Published in final edited form as:
J Am Chem Soc. 2011 August 17; 133(32): 12406–12409. doi:10.1021/ja204924j.

Silanol - a Traceless Directing Group for Pd-Catalyzed o-Alkenylation of Phenols

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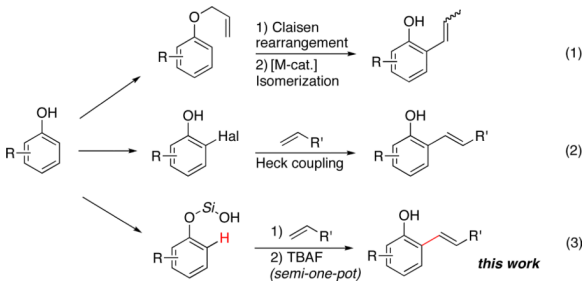
Abstract

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 over-bromination byproducts significantly limit wide applicaton 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

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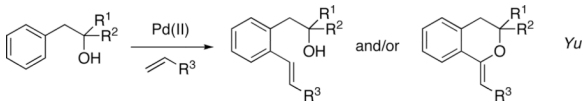
Supporting Information. Detailed experimental procedures and charcterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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

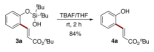


(4)

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).

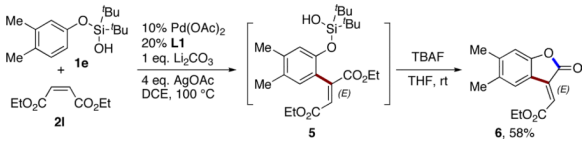


(5)

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 *mono-selective*. 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 **4p-4s** 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.



(6)

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**

(7)

as a single regioisomer in 89% yield (eq 7).[21] This example showcases the viability of employment of this 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 usefullness of this novel alkenylation method was further demonstrated in the efficient synthesis of benzofuranone and alkenylated estrone derivative.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the National Institutes of Health (GM-64444) for financial support of this work.

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15. For hydroxyl group as a directing group, see also: (a) Terao Y, Wakui H, Satoh T, Miura M, Nomura M. J. Am. Chem. Soc. 2001; 123:7725. [PubMed: 11481006] (b) Satoh T, Kawamura Y, Miura M, Nomura M. Angew. Chem., Int. Ed. 1997; 36:1740. (c) Wang X, Lu Y, Dai H-X, Yu J-Q. J. Am. Chem. Soc. 2010; 132:12203. [PubMed: 20715820] (d) Lu Y, Leow D, Wang X, Engle KM, Yu J-Q. Chem. Sci. 2011; 2:967.

16. To the best of our knowledge, there are no reports on employment of silanol as a directing group in C-H functionalization reactions.

17. Silanols **1** were prepared in a semi-one-pot reaction of phenols with di-*t*-butylchlorosilane, followed by bromination and hydrolysis. See Supporting Information for details. For published two-step procedure, see: Petit M, Chouraqui G, Aubert C, Malacria M. Org. Lett. 2003; 5:2037. [PubMed: 12790522]

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20. The stereochemistry was determined by NOE experiments.

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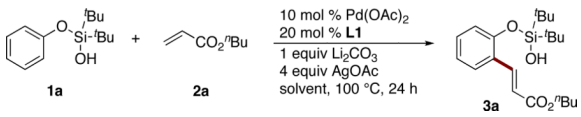
Table 1

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

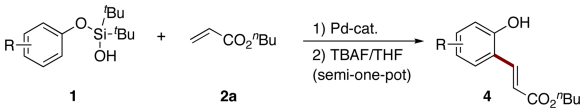
[a] **1a**/**2a** = 1 : 2, **L1** = (+)Menthyl(O_2C)-Leu-OH.

[b] Consumption of starting material **1a** measured by GC/MS.

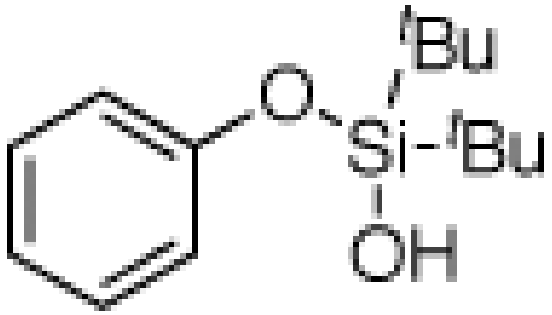
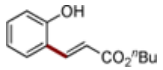
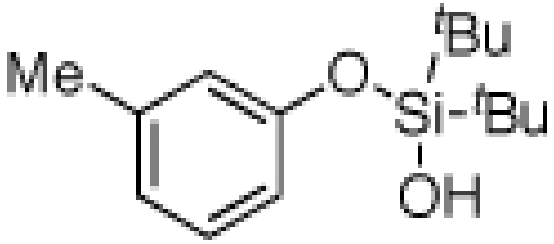
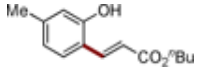
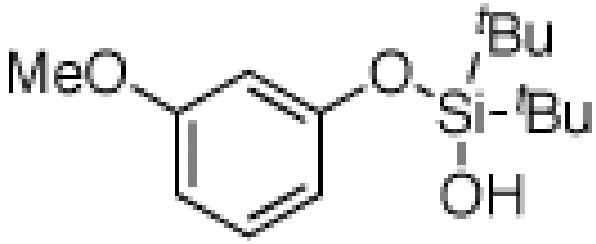
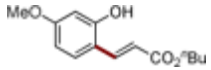
[c] ^{1}H NMR yield.

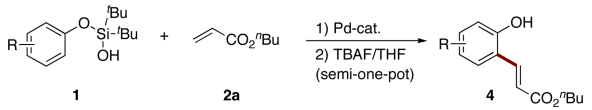
Table 2

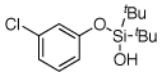
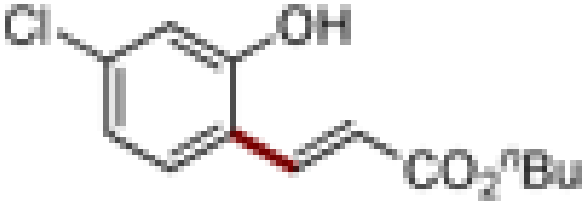
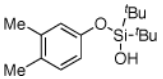
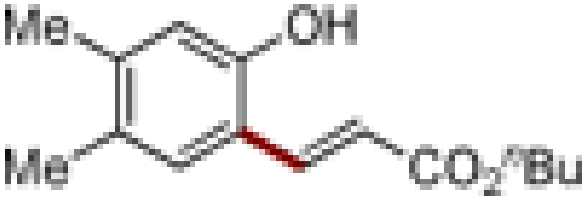
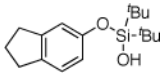
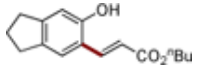
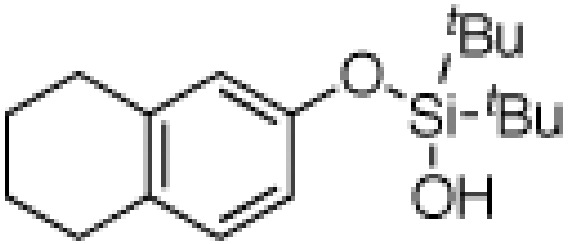
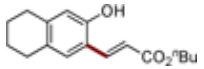
Phenol Scope for Silanol-Directed Alkenylation



1 2a 4

entry	substrate		product		yield, %[a]
1		**1a**		**4a**	72
2		**1b**		**4b**	94
3		**1c**		**4c**	97



entry	substrate		product		yield, %[a]
4		**1d**		**4d**	53[b]
5		**1e**		**4e**	97
6		**1f**		**4f**	88[b]
7		**1g**		**4g**	97

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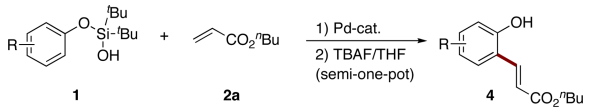
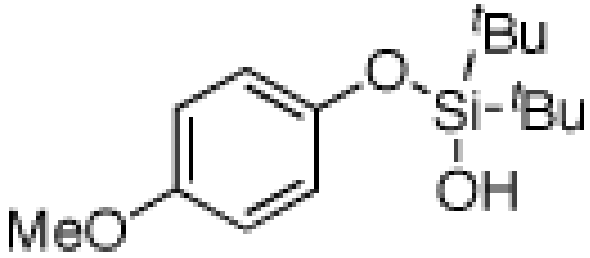
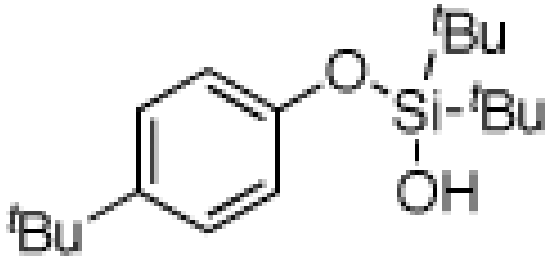
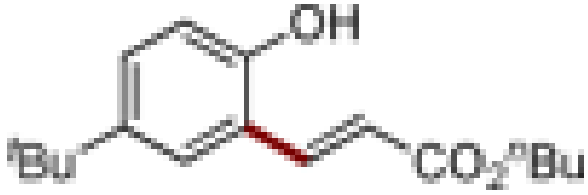
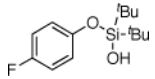
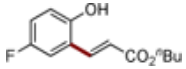
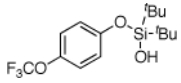


1 2a 4

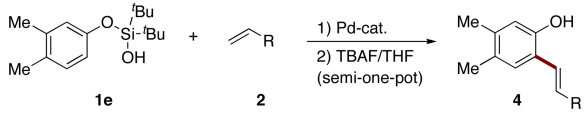
entry	substrate		product		yield, %[a]
8		**1h**		**4h**	81
9		**1i**		**4i**	89
10		**1j**		**4j**	58[b]
11		**1k**		**4k**	52[b]

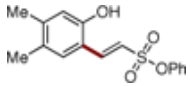
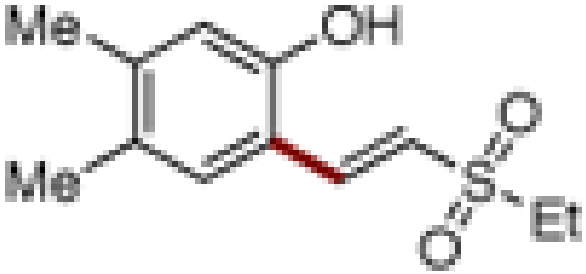
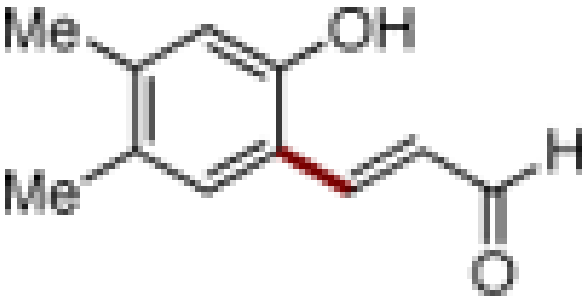
[a] Isolated yield.

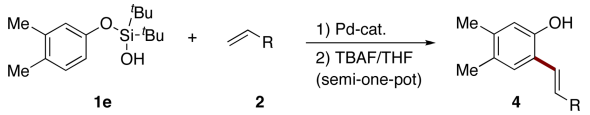
[b] The yield was measured by ^{1}H NMR analysis using CH_2Br_2 as internal standard.

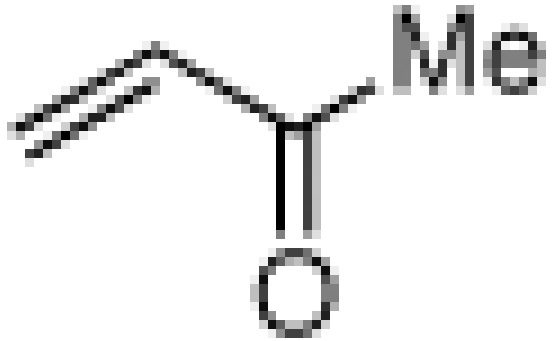
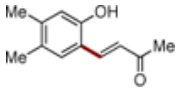
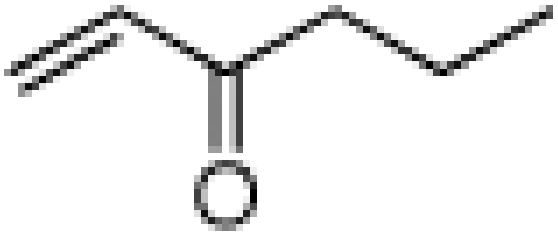
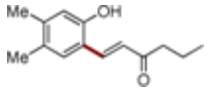
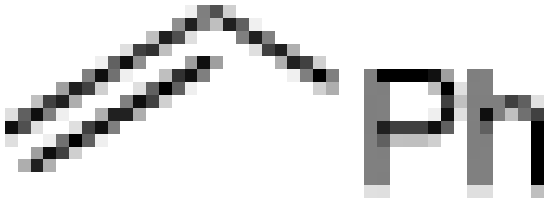
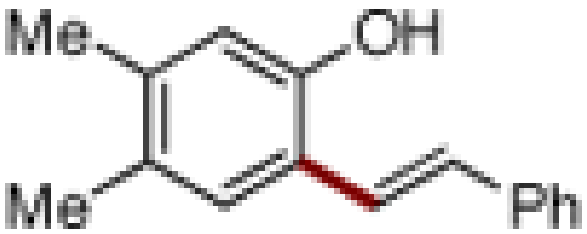
Table 3

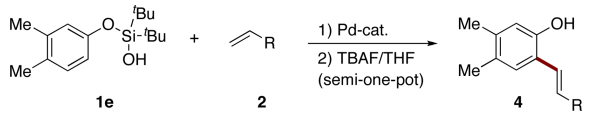
Alkene Scope for Silanol-Directed Alkenylation

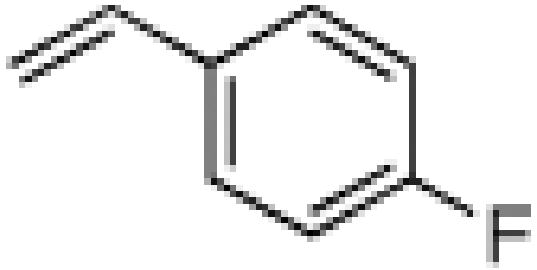
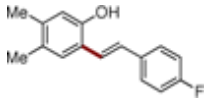
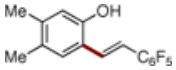
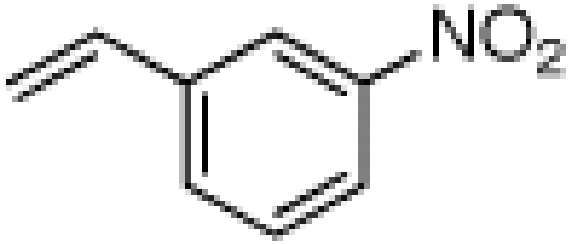
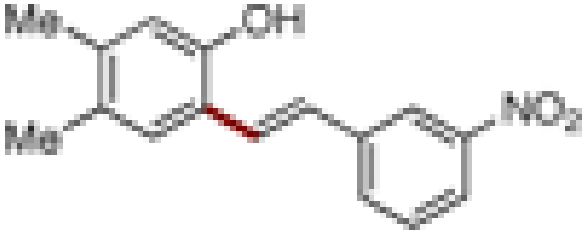
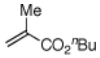


entry	substrate		product		yield, %[a]
1		**2b**		**4l**	96
2		**2c**		**4m**	87[b]
3		**2d**		**4n**	70[b]



entry	substrate		product		yield, %[a]
4		**2e**		**4o**	67[b]
5		**2f**		**4p**	69[b]
6		**2g**		**4q**	64[c,d]



entry	substrate		product		yield, %[a]
7		**2h**		**4r**	79
8		**2i**		**4s**	83
9		**2j**		**4t**	66
10		**2k**			

[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.

J Am Chem Soc. Author manuscript; available in PMC 2012 August 17.