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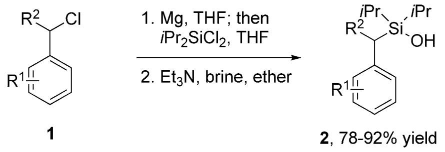
Silanol as a Removable Directing Group for the Pd^{II}-Catalyzed Direct Olefination of Arenes

Cong Wang and Haibo Ge*[a]

Aryl alkenes are important structural units in natural products, organic materials, and medicinal compounds, therefore a variety of synthetic methods have been developed to introduce this group.[1] Among them, the palladium-catalyzed Mizoroki-Heck reaction of aryl halides is a frequently used approach due to its high regio- and stereoselectivity, high functional group tolerance, and mild reaction conditions.[2] In many cases, the prerequisite regioselective introduction of a halide onto an arene requires several synthetic steps, which reduces the overall efficiency of this method.

The oxidative Heck-type reaction of arenes through Pd^{II}-catalyzed C–H functionalization offers an attractive alternative since this method does not require the prefunctionalization of arenes.[3] Such reactions often rely on the use of directing groups, which coordinate a metal and subsequently direct the metalation of a specific C–H bond.[4] Often, the installation and removal of common directing groups requires multiple steps and/or harsh reaction conditions, which limits the potential application of this transformation. Therefore, the need for novel, readily accessible substrates containing easily attachable and removable directing groups is clear. In such cases, the reactions will be directed by these groups to ensure the regioselectivity, and the initial products will, following removal of the directing group, be transformed into synthetically useful products.[5] In pursuit of this objective, we directed our attention to silanol-based arenes because of their ready accessibility (Scheme 1)[6] and the easy removability of the silanol group.[7] Herein, we report the Pd^{II}-catalyzed silanol-directed oxidative Heck-type reaction of benzyldiisopropylsilanols (**2a**).[8]

Inspired by the recent reports of the Pd^{II}-catalyzed hydroxyl-directed C–H activation from the Yu group,[4n,9] we began our investigation on direct olefination of benzyldiisopropylsilanol (**2a**) with ethyl acrylate (**3a**) in the presence of [Pd(OAc)$_2$] (20 mol%), AgOAc (2 equiv), and Li_2CO_3 (2 equiv; Table 1). Solvent screening demonstrated that halogen-containing solvents are the best for this reaction, with optimal results obtained with $CHCl_3$ (Table 1, entry 1). Further investigation showed that a Pd^{II} source is required for this reaction (Table 1, entry 5), whereas the use of Li_2CO_3 is optional (Table 1, entry 6). Thus, other sources of palladium were examined, and it was found that this reaction could also be catalyzed by 10 mol% of [Pd(MeCN)$_2$Cl$_2$] or 20 mol% of [(η^3-C$_3$H$_5$)$_2$Pd$_2$Cl$_2$], albeit with a lower yield (Table 1, entries 7 and 8). It is noteworthy that increasing the amount of [Pd(MeCN)$_2$Cl$_2$] to 20 mol% did not improve the reaction yield. Interestingly, the addition of a stoichiometric or catalytic amount of acid such as KH_2PO_4, AcOH, $EtCO_2H$, H_3PO_4, or HO_2CCO_2H improved the reaction yield, with optimal results obtained with KH_2PO_4 (Table 1, entries 11–15). Further investigation of the reaction conditions showed that the choice of an oxidant is crucial in this reaction (Table 1, entries 16 and 17). Furthermore, the yield slightly decreased with a lower concentration of alkene **3a** (Table 1, entry 18), or when the reaction was performed at an elevated reaction temperature (Table 1, entry 19). In addition, it was observed that reducing the amount of [Pd(OAc)$_2$] significantly decreased the reaction yield (Table 1, entry 20). It is also worth noting that although benzyldimethylsilanol[5] could be used to replace **2a** as the substrate to produce the corresponding desired product in a moderate yield, decomposition of this substrate occurred using the current catalytic system.



Scheme 1. Synthesis of benzyldiisopropylsilanols (**2**).

The compatibility of alkenes **3** is summarized in Table 2. All terminal acrylates gave the corresponding products in good yields (**4a–f**, 72–83%), whereas *N*,*N*-dimethylacrylamide provided a moderate yield of the product (**4g**, 56%). Furthermore, α,β-unsaturated ketones, sulfonates, and nitriles were also effective substrates (**4h–j**, 50–60%). In comparison, the more electron-rich olefin such as styrene and 2-vinylnaphthalene gave poor or no yield of the product (**4k** and **4l**) due to their low reactivity, which is an often encountered limitation in the Pd^{II}-catalyzed C–H activation of arenes.[10]

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[a] Dr. C. Wang, Prof. Dr. H. Ge
Department of Chemistry and Chemical Biology
Indiana University Purdue University Indianapolis
402 N. Blackford St. Indianapolis, IN 46202 (USA)
Fax: (+1) 317-274-4701
E-mail: geh@iupui.edu

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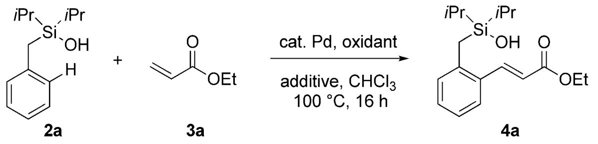
Table 1. Optimization of reaction conditions.[a]



Entry	$[PdX_2]$ (mol %)	Oxidant [2 equiv]	Additive (equiv)	Solvent	Yield [%][b]
1	$[Pd(OAc)_2]$ (20)	AgOAc	Li_2CO_3 (2)	$CHCl_3$	63
2	$[Pd(OAc)_2]$ (20)	AgOAc	Li_2CO_3 (2)	CH_2Cl_2	45
3	$[Pd(OAc)_2]$ (20)	AgOAc	Li_2CO_3 (2)	CH_2Br_2	41
4	$[Pd(OAc)_2]_2$ (20)	AgOAc	Li_2CO_3 (2)	DCE	32
5	–	AgOAc	Li_2CO_3 (2)	$CHCl_3$	0
6	$[Pd(OAc)_2]$ (20)	AgOAc	–	$CHCl_3$	51
7	$[Pd(MeCN)_2Cl_2]$ (10)	AgOAc	Li_2CO_3 (2)	$CHCl_3$	54
8	$[(\eta^3\text{-}C_3H_5)_2Pd_2Cl_2]$ (20)	AgOAc	Li_2CO_3 (2)	$CHCl_3$	40
9	$[Pd(OAc)_2]$ (20)	AgOAc	$KHCO_3$ (2)	$CHCl_3$	55
10	$[Pd(OAc)_2]$ (20)	AgOAc	NaOAc (2)	$CHCl_3$	48
11	$[Pd(OAc)_2]$ (20)	AgOAc	KH_2PO_4 (2)	$CHCl_3$	76 (73)[c]
12	$[Pd(OAc)_2]$ (20)	AgOAc	HOAc (0.1)	$CHCl_3$	66
13	$[Pd(OAc)_2]$ (20)	AgOAc	$EtCO_2H$ (0.1)	$CHCl_3$	60
14	$[Pd(OAc)_2]$ (20)	AgOAc	H_3PO_4 (0.1)	$CHCl_3$	62
15	$[Pd(OAc)_2]$ (20)	AgOAc	HO_2CCO_2H (0.05)	$CHCl_3$	65
16	$[Pd(OAc)_2]$ (20)	Ag_2CO_3	KH_2PO_4 (2)	$CHCl_3$	35
17	$[Pd(OAc)_2]$ (20)	$Cu(OAc)_2$	KH_2PO_4 (2)	$CHCl_3$	23
18[d]	$[Pd(OAc)_2]$ (20)	AgOAc	KH_2PO_4 (2)	$CHCl_3$	66
19[e]	$[Pd(OAc)_2]$ (20)	AgOAc	KH_2PO_4 (2)	$CHCl_3$	62
20	$[Pd(OAc)_2]$ (10)	AgOAc	KH_2PO_4 (2)	$CHCl_3$	44

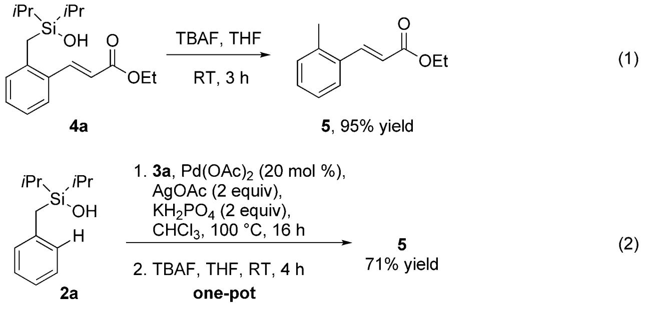
[a] Conditions: **2a** (0.3 mmol), **3a** (0.6 mmol), $[PdX_2]$, oxidant, solvent (3.0 mL), 100 °C, 16 h unless otherwise noted. [b] Yields determined by crude ^1H NMR spectroscopy using an internal standard based on **2a**. [c] Isolated product yield based on **2a**. [d] **3a** (0.45 mmol). [e] 120 °C.

The compatibility of benzyldiisopropylsilanols (**2**) is surveyed in Table 3. Both electron-donating and electron-withdrawing groups were successful with our catalytic system, with the former generally providing higher yields. In addition, halogens such as Cl and F were tolerated under these reaction conditions (**4n**, **4q**, and **4r**). Furthermore, diisopropyl(1-phenylethyl)silanol and diisopropyl(naphthalen-2-ylmethyl)silanol also provided good yields of the products (**4x** and **4y**).

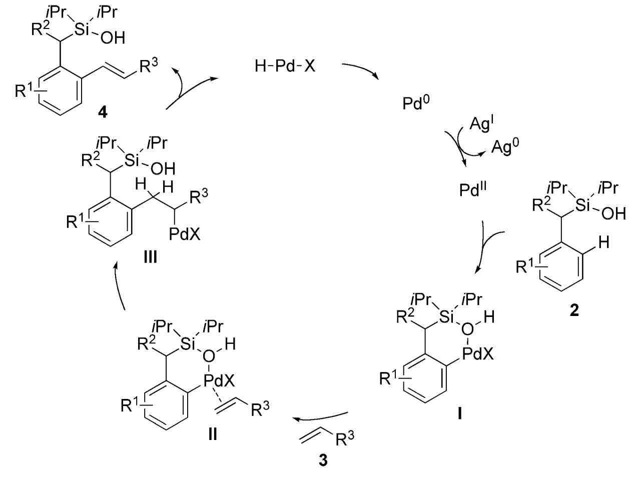
The removability of the silanol directing group was confirmed by the treatment of **4a** with tetrabutylammonium fluoride (TBAF) at room temperature to provide a high yield of product **5** (Scheme 3, reaction 1). In addition, a sequential one-pot, two-step C–H functionalization followed by desilylation, could be carried out to provide the desired product **5** in a good yield, making this transformation a powerful approach for the synthesis of *ortho*-alkenyl-substituted alkylarenes, which are not easily or efficiently achieved by current methods (Scheme 2, reaction 2).[2c] It is noteworthy that a one-pot Pd^{II}-catalyzed direct olefination of *N*,*N*-dimethylbenzylamines followed by removal of the group under reductive conditions was achieved recently by Shi and co-workers, to selectively functionalize the *ortho*-position of toluene derivatives.[11] However, alkenes and halogens were not compatible under conditions used for removal of the *N*,*N*-dimethylamino group, thus restricting the product diversity.

According to our proposed reaction pathway, this process is initiated by the regioselective cyclopalladation of benzyldiisopropylsilanols (**2**) with a Pd^{II} source, directed by the silanol group (Scheme 3). Coordination of the resulting Pd^{II}–Ar species **I** with an olefin **3**, followed by 1,2-migratory insertion and subsequent β-hydride elimination, provides the desired product **4**. Pd^0 generated in situ is re-oxidized to Pd^{II} by the Ag^I species.

In summary, silanol was demonstrated as an effective directing group for the direct olefination of arenes through palladium-catalyzed C–H activation. In addition, the remov-

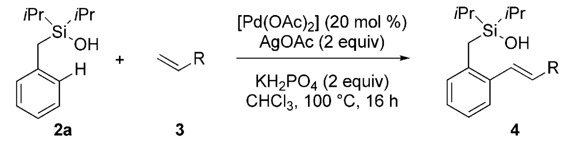


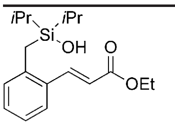
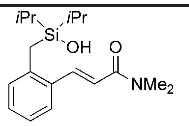
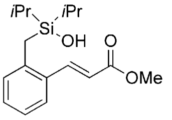
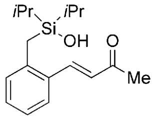
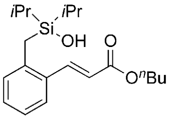
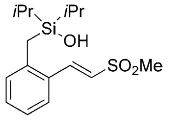
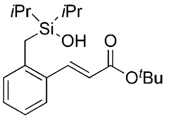
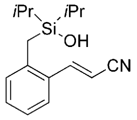
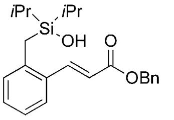
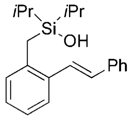
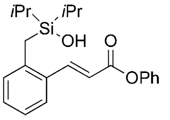
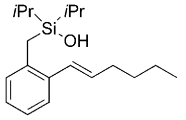
Scheme 2. Desilylation of *ortho*-olefinated benzyldiisopropylsilanol (**4a**), and a one-pot C–H activation/desilylation.



Scheme 3. Plausible catalytic cycle.

Table 2. Scope of olefins (**3**).[a,b]



Product		Yield [%]	Product		Yield [%]
	**4a**	73		**4g**	56
	**4b**	76		**4h**	56
	**4c**	81		**4i**	60
	**4d**	72		**4j**	50
	**4e**	73		**4k**	36
	**4f**	83		**4l**	0

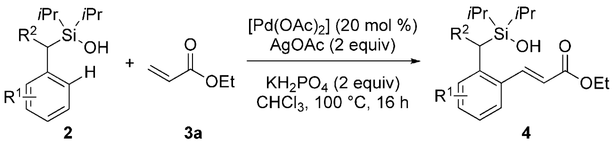
[a] Conditions: **2a** (0.3 mmol), **3** (0.6 mmol, 2 equiv), [Pd(OAc)$_2$] (0.06 mmol, 20 mol%), AgOAc (0.6 mmol, 2 equiv), KH$_2$PO$_4$ (0.6 mmol, 2 equiv), CHCl$_3$ (3.0 mL), 100 °C, 16 h. [b] Isolated product yields based on **2a**.

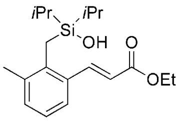
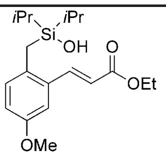
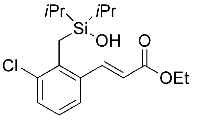
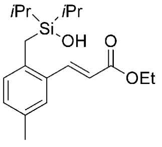
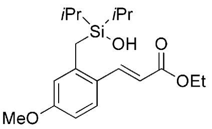
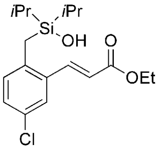
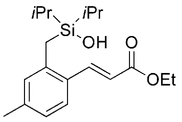
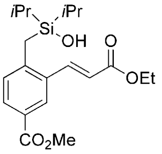
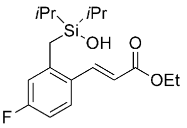
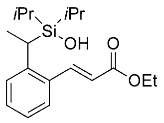
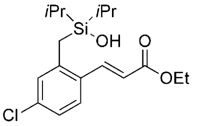
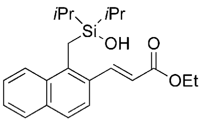
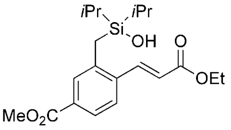
ability of the silanol group on the product **4a** was confirmed under mild conditions. Furthermore, a one-pot C–H activation/desilylation process of benzyldiisopropylsilanol was also developed. The reaction sequence provides a novel and attractive approach for the synthesis of *ortho*-alkenyl-substituted alkylarenes.

Experimental Section

General procedure for direct olefination of benzyldiisopropylsilanols: A 20 mL oven-dried pressure tube was charged with benzyldiisopropylsilanol (**2**, 0.3 mmol), olefin (**3**, 0.6 mmol), KH$_2$PO$_4$ (0.6 mmol), [Pd(OAc)$_2$] (0.06 mmol), AgOAc (0.6 mmol), and CHCl$_3$. The reaction tube was then sealed, heated to 100 °C, and stirred for the noted time. The reaction mixture was cooled to room temperature, diluted with EtOAc, filtered through a pad of Celite, and the filtrate was then removed under vacuo. The crude product was purified by flash chromatography on silica gel (gradient eluent of EtOAc in hexane: 0 to ca. 10%, v/v) to yield the product **4**.

Table 3. Scope of benzyldiisopropylsilanols (**2**).[a,b]



Product		Yield [%]	Product		Yield [%]
	**4m**	71		**4t**	68
	**4n**	49		**4u**	68
	**4o**	91		**4v**	59
	**4p**	88		**4w**	62
	**4q**	71		**4x**	85
	**4r**	70		**4y**	79
	**4s**	36			

[a] Conditions: **2** (0.3 mmol), **3a** (0.6 mmol, 2 equiv), [Pd(OAc)$_2$] (0.06 mmol, 20 mol%), AgOAc (0.6 mmol, 2 equiv), KH$_2$PO$_4$ (0.6 mmol, 2 equiv), CHCl$_3$ (3.0 mL), 100 °C, 16 h. [b] Isolated product yields based on **2**.

Acknowledgements

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Keywords: arenes · directing groups · olefination · palladium · silanols

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