

## A General and Highly Selective Chelate-Controlled Intermolecular Oxidative Heck Reaction

Jared H. Delcamp, Alexandria P. Brucks, and M. Christina White\*  
University of Illinois Urbana–Champaign, 600 S. Mathews, Urbana, Illinois 61801  
Received June 1, 2008; E-mail: white@scs.uiuc.edu

C–C bond forming reactions are vital to the synthesis of natural products and pharmaceuticals. The intermolecular Heck reaction is unique among cross-coupling reactions due to the direct formation of C–C bonds from vinylic C–H bonds of  $\alpha$ -olefins.<sup>1</sup> The inertness of  $\alpha$ -olefins relative to the oxidized substrates needed for other C–C bond forming methods means that fewer steps are required for their installation and maintenance throughout a synthetic sequence. Despite significant advances in the scope of the arylating reagent, the intermolecular Heck reaction has enjoyed limited application in complex molecule synthesis due to restricted olefin scope.<sup>2</sup> Generally, resonance bias on the olefin is necessary for high reactivity and for control of the regioselectivity of insertion (internal vs terminal olefin products) and direction of  $\beta$ -hydride elimination (styrenyl vs allylic products), limiting the olefin scope to  $\alpha,\beta$ -unsaturated-carbonyls, styrenes, and enol ethers (Figure 1). Herein we report a chelate-controlled intermolecular, oxidative Heck reaction catalyzed by a versatile Pd(II)/sulfoxide catalyst **1** that proceeds with excellent selectivities for a wide range of non-resonance biased  $\alpha$ -olefins with proximal oxygen and nitrogen functionality.

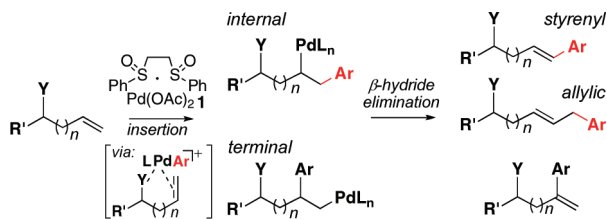


Figure 1. Selectivities for chelate-controlled oxidative Heck reaction.

We reported a Pd(II)/sulfoxide-catalyzed sequential one-pot allylic esterification/vinylic arylation of  $\alpha$ -olefins.<sup>3a</sup> In addition to allylic esters, allylic ethers and *N*-Boc amines all served as a non-resonance directing groups for an oxidative Heck arylation<sup>4</sup> that occurred rapidly (ca. 4 h) at ambient temperature with outstanding yields, regio- and *E:Z* stereoselectivities (>20:1). Allylic methyl substitution yielded significantly poorer selectivities (internal:terminal 8:1)<sup>3a</sup> despite being larger than many of the allylic oxygenates evaluated, suggesting that sterics is not the major directing factor in this reaction. We hypothesized that the high selectivities were due to *in situ* formation of an active, cationic Pd(II) complex<sup>5</sup> sensitive to subtle inductive and/or chelation effects<sup>6</sup> by neighboring oxidized functionality on the olefin substrate.

Inductive effects decrease rapidly based on distance from the reactive site. We therefore examined chelation effects by moving the oxidized functionality away from the allylic position. We found homoallylic carbonyl functionality and bis-homoallylic carbonyl, alcohol, and thiol functionality that could effect 5- and 6-membered ring chelation (respectively) gave outstanding selectivities (Table 1, entries 1–12). Distal carbonyl functionality that would require a 7-membered chelate for direction gave regioselectivities comparable to those seen for unsubstituted olefins (Table 1, entries 13 vs 14).

Several aspects of these oxidative, Heck arylations relative to state-of-the-art processes are noteworthy. Wittig olefination and high temperature

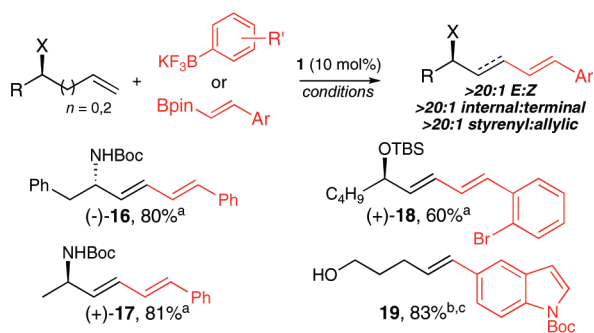
Table 1

entry	product	internal:terminal	styrenyl:allylic	isolated yield <sup>a</sup>
1		16:1	>20:1	64% <sup>b,c</sup>
2		>20:1	>20:1	80% <sup>b</sup>
3		8:1	>20:1	75% <sup>d,e</sup>
4		>20:1	>20:1	77% <sup>b,f</sup>
5		>20:1	>20:1	61% <sup>f</sup>
6		>20:1	>20:1	60% <sup>f</sup>
7		>20:1	>20:1	61% <sup>g</sup>
8		>20:1	>20:1	56% <sup>f</sup>
9		>20:1	<1:20	62% <sup>h</sup>
10		>20:1	1:18	50%
11		>20:1	1:17	51% <sup>i</sup>
12		>20:1	<1:20	60% <sup>j</sup>
13		9:1	2:1	60% <sup>b,f</sup>
14		8:1	1:1	68%

<sup>a</sup> Isolated yield isomerically pure material (except **14**, **15**). Average 2 runs. <sup>b</sup> 2.0 equiv. of arylboronic acid. <sup>c</sup> 13:1 styrene:diene, crude (Supporting Information). <sup>d</sup> 45 °C, 1.2 equiv. of arylboronic acid. <sup>e</sup> Replacing BQ with O<sub>2</sub> (1 atm), air (1 atm.), or H<sub>2</sub>O<sub>2</sub> gave <10% yield (GC). <sup>f</sup> 24 h. <sup>g</sup> 2.5 h. <sup>h</sup> 45 °C, 48 h. <sup>i</sup> PhB(OH)<sub>2</sub> under identical conditions gave diminished styrenyl:allylic ratios of 1:4. <sup>j</sup> THF (0.33 M).

Heck arylation routes to stereochemically well-defined isolated olefins like **2**, **3**, and **4** lead to inseparable mixtures of *E:Z* olefins.<sup>7</sup> Under these mild oxidative Heck-arylation conditions, *E*-olefin products are exclusively

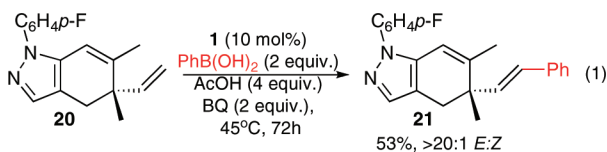
Table 2



<sup>a</sup> 2,6-Dimethylbenzoquinone (2 equiv.), AcOH (4 equiv.), boronic ester (1.5 equiv.), dioxane (1.0 M), rt, 48 h. <sup>b</sup> BQ (2 equiv.), AcOH (4 equiv.), ArBF<sub>3</sub>K (1.5 equiv.), B(OH)<sub>3</sub> (2.0 equiv.), dioxane (0.33 M), rt, 4 h. <sup>c</sup> Crude int.:term. = 16:1.

formed for all substrates evaluated (Table 1 and 2). Selective Heck arylations for amino acid-derived pent-4-enones, -enoic acids, and -enoates like (–)-**5**, (+)-**6**, and (+)-**7** require different Pd(0) catalyst systems that must be empirically determined through extensive ligand and additive screens (Table 1, entries 4–6).<sup>8</sup> In contrast, the versatile Pd(II)/bis-sulfoxide complex **1** is a *general catalyst*, furnishing a wide range of coupled products in uniformly good yields and outstanding selectivities. Finally, standard Heck arylations with olefinic alcohols give aldehyde or ketone products via palladium hydride mediated migration of the double bond.<sup>9</sup> Chiral bis-homoallylic alcohols undergo **1**-catalyzed oxidative Heck arylation without oxidation or erosion in optical purity (Table 1, entry 7; Table 2). Interestingly, bis-homoallylic thioethers which are often incompatible moieties with Pd(II)-mediated catalysis serve as excellent directing groups in this reaction (Table 1, entry 8).

We found that under our oxidative, acidic Heck arylation conditions we could rapidly synthesize 4-arylated-but-2-enoates and -enones generally as single olefin isomers (Table 1, entries 9–12). This method represents the state-of-the-art for synthesizing arylated  $\alpha,\beta$ -unsaturated esters with strongly electron deficient aryl moieties. Horner-Wadsworth-Emmons (HWE) routes to compounds **12** and **13** afford the styrenyl compounds as the major isomer (Table 1, entries 11 and 12).<sup>10</sup>



In addition to the demonstrated broad range of aryl boronic acids, styrenylpinacol boronic esters, aryl potassium trifluoroborates, and aryl stannanes are also competent coupling partners (Table 2).<sup>11</sup> Optically enriched allylic ethers and amines couple with styrenylpinacol boronic esters to form stereochemically defined (*E,E*)-dienes in good yields, outstanding stereoselectivities (>20:1), and no erosion in enantiopurity. In an example of synthetic streamlining, diene (–)-**16**, an intermediate toward a myosin light chain kinase inhibitor, was synthesized in two fewer steps and 20% higher overall yield using an oxidative Heck route rather than the alternative olefination route beginning from the same starting material.<sup>12</sup> Indole potassium trifluoroborate was found to be a competent transmetallating reagent in a reaction to generate **19** upon addition of 2 equiv. of boric acid.<sup>13</sup>

Substantial steric bulk is tolerated on the olefin substrate in this intermolecular Heck reaction without diminished reactivity. Even an  $\alpha$ -olefin comprising a quaternary center and adjacent to an exocyclic methyl group underwent oxidative Heck arylation via relatively mild conditions to afford **21**, a glucocorticoid receptor modulator, in preparatively useful yields (eq 1).<sup>14</sup>

In summary, we have described a general oxidative Heck reaction catalyzed by a versatile Pd/bis-sulfoxide catalyst **1** that proceeds with excellent selectivities for a broad range of non-resonance biased olefins. Electrophilic catalyst **1** is sensitive to chelation effects from proximal oxygen and nitrogen moieties that result in excellent regioselectivities for olefin insertion. It is noteworthy that Pd–H isomerization<sup>15</sup> is not observed under these mild, oxidative conditions as evidenced by excellent *E:Z* selectivities (>20:1 in all cases examined), no erosion in optical purity for proximal stereogenic centers, and a tolerance for unprotected alcohol moieties. This report represents a significant expansion in scope for the intermolecular Heck reaction that brings it a step closer to realizing its tremendous streamlining potential in complex molecule synthesis.

**Acknowledgment.** M.C.W. acknowledges the NSF (CAREER CHE-0548173), Merck, Bristol-Myers Squibb, and Pfizer for financial support. Sigma-Aldrich is thanked for a generous gift of Pd(II)/sulfoxide catalyst **1** and a Graduate Innovation Award to J.H.D. E. Stang confirmed entry 7, Table 1.

**Supporting Information Available:** Experimental procedures, full characterization, complete ref 8a, and additional experiments. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## References

- (1) For reviews, see: (a) Bräse, S.; de Meijere, A. *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: New York, 2004; Chapter 5. (b) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945. (c) Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427. (d) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2. (e) Heck, R. F. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 4, Chapter 4.3.
- (2) Aryl chlorides: (a) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989. Disubstituted alkenes: (b) Gürtler, C.; Buchwald, S. L. *Chem. Eur. J.* **1999**, *5*, 3107. (c) Internal olefins react poorly in our system (Supporting Information). Allyltrimethylsilanes: (d) Jeffery, T. *Tetrahedron Lett.* **2000**, *41*, 8445.
- (3) (a) Delcamp, J. H.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 15076. Our discovery of the acetate directing effect for the Heck appears general: (b) Pan, D.; Chen, A.; Su, Y.; Zhou, W.; Li, S.; Jia, W.; Xiao, J.; Liu, Q.; Zhang, L.; Jiao, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4729.
- (4) Oxidative Heck reactions: (a) Cho, C. S.; Uemura, S. *J. Organomet. Chem.* **1994**, *465*, 85. (b) Du, X.; Suguro, M.; Hirabayashi, K.; Mori, A.; Nishikata, T.; Hagiwara, N.; Kawata, K.; Okeda, T.; Wang, H.; Fugami, K.; Kosugi, M. *Org. Lett.* **2001**, *3*, 3313. (c) Yoo, K. S.; Yoon, C. H.; Jung, K. W. *J. Am. Chem. Soc.* **2006**, *128*, 16384. (d) Lindh, J.; Enquist, P.; Pilotti, A.; Nilsson, P.; Larhed, M. *J. Org. Chem.* **2007**, *72*, 7957.
- (5) Transmetalation of ArB(OH)<sub>2</sub> with cationic Pd: (a) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 2768. **1** catalyzes C–H oxidation and aminations: (b) Chen, M. S.; Prabakaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970. (c) Reed, S. A.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 3316.
- (6) Other examples of chelate-controlled Heck: (a) Filippini, L.; Gusmeroli, M.; Riva, R. *Tetrahedron Lett.* **1993**, *34*, 1643. (b) Kang, S.-K.; Lee, H.-W.; Jang, S.-B.; Kim, T.-H.; Pyun, S.-J. *J. Org. Chem.* **1996**, *61*, 2604. (c) Olofsson, K.; Sahlin, H.; Larhead, M.; Hallberg, A. *J. Org. Chem.* **2001**, *66*, 544. (d) Buezo, N. D.; Rosa, J. C.; Priego, J.; Alonso, I.; Carretero, J. C. *Chem. Eur. J.* **2001**, *7*, 3890.
- (7) (a) Gangjee, A.; Zeng, Y.; McGuire, J. J.; Kisliuk, R. L. *J. Med. Chem.* **2005**, *48*, 5329. (b) Lambert, J.; Rice, J.; Hong, J.; Hou, J.; Yang, C. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 873.
- (8) (a) Wu, Y. Q.; et al. *J. Med. Chem.* **2002**, *45*, 3558. (b) Whitehouse, D.; Hu, S.; Van Zandt, M. C.; Parker, G. U.S. Patent 055725, 2006. (c) Hirano, N.; Inoue, H.; Nagahara, T.; Ohyama, T.; Kaino, M.; Hayashi, K.; Hara, S.; Suzuki, R. U.S. Patent 068213, 2006.
- (9) (a) Larock, R.; Leung, W.-Y.; Stolz-Dunn, S. *Tetrahedron Lett.* **1989**, *30*, 6629. (b) Berthiol, F.; Doucet, H.; Santelli, M. *Synthesis* **2005**, *20*, 3589.
- (10) **12**: (a) Angelaud, R.; Zhong, Y.-L.; Maligres, P.; Lee, J.; Askin, D. *J. Org. Chem.* **2005**, *70*, 1949. **13**: (b) Kanuma, K.; Nishiguchi, M.; Funakoshi, T.; Chaki, S.; Nagase, Y.; Iida, I.; Yamaguchi, J.; Semple, G.; Tran, T.; Sekiguchi, Y. *Bioorg. Med. Chem.* **2006**, *14*, 3307.
- (11) *t*-Butyl ethylene and PhSnBu<sub>3</sub> coupled in 60% yield (see Supporting Information).
- (12) **16**: Gaeta, F. C. A.; Lehman de Gaeta, L. S.; Kogan, T. P.; Or, Y.; Foster, C.; Czarniecki, M. *J. Med. Chem.* **1990**, *33*, 964.
- (13) Boric acid is likely a fluoride acceptor that opens a p-orbital on the aryl boron for transmetalation. For a review of these reagents, see: Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275, and references therein.
- (14) Duan, J.; Lu, Z.; Weinstein, D.; Jiang, B. U.S. Patent 138373, 2006.
- (15) A PdH(OAc) intermediate should be short-lived under these oxidative conditions [PdH(OAc) + AcOH  $\rightleftharpoons$  Pd(0) + 2 AcOH + BQ  $\rightarrow$  Pd(II)OAc<sub>2</sub> + DHQ]. For an important study on PdH in Heck reactions, see: Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 13178.

JA804120R