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COMMUNICATIONS

Published on Web 11/07/2006

Sequential Hydrocarbon Functionalization: Allylic C−H Oxidation/Vinylic C−H Arylation

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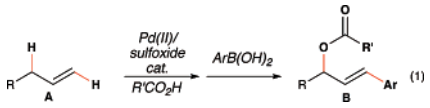
Sequential C−H bond transformations have the potential to streamline the synthesis of small molecules by enabling the rapid buildup of molecular complexity from inert functionality with minimal functional group manipulations. Herein we report a one-pot Pd(II)/sulfoxide-catalyzed allylic C−H oxidation/vinylic C−H arylation of α-olefins to furnish *E*-arylated allylic esters with high regio- and stereoselectivities (eq 1).



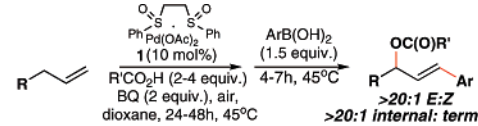
Palladium(II)-mediated vinylic C−H arylations (a Heck-type coupling) under oxidative conditions are known where transmetalation between organosiloxane, organotin, or organoboron reagents and Pd(II) generates the key organopalladium intermediate.[1] These reactions generally proceed in the presence of base to promote transmetalation/catalyst regeneration[2] and typically use electronically biased olefins (e.g., α,β-unsaturated carbonyls, styrenes) to achieve high regioselectivities and reactivities over homocoupling pathways (Ar−Ar). We now report a novel vinylic C−H arylation reaction of electronically unbiased olefins with aryl boronic acids catalyzed by Pd(II)/bis-sulfoxide complex **1** that proceeds under acidic, oxidative conditions and mild temperatures (room temperature to 45 °C) to provide *E*-arylated allylic esters with high regio- and *E*/*Z* selectivities (eq 1). To the best of our knowledge, this represents the first example of a Pd(II)-mediated cross-coupling reaction with boronic acids run under acidic, oxidative conditions.[3]

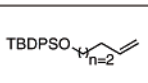
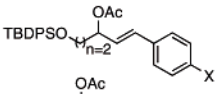
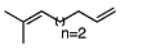
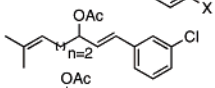
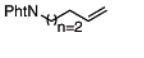
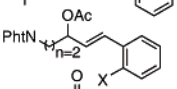
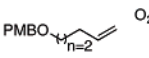
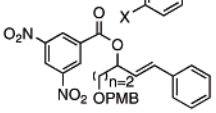
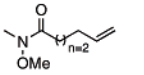
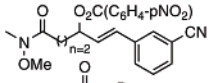
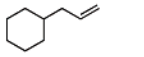
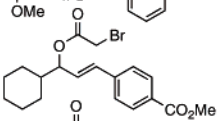
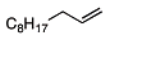
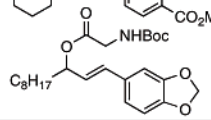
We have previously reported highly selective allylic C−H oxidation reactions catalyzed by 10 mol % of $Pd(OAc)_2$/phenyl bis-sulfoxide **1** that furnish allylic esters from α-olefins and carboxylic acids.[4] These reactions proceed via a Pd(II)/sulfoxide-catalyzed heterolytic C−H cleavage step that is most likely promoted by a transient electrophilic Pd(II) species. Cationic Pd(II) complexes have been shown to be highly active catalysts for transmetalation and C═C bond insertions in conjugate addition reactions of aryl boronic acids to enones.[5] This suggested to us that a novel sequential allylic C−H oxidation/vinylic C−H arylation method may be possible using catalyst **1**. To determine the feasibility of this process, we simply added 1.5 equiv of phenyl boronic acid to our allylic oxidation reaction upon complete consumption of α-olefin **A** (eq 1). We were gratified to discover that, in the presence of carboxylic acid and with no additional catalyst, the corresponding arylated allylic ester **B** was generated in good yield with high stereo- and regioselectivities [R′ = CH_3, R = C_8H_{17}, 74%, >20:1 *E*:*Z* (^{1}H NMR, crude); 41:1 internal:terminal olefin (GC, crude) eq 1]. We report herein that **1** catalyzes a novel three-component coupling reaction of α-olefins, carboxylic acids, and aryl boronic acids to furnish a wide range of *E*-arylated allylic esters (Table 1 and eqs 2 and 3).

Entries in Table 1 establish that 10 mol % of **1**/2 equiv of BQ effects the sequential allylic C−H esterification/vinylic C−H arylation of a variety of α-olefin substrates with electronically and sterically diverse carboxylic and aryl boronic acids. Arylated allylic esters **2**−**13** are furnished in good isolated yields as *single regio- and olefin isomers* (^{1}H NMR spectroscopy). *ortho*-Substituted and electron-poor boronic acids, which are typically sensitive to protodeborylation under the standard basic Heck conditions, are excellent arylating reagents under these mild, acidic conditions (entries 7 and 8, and 3−6, 10, and 11, respectively, Table 1).[6] Reactions with electron-rich boronic acids proceed in useful yields when conducted at room temperature (entries 2, 8, and 12, Table 1). Aryl bromide-substituted boronic acids that are typically reactive under Pd(0)-mediated reductive Heck conditions are stable under these Pd(II)-mediated oxidative conditions (eq 2).

The utility of this process as a three-component coupling method was probed by investigating its scope with respect to the α-olefin and carboxylic acid components. A wide range of polar functionality may be present on the α-olefin component that may serve as functional handles for further elaboration, for example, silyl and benzyl ethers, phthalimides, and Weinreb amides (entries 1−5 and 7−10, Table 1). Chemoselectivity is illustrated by oxidation/arylation of α-olefins with internal olefin functionality (entry 6, Table 1). Substitution proximal to the α-olefin is not required but is well-tolerated (entry 11, Table 1).

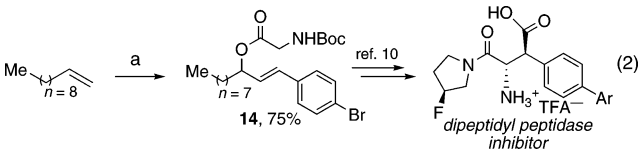
Table 1. Three-Component Coupling Reaction Furnishing a Wide Range of *E*-Arylated Allylic Esters



entry	olefin	product	isolated yield[a]
1 2 3 4 5			X: **2**, H = 74% **3**, OMe = 52%[b] **4**, Cl = 63%[c] **5**, F = 74%
6			**6**,  = 60% **7**, 63%[d]
7 8			X: **8**, Me = 73%[d,e] **9**, OMe = 55%[b,d]
9			**10**, 53%[d]
10			**11**, 77%[d,f]
11			**12**, 62%[c,d]
12			**13**, 69%[b,f]

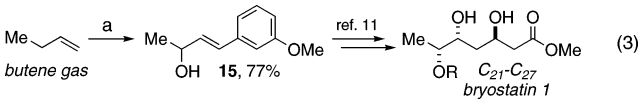
[a]Average yields of purified material (>20:1 *E*:*Z*; >20:1 internal:terminal olefin 1H NMR) for two runs at 1.0 mmol. [b] Arylation performed at rt. [c] Arylation run for 24h. [d] BQ (1 equiv.), AcOH (1 equiv.) added for arylation when oxidation run >24h. [e]2.0 equiv. *o*-MePhB(OH)$_2$. [f]2.0 equiv. R'CO_2H.

10.1021/ja066563d CCC: $33.50



Broad scope with respect to the carboxylic acid component was also noted. Arylated 3,5-dinitrobenzoate and 2-bromoacetate allylic esters such as **10** and **12** (entries 9 and 11, Table 1) may be further elaborated via asymmetric Pd(0)−π-allyl substitution reactions and enolate-type Claisen rearrangements, respectively.[7,8] Arylated *p*-nitrobenzoate allylic esters such as **11** may be readily hydrolyzed during workup to afford the corresponding arylated allylic alcohols (eq 3). Significantly, yields for the tandem sequence were observed to be higher with excess carboxylic acid.[9]

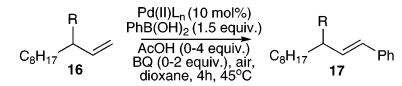
The ability to use inexpensive and abundant hydrocarbon starting materials to rapidly generate densely functionalized fragments for complex molecule synthesis is a significant feature of this methodology. Medicinally relevant arylated *N*-Boc glycine allylic esters **13** and **14** are accessible in isomerically enriched form (*E:Z* = >20:1; internal:terminal olefin = >20:1) and in one step from commercial hydrocarbon, amino acid, and aryl boronic acid reagents (entry 12, Table 1, eq 2). Compounds related to **14** have been transformed to medicinally important dipeptidyl peptidase IV inhibitors via a series of steps that feature enolate−Claisen rearrangement of the *N*-Boc glycine allylic ester to γ,δ-unsaturated amino acids, Suzuki cross-coupling of the aryl bromide to biaryls, and ozonolysis/oxidation of the olefin to a carboxylic acid moiety (eq 2).[10]



Allylic alcohol **15** was synthesized in 77% yield directly from *butene gas* as the limiting reagent (eq 3). Significantly, improved yields of **15** were obtained when the reaction was run under an O_2 (1 atm) rather than the standard air atmosphere. The cinnamyl alcohol unit may be further elaborated via enantioselective epoxidation/resolutions, and the *meta*-substituted anisyl ring may be transformed via Birch reduction/ozonolysis to a β-keto ester.[11] Using these transformations followed by selective reduction reactions, **15** has been converted to 1,3-diol subunits found in polyacetate-derived natural products such as bryostatin 1.[11]

Vinylic C−H arylation most likely proceeds via an electrophilic Pd(II)-promoted transmetalation/C=C bond insertion mechanism. Consistent with this, substrates bearing allylic acetoxy and small alkoxy substituents undergo highly regioselective vinylic C−H arylation to yield internal olefin products,[12] whereas substrates with small allylic alkyl substituents yield mixtures of internal and terminal olefins (Table 2, entries 1a−c vs 1d).[13] Steric bulk in the allylic position also furnishes product in high regioselectivities and yields (Table 2, entry 1e).[13] Catalyst **1** and BQ and carboxylic acid reagents were needed for efficient vinylic C−H arylation. Although $Pd(OAc)_2$ has been shown to undergo transmetalation with boronic acids under stoichiometric conditions in the absence of activating agents,[14] the bis-sulfoxide ligand was found to be critical for efficient catalysis (entries 1 vs 2, Table 2). In support of a Pd(II) cycle, in the absence of BQ oxidant, the reaction furnished only trace amounts of **17**, corresponding to one turnover of the catalyst (entry 3, Table 2).[15] Consistent with the noted increase in overall yields with excess carboxylic acid, increased reactivity for the arylation reaction was observed in the presence of AcOH (entry 1 and 5 vs 4, Table 2). Carboxylic acid may facilitate generation of the electrophilic Pd(II) complex needed for efficient catalysis.[16]

Table 2



entry	R	Pd(II)L_n	AcOH	BQ	isolated yield[a]	internal:terminal[b,c]
1a	OAc	**1**	4 equiv.	2 equiv.	98%	41:1[d]
1b	OBn				92%	>20:1[e]
1c	OMe				95%	>20:1[e]
1d	Me[g]				75%	8:1[f]
1e	OTBDPS				94%	>20:1[e]
2		$Pd(OAc)_2$	4 equiv.	2 equiv.	37%	---
3		**1**	4 equiv.	---	8%	---
4		**1**	---	2 equiv.	71%	---
5		**1**	1 equiv.	2 equiv.	94%	---

[a]Average yields for 2 runs done at 1.0 mmol. [b]*E:Z* and olefin isomer ratios determined on crude material. [c]*E:Z* = >20:1, 1H NMR. [d]GC using authentic terminal olefin. [e]1H NMR. [f]Internal:trisubstituted:terminal = 8:1:1 (1H NMR). [g]3-methyl-1-hexene.

We have described a new one-pot transformation that converts α-olefin hydrocarbons to *E*-arylated allylic esters with high regio- and *E:Z* selectivities. The ease with which densely functionalized building blocks are constructed from robust, commercial starting materials makes this method well-suited for high-throughput applications. The demonstrated ability of $Pd(OAc)_2$/bis-sulfoxide **1** to effect vinylic C−H arylation under acidic, oxidative conditions provides a new reaction manifold that is complementary to the standard basic, reductive one, for generating Pd−aryl intermediates for cross-coupling reactions.

Acknowledgment. M.C.W. acknowledges the NSF (CAREER CHE-0548173) and Merck for financial support. J.H.D. is a Pytosh Fellow. M. S. Chen confirmed eq 3.

Supporting Information Available: Experimental procedures, full characterization, and a complete list of authors for ref 10. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) (a) BQ oxidation: 2 HX + Pd(0) + BQ → DHQ + Pd(II)X_2. (b) AcOH as an oxidant for Pd(0) → Pd(II)H(OAc): Trost, B.M. *Chem.−Eur. J.* **1998**, *4*, 2405. (c) Electrophilic Pd(II) catalyst hydroarylations of alkenes promoted by acid: Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633.

JA066563D