

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

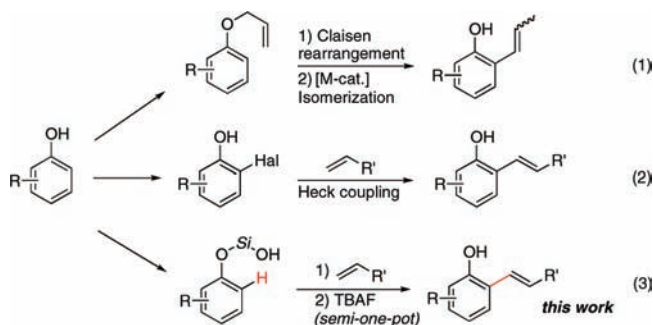
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Supporting Information

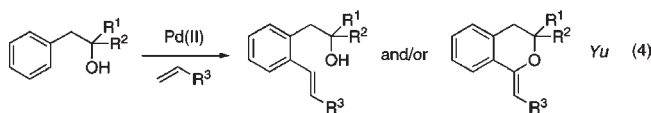
ABSTRACT: A silanol-directed, Pd(II)-catalyzed C–H alkenylation of phenols is reported. This work features silanol, as a novel traceless directing group, and a directed *o*-C–H alkenylation of phenols. This new method allows for efficient synthesis of diverse alkenylated phenols, including an estrone 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 reaction³ 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, *ortho*-alkenylation reaction of phenols with terminal alkynes can be promoted by a Lewis acid, such as SnCl₄.⁵ An obvious drawback of this method is an employment of stoichiometric amounts⁶ 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–H⁷ alkenylation⁸ 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 group¹² (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 alkenylated 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



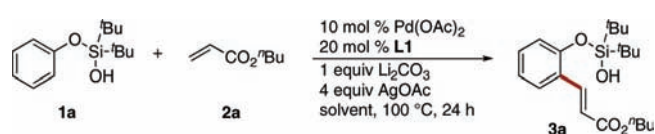
To test this hypothesis, silanol¹⁷ **1a** (1 equiv) was treated with butyl acrylate (**2a**, 2 equiv) under the conditions employing amino acid-derived ligand developed by Yu¹⁴ (10 mol % Pd(OAc)₂, 20 mol % (+)-menthyl(O₂C)-Leu-OH (**L1**), 1 equiv Li₂CO₃, 4 equiv AgOAc, in C₆F₆ at 100 °C). To our delight, the desired *ortho*-alkenylated product **3a** was formed in 52% NMR yield (Table 1, entry 1). Solvent optimization indicated PhCF₃ 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* fashion¹⁸ (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 ₆ F ₆	77	52
2	PhCF ₃	79	50
3	PhMe	43	24
4	dioxane	18	<3
5	THF	4	<3
6	<i>t</i> -AmylOH	26	<3
7	DCE	90	78
8	DMF	55	0

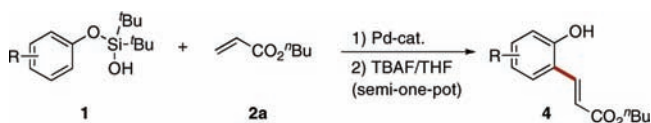
^a 1a/2a = 1: 2, L1 = (+)menthyl(O₂C)-Leu-OH. ^b Consumption of starting material 1a measured by GC/MS. ^c ¹H NMR yield.

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

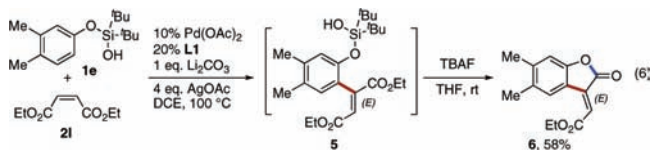
Table 2. Phenol Scope for Silanol-Directed Alkenylation



entry	substrate	product	yield, % ^a
1			72
2			94
3			97
4			53 ^b
5			97
6			88 ^b
7			97
8			81
9			89
10			58 ^b
11			52 ^b

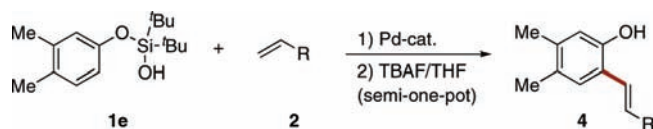
^a Isolated yield. ^b The yield was measured by ¹H NMR analysis using CH₂Br₂ as internal standard.

benzofuranone from a simple phenol featuring a C–H activation strategy.



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

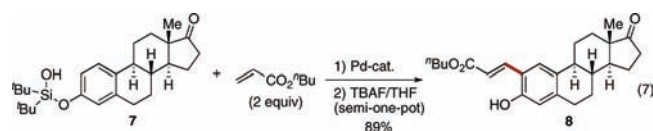
Table 3. Alkene Scope for Silanol-Directed Alkenylation



entry	substrate	product	yield, % ^a
1			96
2			87 ^b
3			70 ^b
4			67 ^b
5			69 ^b
6			64 ^{c,d}
7			79
8			83
9			66
10			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 ¹H 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*-butylsilyl 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

S 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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