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Silanol: A Traceless Directing Group for Pd-Catalyzed *o*-Alkenylation of Phenols

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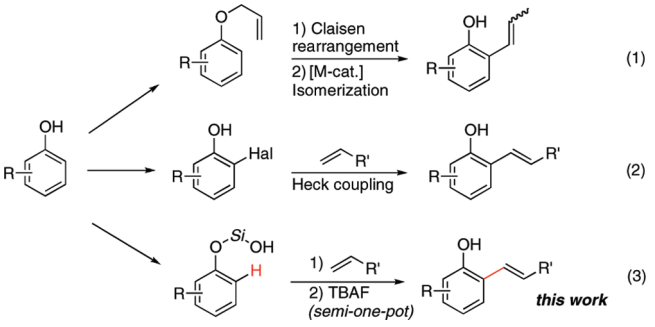
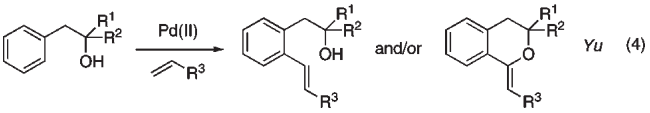
Supporting Information

ABSTRACT: A silanol-directed, Pd(II)-catalyzed C−H alkenylation of phenols is reported. This work features silanol, as a novel traceless directing group, and a directed *o*-C−H alkenylation of phenols. This new method allows for efficient synthesis of diverse alkenylated phenols, including an estrone derivative.

Ortho-Alkenyl phenols are important building blocks for synthetic organic chemistry.[1] Traditionally, these synthons can be assembled via a combined Claisen rearrangement of *O*-allylphenols to *C*-allylphenols followed by a transition metal-catalyzed double bond isomerization process (eq 1).[2] This method is not general, as the Claisen rearrangement may produce a mixture of *ortho*- and *para*-allylphenols. Besides, the stereoselectivity of the isomerization step is ambiguous. Another common route to *ortho*-alkenyl phenols involves consecutive *ortho*-halogenation/Mizoroki-Heck cross-coupling reaction[3] with alkenes (eq 2). The requisite of extra *ortho*-prefunctionalization step and concomitant overbromination byproducts significantly limits the wide application of this approach.[4] More directly, *orhto*-alkenylation reaction of phenols with terminal alkynes can be promoted by a Lewis acid, such as $SnCl_4$.[5] An obvious drawback of this method is an employment of stoichiometric amounts[6] of a toxic tin reagent. Herein, we wish to report a silanol group-directed Pd-catalyzed *ortho* C−H alkenylation of phenols to produce diverse *ortho*-alkenyl derivatives in good to high yields (eq 3).



Transition metal-catalyzed directed C−H[7] alkenylaton[8] reactions have emerged as attractive alternative to the Mizoroki−Heck reaction. A directing group is usually introduced to control the regioselectivity as well as to enhance the reactivity of the reaction.[9] We were intrigued by the possibility to develop a method that would employ an easily removable directing group at the phenol, which would allow for a general synthesis of alkenylated phenols.[10,11] Recently, we reported a traceless/modifiable silicon-tethered directing group[12] (PyDipSi) for *ortho*-acyloxylation and halogenation of arenes.[13] Hence, we envisioned that employment of a temporary silicon-tethered directing group for phenols might be beneficial as it can efficiently be removed under mild conditions. In a recent report, Yu disclosed an elegant hydroxyl-directed *ortho*-C−H alkenylation of β-phenethylalcohols en route to alkenylaed arenes and/or benzopyrans (eq 4).[14,15] Inspired by the successful alcohol-directed C−H functionalization reactions[14,15] and efficient silicon-tethered directing group employment in C−H functionalizations,[13] we hypothesized that silanol may serve as an ideal easily removable directing group for C−H alkenylation of phenols.[16]



To test this hypothesis, silanol[17] **1a** (1 equiv) was treated with butyl acrylate (**2a**, 2 equiv) under the conditions employing amino acid-derived ligand developed by Yu[14] (10 mol % $Pd(OAc)_2$, 20 mol % (+)menthyl(O_2C)-Leu-OH (**L1**), 1 equiv Li_2CO_3, 4 equiv AgOAc, in C_6F_6 at 100 °C). To our delight, the desired *ortho*-alkenylated product **3a** was formed in 52% NMR yield (Table 1, entry 1). Solvent optimization indicated $PhCF_3$ to be similarly efficient (entry 2), whereas employment of other solvents, such as toluene, dioxane, THF, *t*-AmylOH, and DMF gave poor yields. Finally, switching to DCE improved the yield of the reaction (78% NMR yield, entry 7).

Next, the removal of the silanol directing group was examined. Expectedly, desilylation of **3a** with TBAF proceeded uneventfully, producing the unprotected phenol **4a** in 84% yield (eq 5) or in 66% yield over two steps. It deserves mentioning that better efficiency was achieved by carrying out two steps, C−H alkenylation/desilylation, in *semi-one-pot* fashion[18] (Table 2, entry 1).

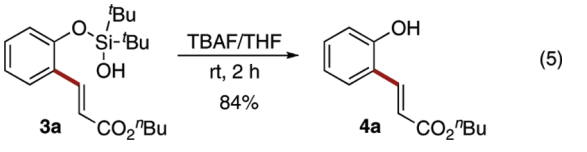


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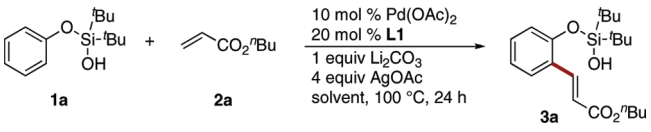
Table 1. Solvent Screening for Silanol-Directed Alkenylation[a]



entry	solvent (0.1 M)	conversion,%[b]	yield, %[c]
1	C_6F_6	77	52
2	$PhCF_3$	79	50
3	PhMe	43	24
4	dioxane	18	<3
5	THF	4	<3
6	*t*-AmylOH	26	<3
7	**DCE**	**90**	**78**
8	DMF	55	0

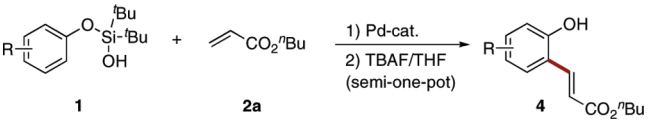
[a] **1a**/**2a** = 1: 2, **L1** = (+)menthyl(O_2C)-Leu-OH. [b] Consumption of starting material **1a** measured by GC/MS. [c] ^{1}H NMR yield.

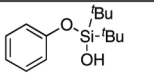
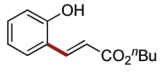
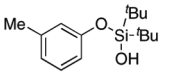
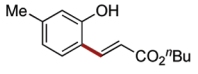
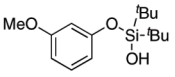
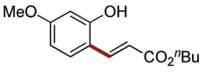
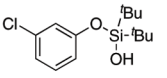
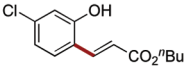
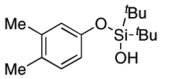
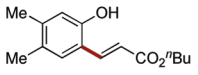
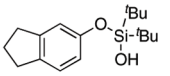
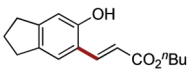
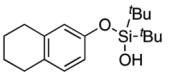
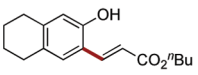
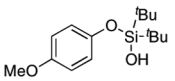
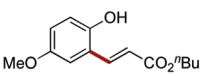
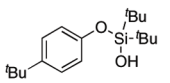
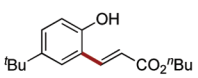
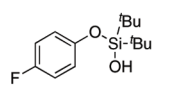
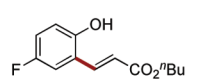
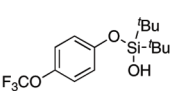
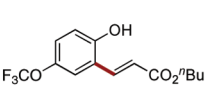
After developing the semi-one-pot procedure for the Pd-catalyzed silanol-directed C−H alkenylation/deprotection sequence, the scope of this new method was investigated. Table 2 summarizes olefinations of various phenol-derived silanols with butyl acrylate (**2a**) to produce the corresponding 2-hydroxy butyl cinnamates **4**. It was found that diverse alkyl-, methoxy-, trifluoromethoxy-, chloro-, and fluoro-substituents (entries 1−5, 8−11) were tolerated well under these reaction conditions. Moreover, 5-indanol and tetrahydro-2-naphthol reacted smoothly to afford the olefinated phenols in good to excellent yields (entries 6 and 7). Notably, *meta*-substituted substrates (entries 2−4) reacted regioselectively at the sterically less hindered C−H site. In general, electron-rich phenols gave better yields of the olefinated products compared to their electron-deficient counterparts. Remarkably, in contrast to most of the reported C−H alkenylation reactions,[19] this Pd(II)-catalyzed olefination reaction is *monoselective*. Most likely, the bulky *tert*-butyl groups at the silanol moiety prevent orientation of the silanol directing group toward the less hindered C−H site, thus, effectively stopping the reaction at the monoalkenylation stage.

Next, we turned our attention to the scope of olefins. It was found that a wide range of electron-deficient alkenes could be successfully employed in this transformation (Table 3). Thus, vinylsulfonate **2b** and vinylsulfone **2c** readily reacted with silanol **1e** to give the olefinated products in very good yields (entries 1, 2). Acrolein (**2d**) and alkyl vinyl ketones **2e** and **2f** are also capable reactants in this olefination reaction (entries 3−5). Moreover, styrene and its derivatives, smoothly reacted with **1e** to give (*E*)-2-styrylphenols **4q**−**4t** in reasonable yields (entries 6−9). 1,1-Disubstituted acrylate **2k** reacted with **1e** to give expected product **4u**,[20] along with its isomer **4v** in 45% and 39% NMR yields, respectively.[9b]

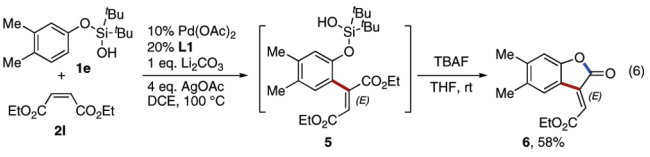
Furthermore, the reaction of **1e** with diethyl maleate (**2l**) under the standard reaction conditions produced alkenylated product **5**, which upon desilylation/cyclization, led to the formation of lactone **6** in 58% yield (eq 6).[20] It should be mentioned that this example represents the first synthesis of a benzofuranone from a simple phenol featuring a C−H activation strategy.

Table 2. Phenol Scope for Silanol-Directed Alkenylation



entry	substrate		product		yield, %[a]
1		**1a**		**4a**	72
2		**1b**		**4b**	94
3		**1c**		**4c**	97
4		**1d**		**4d**	53[b]
5		**1e**		**4e**	97
6		**1f**		**4f**	88[b]
7		**1g**		**4g**	97
8		**1h**		**4h**	81
9		**1i**		**4i**	89
10		**1j**		**4j**	58[b]
11		**1k**		**4k**	52[b]

[a] Isolated yield. [b] The yield was measured by ^{1}H NMR analysis using CH_2Br_2 as internal standard.



Finally, an application of this novel alkenylation methodology on the olefination of a more complex substrate estrone was tested. Thus, the corresponding silanol **7** underwent a smooth alkenylation/desilylation reaction sequence to produce the olefinated estrone **8** as a single regioisomer in 89% yield (eq 7).[21] This example showcases the viability of employment of this

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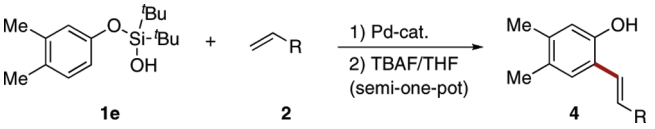
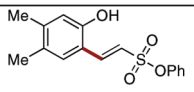
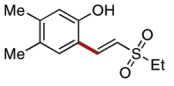
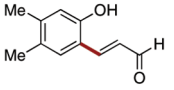
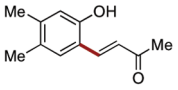
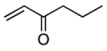
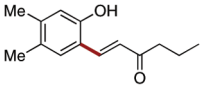
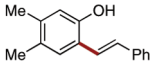
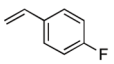
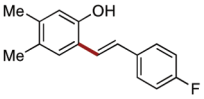
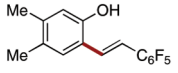
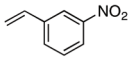
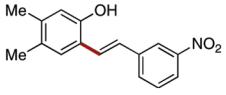
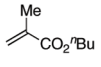
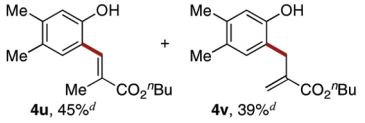
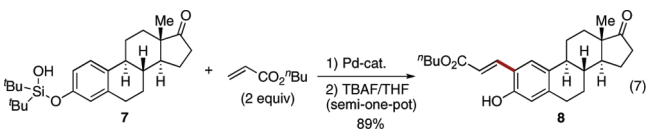
Table 3. Alkene Scope for Silanol-Directed Alkenylation



entry	substrate		product		yield, %[a]
1		**2b**		**4l**	96
2		**2c**		**4m**	87[b]
3		**2d**		**4n**	70[b]
4		**2e**		**4o**	67[b]
5		**2f**		**4p**	69[b]
6		**2g**		**4q**	64[c,d]
7		**2h**		**4r**	79
8		**2i**		**4s**	83
9		**2j**		**4t**	66
10		**2k**	 **4u**, 45%[d] + **4v**, 39%[d]		

[a] Isolated yield. [b] Alkene **2** (4 equiv), Boc-Val-OH (20 mol %) as the ligand, 110 °C. [c] Styrene (4 equiv), 120 °C. [d] ^{1}H NMR yield.

method for a late-stage modification of complex phenol-containing bioactive molecules toward a diversity-oriented drug discovery.[22]



In summary, we have shown that the di-*tert*-butylsilanol can serve as a new and efficient directing group for the palladium-catalyzed *ortho*-alkenylation of phenols. Employment of this directing group is very convenient as it can easily be removed under mild conditions. A synthetic usefulness of this novel alkenylation method was further demonstrated in the efficient synthesis of benzofuranone and alkenylated estrone derivative.

■ ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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