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Oxidative Heck Vinylation for the Synthesis of Complex Dienes and Polyenes

Jared H. Delcamp,[†] Paul E. Gormisky,[‡] and M. Christina White*[,‡]

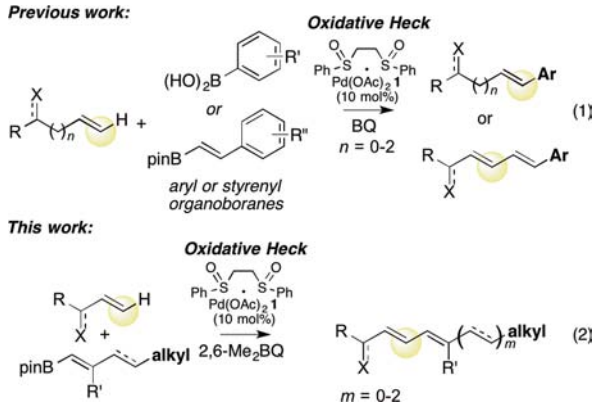
[‡]University of Illinois Urbana−Champaign, 600 South Mathews Avenue, Urbana, Illinois 61801, United States
[†]University of Mississippi, University, Mississippi 38677, United States

Supporting Information

ABSTRACT: We introduce an oxidative Heck reaction for selective complex diene and polyene formation. The reaction proceeds via oxidative Pd(II)/sulfoxide catalysis that retards palladium-hydride isomerizations which previously limited the Heck manifold's capacity for furnishing stereodefined conjugated dienes. Limiting quantities of nonactivated terminal olefins (1 equiv) and slight excesses of vinyl boronic esters (1.5 equiv) that feature diverse functionality can be used to furnish complex dienes and polyenes in good yields and excellent selectivities (generally *E*:*Z* = >20:1; internal:terminal = >20:1). Because this reaction only requires prior activation of a single vinylic carbon, improvements in efficiency are observed for synthetic sequences relative to ones featuring reactions that require activation of both coupling partners.

Dienes and polyenes are of high synthetic interest due to their frequent presence in medicinally relevant molecules and natural products. Current synthetic strategies for accessing such motifs in complex molecule synthesis involve carbonyl olefination reactions or transition metal-catalyzed cross-coupling reactions.[1−3] All of these methods share in common the requirement for using preactivated coupling partners. Such oxidized materials require several steps for their installation and are often challenging to maintain throughout a synthetic sequence.[4] Alternatively, the Heck vinylation reaction enables direct formation of dienes from the vinylic C−H bonds of abundant and relatively inert terminal olefin substrates.[5−9] Despite this potential, the Heck vinylation has had limited cross-coupling applications in synthesis because the scope is often limited to resonance activated olefins (e.g., α,β-unsaturated carbonyls, stryenes, and enol ethers) that are used in excess (typically 3−5 equiv) and Pd−H isomerization limits its applicability to the selective synthesis of stereodefined conjugated polyenes.[10] Herein we report an oxidative Heck vinylation under Pd(II)/sulfoxide catalysis that proceeds with limiting amounts of nonresonance stabilized olefins in good yields and excellent regio- and stereoselectivities to furnish complex diene and polyene products. Its streamlining potential[4] in complex molecule synthesis is evaluated.

In 2004, our lab introduced electrophilic Pd(II)/sulfoxide catalysis that has since proven itself to be a general reaction manifold for allylic C−H esterifications, aminations, alkylations, and dehydrogenations of terminal olefins.[11] In 2006, we also discovered Pd(II)/sulfoxide catalysis can alternatively promote



oxidative Heck arylations of nonresonance-biased olefins with organometallic reagents, such as aryl boronic acids and aryl trifluoroborate salts,[12] under uniform and preparatively useful conditions of fragment coupling quantities of valuable olefin (1.0 equiv) and organoboron reagent (1.5 equiv) required for efficient application in complex molecule synthesis.[13] Although styrenyl boronic esters were effective coupling partners under these conditions, attempts to utilize nonarylated vinyl boronic esters resulted in modest yields (Table 1, entry 1). We hypothesized side reactions with the benzoquinone oxidant could be problematic since we have seen that insertion of the Pd-vinyl intermediate is favorable with sterically accessible activated olefins. Accordingly, changing the oxidant to the more sterically hindered 2,6-dimethylbenzoquinone gave a significant increase in yield of diene product (entry 2, 43%). Increasing both the molarity (0.33 M → 2.0 M, entry 2 to 3) of the limiting reactant and polarity (THF → DMF, entry 3 to 4) of the solvent and lowering the equivalents of oxidant (entry 4) led to an improvement in yield to 55%. Other sterically hindered quinones (2,5-dimethylbenzoquinone or duroquinone, entries 5 and 6) provided lower or no reactivity, even under these optimized conditions. Although reaction yields were adversely affected by water, an oxygen atmosphere had no effect (entries 7 and 4). Despite the known role of DMF as a ligand for oxidative Pd(II) catalysis,[6b,7b] a catalytic bis-sulfoxide ligand was crucial for this reaction as $Pd(OAc)_2$ under otherwise identical conditions gave only 9% yield of diene (entry 8). Consistent with our previous observations, less stable vinyl boronic acids were unsuitable coupling partners for this

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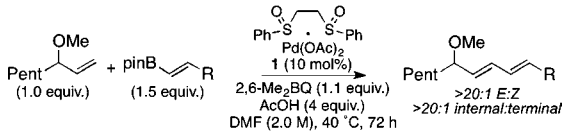
Table 1. Optimization of the Oxidative Heck Vinylation



entry	R	quinone (equiv)	solvent	isolated yield (%)[a,b]
1	Bu **2**	BQ (2.0)	THF (0.33 M)	16
2	Bu	2,6-Me_2BQ (2.0)	THF (0.33 M)	43
3	Bu	2,6-Me_2BQ (2.0)	THF (2.0 M)	49
4	**Bu**	**2,6-Me_2BQ (1.1)[c]**	**DMF (2.0 M)**	**55**
5	Bu	2,5-Me_2BQ (1.1)	DMF (2.0 M)	40
6	Bu	duroquinone (1.1)	DMF (2.0 M)	<5
7	Bu	2,6-Me_2BQ (1.1)[d]	DMF (2.0 M)	41
8	Bu	2,6-Me_2BQ (1.1)[e]	DMF (2.0 M)	9
9	Pent[f]	2,6-Me_2BQ (1.1)	DMF (2.0 M)	0

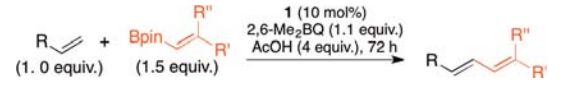
[a]Average of two runs at 0.5 mmol. [b]Selectivities determined by crude ^{1}H NMR. [c]O_2 atmosphere gave identical yield. [d]1 μL H_2O added. [e]No sulfoxide ligand. [f]Boronic acid.

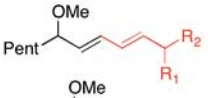
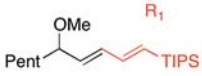
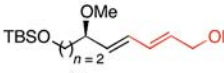
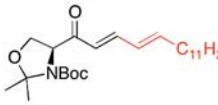
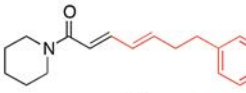
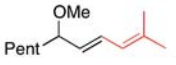
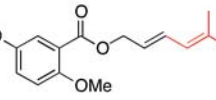
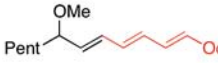
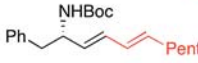
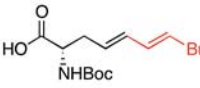
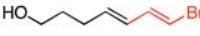
reaction (entry 9). Notably, in all cases, (*E*,*E*)-diene products were furnished as one regioisomer (internal:terminal olefin ratios >20:1) in outstanding *E*:*Z* selectivities (>20:1).

Examination of the boron component indicated a wide range of aliphatic vinyl boron reagents couple under these optimized conditions. Vinyl boronic esters substituted in the allylic position with both alkyl and oxygen moieties are excellent coupling partners (Table 2, entries 1 and 2). Interestingly, bulkier vinyl boron reagents afford diene products in higher yields than unsubstituted reagents, presumably by slowing homocoupling pathways. Ethylene triisopropylsilyl (TIPS) boronic ester coupled in synthetically useful yields to give the ethylene homologated TIPS product **5**, which is amenable to further cross-couplings upon activation (entry 3). Optically enriched compounds substituted with stereogenic centers in the allylic position undergo vinylation with no erosion in optical purity (entry 4). Although not a requirement for high selectivities, resonance activated α-olefins also undergo vinylation using only one equivalent of substrate (entries 5 and 6). In addition to *trans*-disubstituted reagents, trisubstituted-vinyl boronic esters couple smoothly (entries 7 and 8).[14] Excitingly, triene products are synthetically accessible in excellent selectivities and good yields (entry 9).

Examination of the olefin coupling partner showed that substrates with allylic oxygen or nitrogen functionality, capable of chelating to the palladium, provide excellent regio- and stereoselectivities (generally >20:1 internal:terminal and >20:1 *E*:*Z*) that are not highly sensitive to the vinyl boron reagent (entries 1−10). Significantly, as the functionality is transposed to the homoallylic or bis-homoallylic positions, the regioselectivity of insertion (internal vs terminal olefin products) remains >20:1; however, the stereoselectivity (*E*:*Z* selectivity) decreases to 6:1 (entries 11 and 12). Previously, we had observed that Pd(II)/bis-sulfoxide-catalyzed oxidative Heck *arylations* provide uniformly high (>20:1) stereoselectivity, irrespective of allylic substitution. This variance may be due to the smaller size of the vinyl vs aryl group resulting in higher rotational freedom prior to β-hydride elimination. Consistent with our previous observations, olefinic alcohols do not give carbonyl compounds via palladium hydride-mediated migration of the double bond, a common feature of many other Heck

Table 2. Scope of the Oxidative Heck Vinylation



entry	product[a]		*E*:*Z*[b]	% isolated yield[c,d]
1		**3**	>20:1	79
2		**4**	>20:1	62
3		**5**	>20:1	62[e]
4		(+)-**6**	>20:1	50
5		(-)-**7**	>20:1	53
6		**8**	>20:1	66
7		**9**	>20:1	71
8		**10**	10:1	72
9		**11**	14:1	52
10		(-)-**12**	>20:1	54
11		(+)-**13**	6:1	51
12		**14**	6:1	54[f]
13		**15**	6:1	42[g,h]

[a]Internal:terminal and conjugated:allylic olefin isomer ratios are >20:1 unless otherwise noted. [b]Selectivities based on crude ^{1}H NMR. [c]Average of two runs at 0.5 mmol scale. [d]Generally 20−30% olefin starting material remained with mass balances of 80−90%. The boron coupling partner was generally completely consumed. [e]17:1 internal:terminal. [f]1.75 equiv. of Bpin used. [g]2:1 conjugated:allylic and 5:1 internal:terminal. [h]40% recovered starting material (82% mass balance).

systems (entry 12).[15] Finally, unsubstituted aliphatic substrates undergo oxidative Heck arylations with diminished regio- and stereoselectivities (5:1 internal:terminal; 6:1 *E*:*Z*), poor directionality in β-hydride elimination (2:1 conjugated vs allylic diene products), and low yields due to a loss in reactivity (entry 13).

The ability of the Pd(II)/sulfoxide-catalyzed Heck vinylation to operate stereoselectively with broad scope using fragment coupling levels of substrates enables the streamlining potential of this powerful cross-coupling reaction to be explored in the synthesis of medicinally relevant complex diene targets. Macrolactin A, a scarce marine macrolide with potent antiviral properties, has three diene moieties embedded in its 24-membered macrocyclic ring.[16] The synthesis of the C16,C18 (*E*,*E*)-diene segment, has been previously achieved via Stille and Sonogashira cross-couping[17] methods as well as Julia olefination/elimination sequences.[18] We envisioned that an

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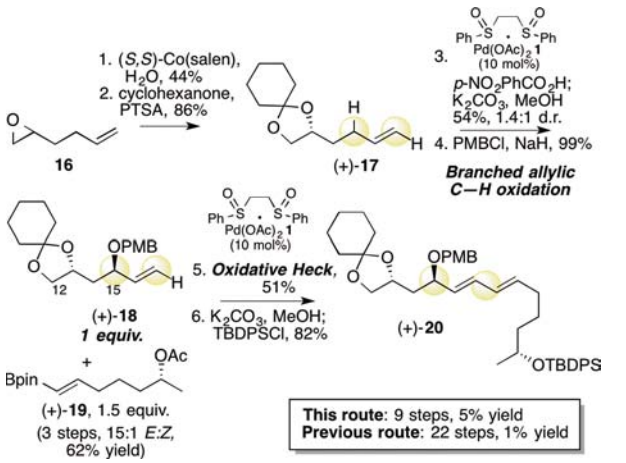
oxidative Heck vinylation approach would be highly efficient, in part because of the relative ease of accessing functionalized, optically enriched α-olefin building blocks. Utilizing the HKR reaction,[19] the C12−C13 diol was readily accessed from epoxy hexene **16** in high enantiomeric purity (99% ee). Exploiting the allylic C−H bond, the C15 alcohol was directly installed via Pd/sulfoxide-catalyzed allylic esterification.[11b] Synthesis of the optically enriched olefin coupling partner (+)-**18** proceeded in just four steps from commercial material. In contrast, synthesis of the analogous alkyne coupling partner for the Sonagashira route started with fully oxygenated chiral pool material that required nine steps for elaboration (see SI).[17d] The vinyl boronic ester coupling partner (+)-**19** was also generated efficiently (three steps) via cuprate alkylation of (*R*)-propylene oxide followed by cross-metathesis[20] with commercial 1-propenylboronic ester. Oxidative Heck coupling of (+)-**18** and (+)-**19** proceeded in 51% yield and afforded the complex (*E*,*E*)-diene (+)-**20** as one regio- and stereoisomer. In total, the oxidative Heck route to the reported C12−C24 segment (+)-**20** of macrolactin A proceeded in only nine steps and 5% overall yield. This compares favorably to the previously reported Sonagashira route that proceeded in 22 steps and 1% overall yield (Scheme 1).

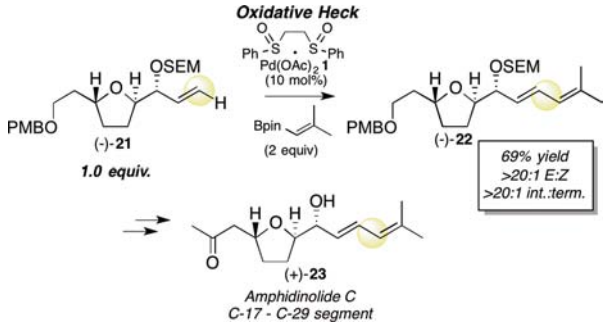
Scheme 1. Streamlined Synthesis of the Macrolactin A C12−C24 Segment



Amphidinolide C is a cytotoxic 25-membered macrolide with two diene units embedded within the structure.[21] We envisioned that our oxidative Heck methodology would allow an efficient synthesis of (*E*,*E*)-trisubstituted diene (−)-**22**, a precursor to the amphidinolide B C17−C29 fragment. Starting from an α-olefin intermediate (−)-**21** and a commercial vinyl boronic ester, the Pd(II)/sulfoxide-catalyzed oxidative Heck furnished (*E*,*E*)-trisubstituted diene (−)-**22**, a precursor to the C17−C29 segment, in a *single step* with 69% yield as one regio- and stereoisomer (Scheme 2). The previously reported route to a similar fragment proceeded via a traditional Julia olefination/sodium amalgam elimination sequence. An analogous α-olefin precursor was used; however, the Julia olefination route required 7 steps, including oxidation state and functional group manipulations, for installation of the diene.[22]

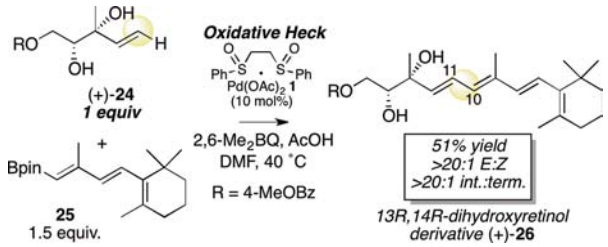
From the outset, we anticipated that higher-order polyene products such as (+)-**26** would be synthetically accessible in excellent selectivities using the Pd(II)/sulfoxide-catalyzed oxidative Heck vinylation (Table 2, entry 9). Palladium-H

Scheme 2. Streamlined Synthesis of the Amphidinolide C C17−C29 Segment



isomerization, which generally limits the stereochemical integrity of Heck vinylations, is retarded under these mild, oxidative conditions.[10,23] We envisioned that the complex tetraene fragment of 13,14-dihydroxyretinol (DHR), a biologically active metabolite of vitamin A,[24] could be retrosynthesized into optically enriched α-olefin (+)-**24** and the pinacol boronate (*E*,*E*,*Z*)-triene **25** using the Pd(II)/sulfoxide-catalyzed oxidative Heck transform (Scheme 3). Members of

Scheme 3. Synthesis of a Highly Conjugated Retinoid



the retinoid family of natural products are routinely synthesized via coupling of preoxidized fragments: classically via olefination/isomerization reactions and more recently through stereoselective Suzuki and Stille cross-couplings.[25] Because of poor *E*:*Z* selectivities, the Heck vinylation has been used sparsely and only to assemble diene fragments. Excitingly, (+)-**24** and **25** were coupled using the Pd(II)/sulfoxide-catalyzed oxidative Heck to furnish the desired (*E*,*E*,*E*,*Z*)-tetraene DHR (+)-**26** in a good yield and as a single stereoisomer (no *Z*-isomer detected by ^{1}H NMR). The excellent stereoselectivities, preservation of optical purity for proximal stereogenic centers, and tolerance for unprotected alcohols support a mechanism where a Pd−H intermediate is very short-lived. To the best of our knowledge, this example represents the longest polyene synthesized highly stereoselectively via the Heck vinylation.[10a]

The Pd(II)/sulfoxide-catalyzed oxidative Heck vinylation reaction offers an alternative cross-coupling strategy for the generation of dienes and polyenes that requires preactivation of only one vinylic partner. The ability to use fragment coupling quantities of olefin (1 equiv) and vinyl borane (1.5−2 equiv) and the suppression of Pd−H isomerization pathways are novel features of this method that make it amenable to furnishing *E*-dienes and polyenes in complex molecule settings.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

white@scs.uiuc.edu

Notes

The authors declare no competing financial interest.

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