ORGANIC LETTERS

2011
Vol. 13, No. 10
2774–2777

Palladium-Catalyzed Hydrofunctionalization of Vinyl Phenol Derivatives with Heteroaromatics

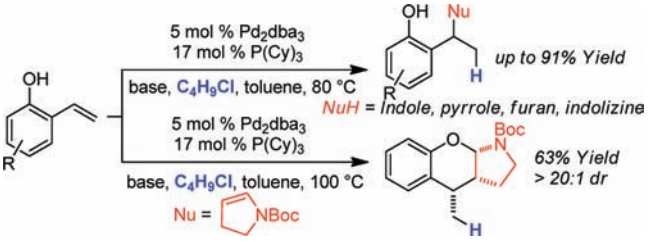
Tejas P. Pathak and Matthew S. Sigman*

Department of Chemistry, University of Utah, 315 South 1400 East, Salt Lake City, Utah 84112, United States

sigman@chem.utah.edu

Received April 7, 2011

ABSTRACT



A hydroheteroarylation reaction of vinyl phenols using an alkyl chloride as the sacrificial hydride source is reported. The method tolerates a wide range of heterocycles as the exogenous nucleophile including indoles and pyrroles. The resulting products are easily processed to biologically relevant scaffolds.

In recent years, substantial attention has been given to metal-catalyzed hydrofunctionalization reactions, in particular to hydroheteroarylation reactions.[1] When using vinyl arenes as substrates, these reactions rapidly generate molecular complexity while also accessing 1,1-diaryl substructures commonly found in biologically active compounds.[2] Various methods have been reported to access such compounds including Au-[3] and Ni-catalyzed[4] hydroheteroarylation reactions. In this regard, our laboratory has reported the use of styrenes[5] and dienes[6] as substrates in oxidative Pd(II)-catalyzed hydrofunctionalization reactions with organometallic reagents and either an alcohol[5−7] or alkylzinc reagents[8] as the hydride source. These reactions have generally been limited to the introduction of simple arenes and alkyl groups as the organometallic reaction partner. Considering this limitation and our recent discovery of lead compounds **1** and **2**, which illicit activity in breast cancer assays and arrest cells in different phases of the cell cycle,[9] we became interested in developing new alkene hydrofunctionalization reactions, which allow for the facile incorporation of broad classes of heteroaromatic compounds (Figure 1a). Herein we present the design and development of such a reaction of vinyl phenol derivatives, to access diverse analogues of **1** and **2**,

(1) (a) Mitchell, D.; Yu, H. *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 876. (b) Goj, L. A.; Gunnoe, T. B. *Curr. Org. Chem.* **2005**, *9*, 671. (c) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885. (d) Foley, N. A.; Lee, J. P.; Ke, Z.; Gunnoe, T. B.; Cundari, T. R. *Acc. Chem. Res.* **2009**, *42*, 585. (e) de Mendoza, P.; Echavarren, A. M. *Pure Appl. Chem.* **2010**, *82*, 801.

(2) Howard, H. R., Jr.; Sarges, R. Preparation and formulation of indolinone derivatives useful in treatment of diabetes-associated chronic complications. EP 252713, 1988. (b) Howard, H. R.; Sarges, R.; Siegel, T. W.; Beyer, T. A. *Eur. J. Med. Chem.* **1992**, *27*, 779. (c) Parenti, M. D.; Pacchioni, S.; Ferrari, A. M.; Rastelli, G. *J. Med. Chem.* **2004**, *47*, 4258. (d) Beaulieu, C.; Guay, D.; Wang, Z.; Leblanc, Y.; Roy, P.; Dufresne, C.; Zamboni, R.; Berthelette, C.; Day, S.; Tsou, N.; Denis, D.; Greig, G.; Mathieu, M.-C.; O'Neill, G. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2696. (e) See Supporting Information for complete list.

(3) (a) Wang, M.-Z.; Wong, M.-K.; Che, C.-M. *Chem.—Eur. J.* **2008**, *14*, 8353. (b) Xiao, Y.-P.; Liu, X.-Y.; Che, C.-M. *J. Organomet. Chem.* **2009**, *694*, 494 and references therein..

(4) (a) Nakao, Y.; Kanyiva, K. S.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 8146. (b) Kanyiva, K. S.; Nakao, Y.; Hiyama, T. *Heterocycles* **2007**, *72*, 677. (c) Nakao, Y.; Kashihara, N.; Kanyiva, K. S.; Hiyama, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 4451.

(5) (a) Gligorich, K. M.; Cummings, S. A.; Sigman, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 14193. (b) Iwai, Y.; Gligorich, K. M.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 3219. (c) Gligorich, K. M.; Iwai, Y.; Cummings, S. A.; Sigman, M. S. *Tetrahedron* **2009**, *65*, 5074.

(6) Liao, L.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 10209.

(7) (a) Zhang, Y.; Sigman, M. S. *Org. Lett.* **2006**, *8*, 5557. (b) Gligorich, K. M.; Schultz, M. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 2794.

(8) Urkalan, K. B.; Sigman, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 18042.

(9) Pathak, T. P.; Gligorich, K. M.; Welm, B. E.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 7870.

10.1021/ol200913r © 2011 American Chemical Society
Published on Web 04/21/2011

which is proposed to be initiated by a Pd(0)-catalyzed oxidative addition of an alkyl chloride to ultimately generate a Pd-hydride.

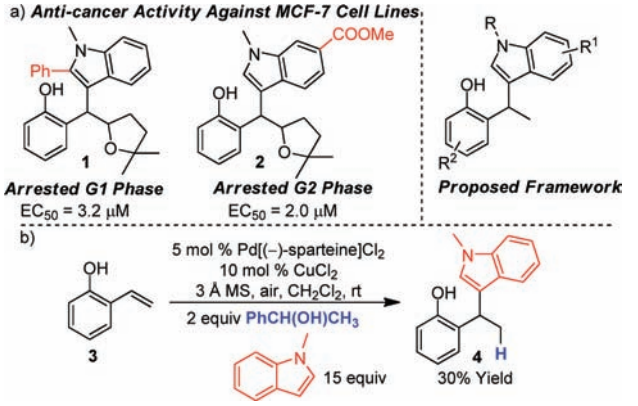
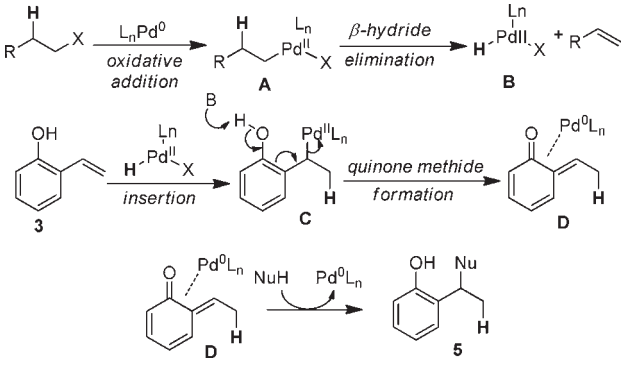


Figure 1. (a) Structure of proposed framework. (b) Addition of *N*-methylindole to a vinyl phenol under previously reported conditions.

We previously reported a hydroalkoxylation reaction of vinyl phenols utilizing a coupled alcohol oxidation to form a Pd-hydride followed by addition of the alcohol to a proposed *o*-quinone methide intermediate.[7a] Under these conditions, poor yields was observed when employing *N*-methylindole as the exogenous nucleophile (Figure 1b). Furthermore, indole derivatives lacking a protecting group on nitrogen are not tolerated under our reported Pd(II) oxidative catalytic conditions severely limiting the scope of the process.[9] On the basis of these observations, alternative methods to generate the requisite Pd-hydride were considered. Specifically, oxidative addition of an alkyl electrophile to form **A** followed by β-hydride elimination to generate a Pd-hydride **B** is proposed (Scheme 1). Of note, β-hydride elimination is generally considered deleterious in cross-coupling of alkyl electrophiles. Using a vinyl phenol as a substrate, addition of the Pd-hydride to yield **C** and subsequent electron transfer from the substrate to Pd

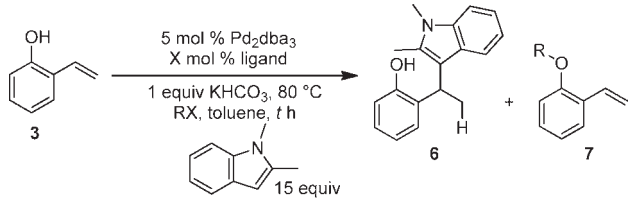
Scheme 1. Proposed Mechanism



forms a quinone methide intermediate of type **D** to provide a potent latent electrophile for nucleophilic addition.[10]

Initial investigation of this proposed process began with the selection of $Pd_2(dba)_3$, $P(Cy)_3$, and an alkyl bromide as the potential hydride source based on Fu's reported Pd-catalyzed alkyl−alkyl cross-couplings.[11] It should be noted that Fu's conditions are generally utilized to slow β-hydride elimination of the Pd-alkyl generated from oxidative addition of an alkyl electrophile. However, when the reaction is performed above 50 °C, β-hydride elimination is observed.[11c] Using vinyl phenol **3** and 1,2-dimethylindole as the exogenous nucleophile, a 33% yield of the desired product was observed at 80 °C. Unfortunately, a 26% yield of the alkylated phenol was also detected (Table 1, entry 1).

Table 1. Optimization of Reaction Conditions



entry	X	ligand	RX	*t*(h)	% conv[a]	% **6**[b]	% **7**[b]
1	20	$P(Cy)_3$	2 equiv $C_{12}H_{25}Br$	48	87	33	26
2	10	dcpe	2 equiv $C_{12}H_{25}Br$	48	71	35	24
3	10	dppf	2 equiv $C_{12}H_{25}Br$	48	68	35	30
4	10	BINAP	2 equiv $C_{12}H_{25}Br$	48	44	20	18
5	17	$P(Cy)_3$	2 equiv $C_{12}H_{25}Br$	48	76	42	26
6	17	$P(Cy)_3$	4 equiv CyBr	60	65	63	<2
7	17	$P(Cy)_3$	4 equiv C_4H_9Cl	60	81	76	<2
8	**17**	**$P(Cy)_3$**	**6 equiv C_4H_9Cl**	**72**	**98**	**82**[c]	**<2**
9	17	$P(Cy)_3$	–	72	98	40[c]	NA
10	–	–	–	72	96	31[c,d]	NA

[a] The conversion was measured by GC with an internal standard. [b] The yield was determined by GC with an internal standard. [c] Isolated yield. [d] No Pd catalyst and base added. Concentration of the reaction mixture (with respect to **3**): 0.1 M.

Use of bidentate ligands did not improve the reaction outcome (Table 1, entries 2−4). Modest improvement was observed by changing the ligand loading (Table 1, compare entries 1 and 5). Considering that the phenol alkylation process most likely is the result of an S_N2 reaction, other less reactive electrophiles were evaluated. Using either a secondary bromide or an alkyl chloride, a significant reduction of the phenol alkylation product was observed with concomitant slowing of the desired hydrofunctionalization reaction (Table 1, entries 6 and 7). The use of butyl chloride was preferred due to the low cost (~$ 0.03/g) and simplicity. Upon further optimization, excellent yield and selectivity is achieved (Table 1, entry 8).

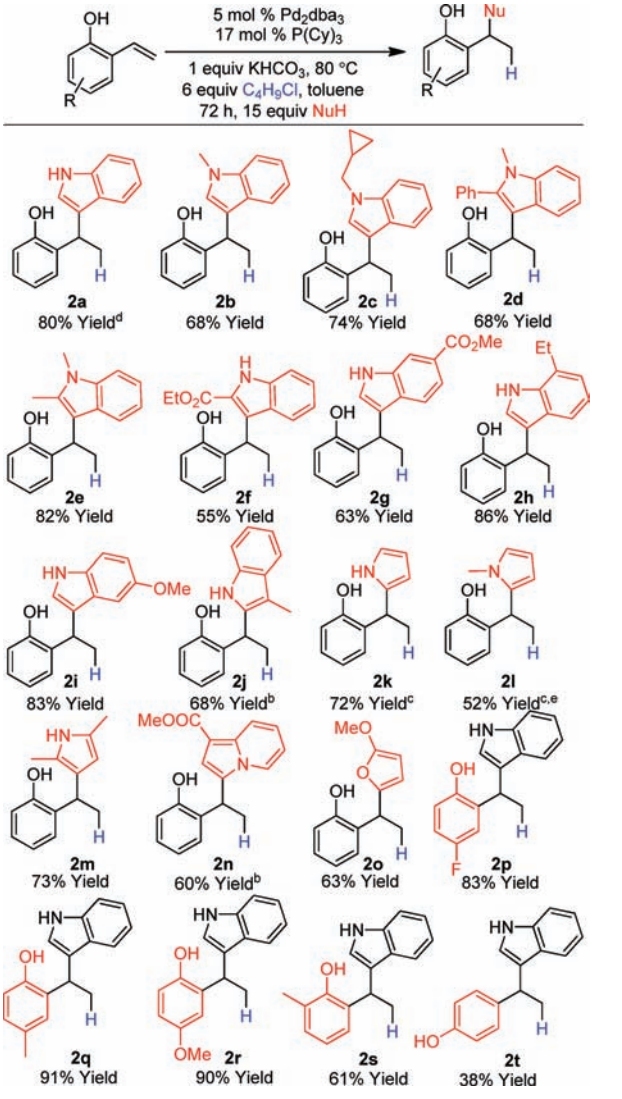
(10) Jensen, K. H.; Webb, J. D.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 17471.

(11) (a) Netherton, M. R.; Dai, C.; Neuschütz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099. (b) Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 13178. (c) Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662.

When, a control experiment in the absence of alkyl chloride was performed (Table 1, entry 9), to our surprise, product formation was observed presumably via a 1,5-sigmatropic rearrangement albeit in lower yield.[12a] Additionally, a reaction of the vinyl phenol with 1,2-dimethyl indole in the absence of any catalyst was performed to achieve a similar yield (Table 1, entry 10). It should be noted that such 1,5-sigmatropic rearrangements are not commonly used for *o*-QM formation and functionalization and often require more forcing conditions.[12] While these control experiments suggest that alternative mechanistic pathways are operational for product formation (vide infra), the presence of the Pd catalyst and the alkyl chloride significantly improves the reaction outcome.

Having optimized the reaction conditions, the reaction scope was evaluated. Unprotected 1*H*-indole gave the product in 80% isolated yield with >90% recovery of the remaining nucleophile (Table 2, entry **2a**).[2e,13] Unprotected indoles/heteroaromatics as nucleophiles are beneficial because they not only avoid an undesired protection−deprotection sequence but also provide flexibility for further synthetic modifications. *N*-alkyl substituted indoles perform well giving products in good yields (entries **2b** and **2c**). Indoles with different steric and electronic parameters are well tolerated under the reaction conditions including various substitution at the 2-position (entry **2d**−**2i**). Additionally, a 3-substituted indole undergoes addition from the 2-position allowing entry into this important compound class (entry **2j**). The reaction is not limited to the use of indoles as the nucleophilic heterocycle as demonstrated by the successful use of pyrroles, an indolizine, and a furan (entry **2k**−**2o**). Additionally, the nature of the phenol was evaluated with both electron withdrawing and electron rich vinyl phenols giving good yields of the desired products (entry **2p**−**2s**). Furthermore, p-vinylphenol also reacts under the optimized conditions, albeit a low yield of the product was observed (entry **2t**).

Table 2. Substrate Scope of Hydrofunctionalization of Vinyl Phenols



[a] Yields are average of at least two runs at 0.3 mmol scale. [b] Reactions performed at 100 °C. [c] 1 mL of nucleophile was used. [d] Performed on 1.5 mmol scale. [e] Ratio of C2/C3 alkylatlon = 4:1.

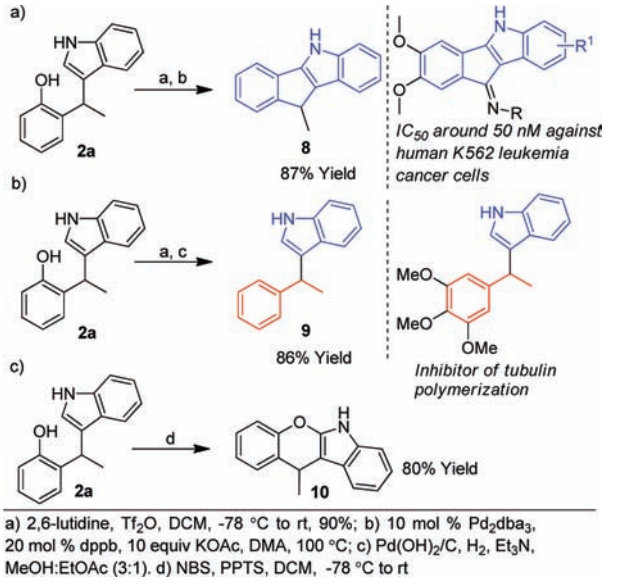


Figure 2. Rapid access to various biologically relevant scaffolds.

The phenol, which is a mechanistic requirement for *o*-QM formation, provides a handle for further functionalization of the products into biologically relevant scaffolds as demonstrated in Figure 2.[2e] Conversion of phenol **2a** to the corresponding aryl triflate followed by intramolecular Heck reaction gives a known antioxidant **8** in 87% yield (Figure 2a).[14] Related tetracyclic indanoindole scaffolds are also found in various biologically active compounds

(12) (a) Hansen, H.-J. *Helv. Chim. Acta* **1977**, *60*, 2007. (b) Hug, R.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1972**, *55*, 1828.

(13) For other examples see: El Kaim, L.; Grimaud, L.; Oble, J. *Org. Biomol. Chem.* **2006**, *4*, 3410.

(14) (a) Talaz, O.; Gulcin, I.; Goksu, S.; Saracoglu, N. *Bioorg. Med. Chem.* **2009**, *17*, 6583. (b) Brown, D. W.; Graupner, P. R.; Sainsbury, M.; Shertzer, H. G. *Tetrahedron* **1991**, *47*, 4383.

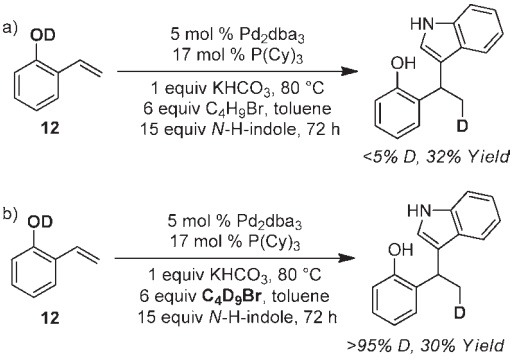
showcasing diverse biological activity.[14a,15] Compound **2a** can also be converted to compound **9** in excellent yield via reduction of the corresponding aryl triflate (Figure 2b), which leads to a styrene hydroheteroarylation product and is a common pharmacological framework.[2] Additionally, the treatment of compound **2a** with NBS gives the tetracyclic compound **10** in excellent yield (Scheme 3c).

To further explore the utility of this method, an inverse electron-demand Diels–Alder reaction with an electron-rich cyclic enamine was conducted (Scheme 2). The reaction proceeds smoothly to give chromane derivative **11** in 63% yield as a single diastereomer. This showcases the utility of the developed method to generate relatively complex frameworks from a simple substrate in a single step.

Scheme 2. Inverse Electron Demand Diels-Alder Reaction

While the control experiments performed in the optimization suggest that the catalyst and the alkyl chloride are not required to observe product, the enhancement of yield advocates for a role of both. Therefore, the origin of the hydrogen atom in product **2a** was explored through two isotopic labeling experiments. First, treating deuterated phenol **12** with an alkyl bromide under otherwise standard reaction conditions results in < 5% deuterium incorporation into the product (Scheme 3a). In contrast, excellent incorporation of deuterium (> 95%) is observed when using a deuterated alkyl bromide (Scheme 3b).[16] These experiments suggest that a mechanism involving a Pd-hydride is directly involved in product formation but does not rule out multiple reaction pathways, including a 1,5-sigmatropic rearrangement, for any specific substrate evaluated.[17]

Scheme 3. Deuterium-Labeling Experiments



In conclusion, we have successfully utilized a simple and inexpensive alkyl chloride to generate a proposed Pd-hydride, which is used to initiate an alkene hydrofunctionalization reaction. This approach offers a distinct mechanistic alternative to most reported hydrofunctionalization reactions including previous work from our laboratory that has focused on oxidative palladium catalysis. The reaction displays a broad scope in reaction partners, and the products formed through this reaction can be rapidly processed to biologically relevant scaffolds. Future work is focused on the evaluation and comparison of the compounds produced using this method to compounds **1** and **2** in breast cancer assays as well as exploiting the use of alkyl halides to generate a Pd-hydride for new reaction development.

Acknowledgment. This research was supported by the National Institutes of Health (RO1GM3540 and R01CA140296).

Supporting Information Available. Experimental procedures and full spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) (a) Alper, P.; Marsilje, T.; Chatterjee, A.; Lu, W.; Mutnick, D.; Roberts, M. J.; He, Y. Preparation of benzo[a]carbazole and indeno-[1,2-b]indole derivatives as TPO mimetics. WO 2007009120, 2007. (b) Marsilje, T. H.; Alper, P. B.; Lu, W.; Mutnick, D.; Michellys, P.-Y.; He, Y.; Karanewsky, D. S.; Chow, D.; Gerken, A.; Lao, J.; Kim, M.-J.; Seidel, H. M.; Tian, S.-S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5259. (c) Wierzbicki, M.; Boussard, M.-F.; Rousseau, A.; Atassi, G.; Hickman, J.; Pierre, A.; Leonce, S.; Guilbaud, N.; Kraus-Berthier, L. Indenoindoline derivatives, process for their preparation, and pharmaceutical compositions containing them, for use in the treatment of cancer. EP 2002291463, 2002.

(16) The major side product in both of these cases was alkylated phenol.

(17) While Brønsted acid catalysis is unlikely under the basic reaction conditions, it should be noted that the use of TsOH (20 mol %) at 80 °C does promote this reaction to give 72% yield of compound **2a**. However, acid-sensitive nucleophiles such as furans and enamines are not compatible under these acidic conditions.