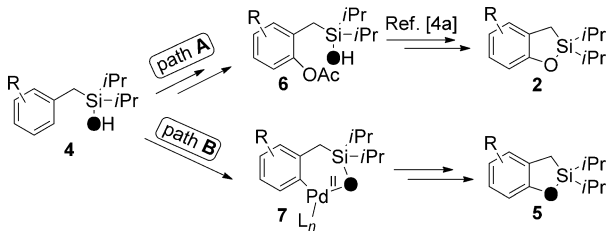
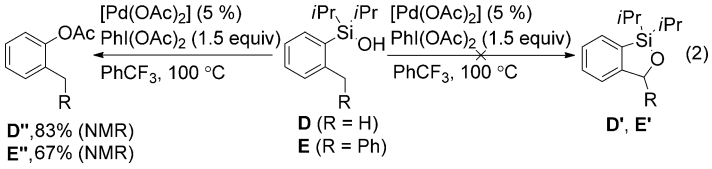


Figure 2. The abundance of ^{18}O incorporation in the starting silanol **4** shown with solid circles, the abundance of ^{18}O incorporation in the cyclized products (additive-free conditions with solid squares; acidic conditions with solid triangles; basic conditions with hollow triangles).

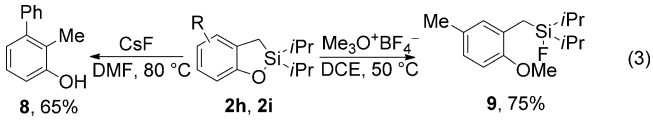


Scheme 1. Possible reaction pathways.

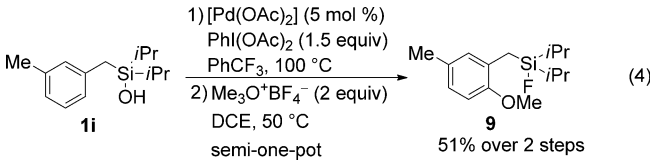
[Eq. (2)]. These results suggest that this method is effective for aromatic C–H oxygenation reaction only.[15]



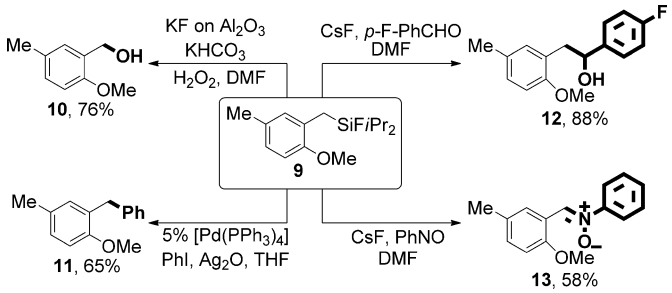
We envisioned that the synthesized cyclic molecules, containing an easily cleavable Si–O bond and a potentially modifiable C–Si bond, could serve as a precursor for a variety of valuable products. Indeed, Tamao and co-workers have showed in a single example that this type of oxasilacycles is useful to achieve functional-group-compatible Kumada cross-coupling reactions.[16] However, their synthetic usefulness has not yet been extensively exploited. Encouraged by our previous success on the modification of silicon-tethered directing groups,[3] we were interested to investigate the synthetic potential of oxasilacycles as useful building blocks in organic synthesis. As expected, desilylation of cyclic product **2h** with CsF in DMF gave phenol **8** in good yield [Eq. (3)]. In addition, thermodynamically stable cyclic structure **2** can be efficiently opened up with Meerwein salt in a single step [Eq. (3)]. In this hitherto unknown transformation, which we proposed to proceed through a cationic concerted asynchronous mechanism (supported by DFT calculations),[12] trimethyloxonium tetrafluoroborate plays a double duty: it delivers the methyl cation to the oxygen atom and the fluoride anion to the silicon atom. The oxygenation and ring opening steps could also be performed in a semi-one-pot manner, affording compound **9** from silanol **1i** in 51% overall yield [Eq. (4)].



The resulted fluorosilane **9** opened up broader opportunities for the subsequent modifications. As illustrated in Scheme 2, Kumada oxidation[17] of **9** gave benzyl alcohol **10** in 76% yield. Fluoride-free Hiyama–Denmark cross-coupling of **9** with phenyl iodide, under conditions reported by Yoshida and co-workers,[18] afforded diarylmethane derivative **11** in 65% yield. Moreover, fluorosilane **9** in the presence of CsF can be employed as an equivalent of Grignard reagent in the reaction with aldehydes.[19] Finally, an unprecedented transformation en route to nitrone derivative **13** was discovered upon treatment of benzylsilane **9** with nitrosobenzene in the presence of CsF.[12]



In summary, Pd-catalyzed benzylsilanol-directed *ortho* C–H oxygenation of aromatic rings was developed. This method allows efficient synthesis of oxasilacycles, which are valuable synthetic intermediates. The synthetic usefulness was highlighted by an efficient removal of the silanol-directing group and by its conversion into a variety of valuable functionalities. These transformations include known Tamao oxidation, Hiyama–Denmark cross-coupling, and nucleophilic addition, as well as unprecedented Meerwein salt-mediated ring-opening of oxasilacycles and nitrone formation from a benzylsilane and a nitroso compound.



Scheme 2. Further transformations.

Experimental Section

General procedure: An oven-dried Wheaton V-vial (10 mL), containing a stirring bar, was charged with benzylsilanols **1** (0.5 mmol), [Pd(OAc)$_2$] (5.6 mg, 0.025 mmol) and PhI(OAc)$_2$ (0.6–0.75 mmol) under N_2 atmosphere. Dry α,α,α-trifluorotoluene (5 mL) was added by syringes, and the reaction vessel was capped with pressure screw cap. The reaction mixture was heated at 100 °C for 7 h. The resulting mixture was cooled to RT and filtered through a short layer of Celite plug with the aid of EtOAc. The filtrate was concentrated under a reduced pressure. The residue was purified by column chromatography on Florisil® (eluent: hexanes/EtOAc) giving the corresponding cyclized products **2**.

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Keywords: C–H activation · oxygenation · palladium · silanol · synthetic methods

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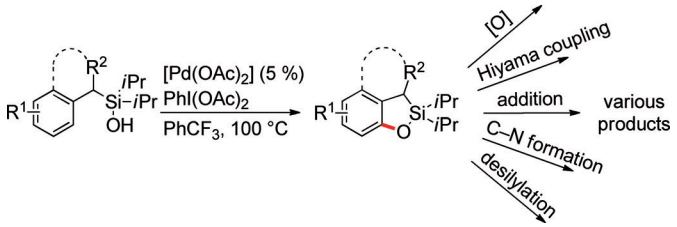

Directing group: A Pd-catalyzed aromatic C–H oxygenation has been developed, featuring a modifiable silanol-directing group. The resulted oxasilacycles can be efficiently modified into a variety of valuable building blocks (see scheme).

