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Palladium-Catalyzed Enantioselective Heck Alkenylation of Acyclic Alkenols Using a Redox-Relay Strategy

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Supporting Information

ABSTRACT: We report a highly enantioselective intermolecular Heck reaction of alkenyl triflates and acyclic primary or racemic secondary alkenols. The mild reaction conditions permit installation of a wide range of alkenyl groups at positions β, γ, or δ to a carbonyl group in high enantioselectivity. The success of this reaction is attributed to the use of electron-withdrawing alkenyl triflates, which offer selective β-hydride elimination followed by migration of the catalyst through the alkyl chain to give the alkenylated carbonyl products. The synthetic utility of the process is demonstrated by a two-step modification of a reaction product to yield a tricyclic core structure, present in various natural products.

Installation of an alkenyl motif represents a widely used strategy for introducing molecular complexity found in natural products and pharmaceuticals.[1] Therefore, enantioselective alkenylation has been a cornerstone of synthetic methods development. However, most methods that enable the introduction of alkenyl/vinyl moieties enantioselectively are restricted to the use of biased α,β-unsaturated carbonyls,[2] allylic moieties,[3] or other functional groups in close proximity to the reaction site.[4] An alternative powerful strategy for the stereoselective introduction of alkenyl groups has been the enantioselective intramolecular Heck reaction of vinyl electrophiles. In spite of its extensive use in natural product synthesis,[5] the effective installation of alkenyl units in an intermolecular fashion has been limited to the use of classical cyclic enol ether substrates.[6] Here we report a method that overcomes this considerable limitation wherein a broad array of alkenyl electrophiles can be combined with acyclic alkenols of various chain lengths to yield alkenylated Heck-type products in high enantioselectivity.

We have reported redox-relay Heck reactions of acyclic alkenols, wherein aryl groups derived from either aryldiazaonium salts[7a] or aryl boronic acids[7b] can be added enantioselectively to an alkenol followed by Pd migration through the alkyl chain to form a carbonyl product (Figure 1a). This process provides a platform for setting absolute stereochemistry remotely to other functionality in a molecule, which was recently highlighted by the use of trisubstituted alkenes to generate quaternary centers at positions β, γ, δ, ε, and ζ to a carbonyl group.[8] Even though the redox-relay strategy leads to remote enantioselective functionalization, the limitation remains that only aryl groups can be effectively introduced using this methodology. In this regard, we sought to develop a general intermolecular enantioselective alkenylative relay Heck reaction, which would install a new alkene motif at distinct positions remote from a carbonyl (Figure 1b).

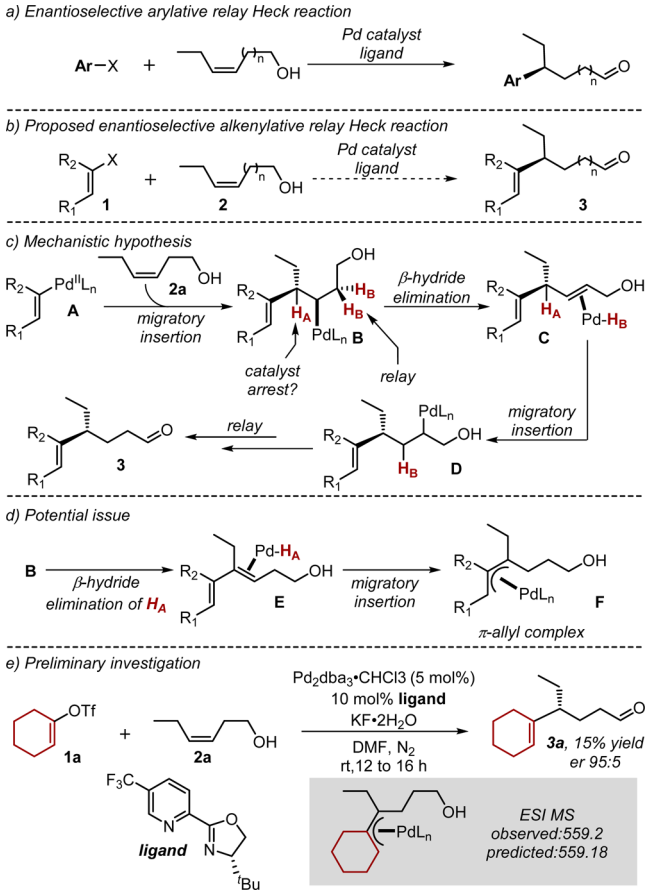

Figure 1. (a) Enantioselective arylative relay Heck reaction. (b) Proposed enantioselective alkenylative relay Heck reaction. (c) Mechanistic hypothesis. (d) Potential challenge. (e) Preliminary result.

The dearth of examples in the area of intermolecular Heck reactions of alkenyl electrophiles is evidence that significant challenges exist to develop viable methods.[9] These likely arise from issues in site selection, with the first of which related to the initial migratory insertion of a relatively unbiased alkene into the Pd-alkenyl species, akin to **A** proceeding to **B** in Figure 1c.[10,11] In our previous arylative redox-relay Heck reactions,[7]

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we observed that substrate control via remote electronic bias is responsible for effective site selection at the alkene carbon distal to the alcohol. This result is consistent with computational analysis wherein the polarization of the alkene in the transition state is stabilized by remote C−O dipole interactions.[12] Therefore, we anticipated that site-selective migratory insertion could be adequately addressed using this substrate class. Another problem we suspected to be of greater significance is that of site-selective β-hydride elimination from an intermediate like **B**.[11] If β-hydride elimination occurs at H_B, the relay reaction is expected to proceed, revealing the carbonyl product through iterative β-hydride elimination and migratory insertion events (**B** → **C** → **D** → **3**). However, if H_A undergoes β-hydride elimination yielding **E** (Figure 1d), migratory insertion of the alkene into the Pd-hydride would result in a π-allyl complex, which could arrest catalysis due to its relative stability. The inherent difference between installing an alkenyl versus an aryl group is the formation of both a more stabilized diene intermediate **E** compared to a styrene and a π-allyl compared to a π-benzyl intermediate. In fact, Pd-π-allyl intermediates have been exploited in our group for difunctionalization reactions of olefins using this precise strategy.[13]

To initiate the investigation, alkenyl triflates were considered to be likely suitable coupling partners, as their oxidative addition is facile and the resultant cationic Pd^{II}-alkenyl intermediate would be highly electrophilic, a requisite for effective relay Heck reactions due to enhanced alkene binding properties.[7,10] Our initial efforts using a simple cyclohexenyl triflate **1a** with (*Z*)-alkenol **2a**, in the presence of a chiral pyrox ligand, resulted in the formation of the desired product **3a** in 15% yield albeit a good enantiomeric ratio (er) of 95:5 (Figure 1e).[14] Attempts to improve the yield of this reaction were met with similar outcomes. Analyzing the reaction mixture with ESI-MS provided evidence of a species with a composition similar to that of the proposed π-allyl intermediate shown in Figure 1e.[15] Such a π-allyl species was anticipated as a result of nonselective β-hydride elimination from an intermediate resembling **B** in Figure 1c, as discussed above.

To tackle this issue, we re-examined putative intermediate **B** and considered approaches to circumvent catalyst arrest derived from formation of a π-allyl intermediate through β-hydride elimination of H_A (Figure 2a). In the most simplistic terms, to promote the relay Heck process, the hydricity of H_A needs to be reduced.[16] As a general approach to accomplish this, the use of electron-deficient alkenyl triflates derived from β-dicarbonyl compounds was considered, since the electron-withdrawing nature of the resulting intermediate should avoid formation of the π-allyl intermediate. Finally, an attractive aspect of alkenyl

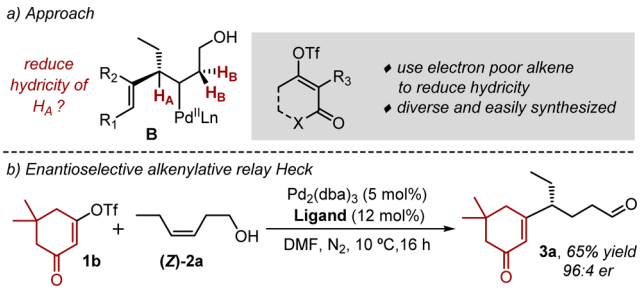
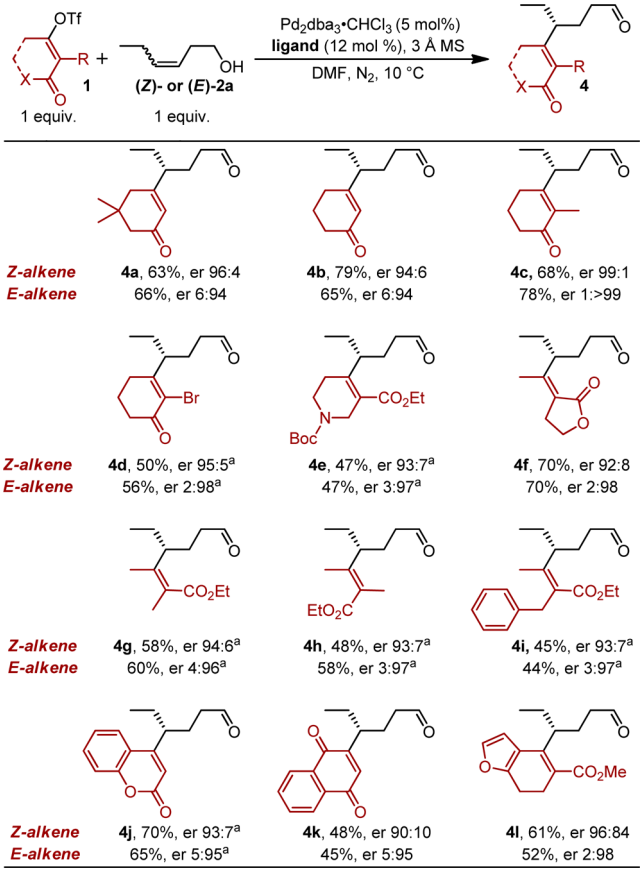


Figure 2. (a) Approach to overcome the formation of π-allyl intermediates. (b) Successful enantioselective alkenylative relay Heck reaction.

triflates derived from β-dicarbonyl compounds is their modular, facile synthesis.[17] To test this hypothesis, alkenyl triflate **1b** and (*Z*)-**2a** were treated with a Pd(0) source in DMF under the conditions in Figure 1e. In this initial event, a modest albeit significantly improved yield (53%) of the desired aldehyde **3a** was observed in 92:8 er. Further improvement of the reaction conditions as depicted in Figure 2b allowed for a 65% yield and 96:4 er of **3a** to be obtained (see SI for detailed optimization of the reaction).[18] As an important note, the resulting electrophilic alkene in the product remains untouched in this reaction, suggesting a high specificity for electron-rich alkenes using this catalyst.

The scope of the enantioselective alkenylation reaction utilizing the redox-relay Heck strategy was evaluated using both (*Z*)- and (*E*)-alkenols as substrates with a wide range of alkenyl triflates (Table 1). Enantiomeric products are observed using the alkenol stereoisomers, as demonstrated by the use of alkenyl triflate **2a**. The (*Z*)-alkene yields the (*R*)-enantiomer of **4a** in 96:4 er, whereas 4:96 er is observed using the corresponding (*E*)-alkene. A simple cyclohexenone-derived alkenyl triflate performs similarly, providing the desired product **4b** in good yield and enantioselectivity. A rather hindered

Table 1. Scope of the Vinyl Triflate Coupling Partner in the Enantioselective Alkenylative Relay Heck Reaction Using Homoallylic Alcohols



Yields are reported as an average of two parallel experiments. Enantioselectivity determined by supercritical fluid chromatography equipped with a chiral column. Reaction performed on 0.5 mmol scale. Absolute configuration determined to be (*R*) for a synthetic derivative of **4b** arising from the (*Z*)-alkene. All others were assigned by analogy. [a]Reaction performed at room temperature.

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tetrasubstituted alkenyl triflate led to the formation of **4c** in good yield and excellent enantioselectivity using either stereoisomer of the alkenol substrate (er 1:>99 with the (*E*)-alkene). Of particular interest, the reaction proceeds well even in the presence of an alkenyl bromide, resulting in a highly enantioselective alkenylative relay Heck reaction to form **4d**.

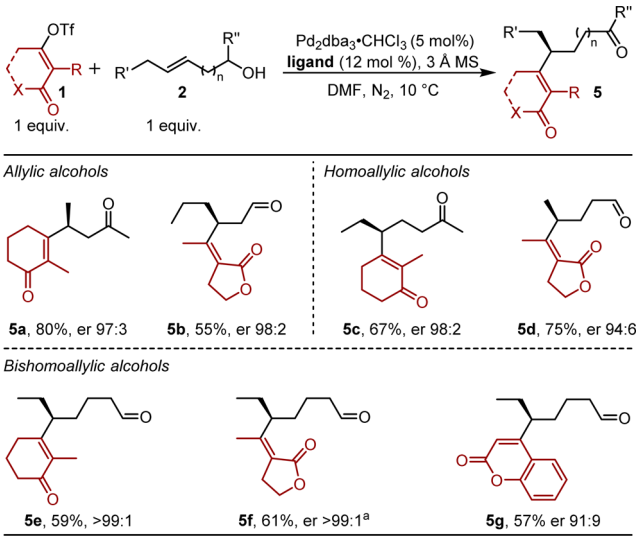
In order to probe the compatibility of an electron-withdrawing functional group other than ketones, several ester-derived alkenyl triflates were evaluated (**4e**–**4i**). The first contained a Boc-protected amine in a ring and was effective, albeit in modest yield, to provide **4e** with a 3:97 er using the (*E*)-alkene. A vinylogous cyclic ester-derived alkenyl triflate was found to be an excellent substrate to afford **4f** in good yields and high er (3:97) using the (*E*)-alkene. Next, (*Z*) and (*E*) acyclic enol triflates were stereoselectively synthesized using modular acetoacetate derivatives and applied to the relay Heck reaction.[19] Although these alkenyl triflates were found to be less reactive, raising the temperature to room temperature provided the products in modest yields and good enantioselectivity (**4g**–**4i**). The geometry of the alkene was preserved during the course of the reaction, showcasing the potential utility of this process. Finally, heteroaromatic-derived alkenyl triflates are also effective coupling partners, generating products **4j**–**4l** in modest to good yield and high enantioselectivity. These building blocks are especially noteworthy, as they incorporate privileged structures including the coumarin and napthoquinone moieties, which are often observed in biologically active compounds.[20] Notably, the use of other electron-withdrawing groups such as halogens and styrenyl units proved to be ineffective compared to a conjugated carbonyl system (see SI for details).

The scope of this method was further evaluated by varying the alkenyl alcohol (Table 2). A racemic secondary *trans*-allylic alcohol was converted to **5a** in high yield and er of 97:3. The use of a similar allylic alcohol and vinylogous ester-derived alkenyl triflate provided the *β*-substituted aldehyde **5b** with high enantioselectivity. A racemic secondary homoallylic alcohol substrate was subjected to the alkenylation reaction to give the *γ*-substituted ketone **5c** in good yield and 98:2 er. A methyl-substituted homoallylic alcohol was converted to **5d** in high yield and good er. With an aim of setting chiral centers more remote from the carbonyl functional group, a *trans*-bishomoallylic alcohol was subjected to the standard conditions using three different alkenyl triflates. Indeed, the alkenyl groups were installed enantioselectively, giving products **5e**–**5g** in moderate yields. Exceptional enantioselectivity was observed for the formation of **5e** and **5f**, but a reduction in enantioselectivity was observed using the coumarin-derived alkenyl triflate. Additionally, a lower enantioselectivity was observed for product **5f** when the *cis*-bishomoallylic alcohol was used as substrate. Unfortunately, trisubstituted alkenols are unreactive under the current reaction conditions.

In general, the alkenyl Heck relay reaction with (*E*)-alkenes provides higher enantioselectivity compared to the use of (*Z*)-alkene substrates, especially when sterically hindered tetrasubstituted alkenyl triflates were employed. This is in contrast to what has been observed in the enantioselective arylation of acyclic alkenols, wherein similar levels of enantioselectivity were observed for both (*Z*)- and (*E*)-alkenes.[7] While a precise explanation for these differences is not clear at present, the absolute configuration of product **4b** arising from the (*Z*)-alkene was determined to be (*R*), which is the same face from which the arene adds in our previous reports. This outcome indicates that the transition states during the migratory insertion step for the alkenylative and arylative Heck reactions are likely to be similar, as the ligand employed is the same in both reactions.

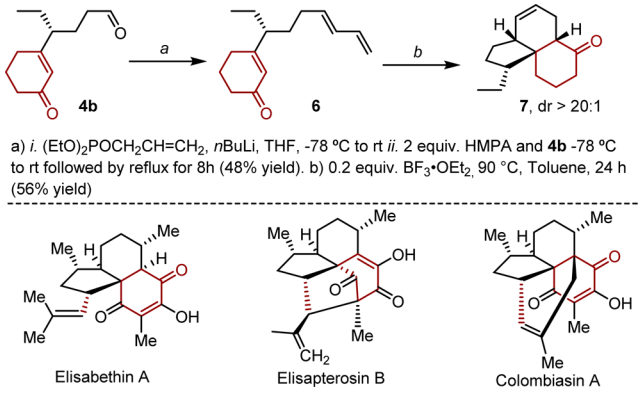
Many of the products accessed during this study are clearly unique chiral building blocks. To highlight the anticipated synthetic utility of this method, product **4b** was further elaborated through two synthetic steps to access the tricyclic core of various natural products, including elisabethin A, elisapterosin A, and colombiasin A.[21] As depicted in Scheme 1, Horner–Wadsworth–Emmons olefination of the aldehyde **4b** delivers diene **6** in high (*E*)-selectivity,[22] which serves as a precursor for an intramolecular Diels–Alder reaction. Treatment of **6** under the conditions reported by Danishefsky and co-workers yields the tricylic product **7** as a single diastereomer.[23] In all, four steps are required from the *β*-dicarbonyl precursor, including a highly enantioselective

Table 2. Evaluation of Alkenol Substrates in the Enantioselective Alkenylative Relay Heck Reaction



Yields are reported as an average of two parallel experiments. Enantiomeric ratio determined by supercritical fluid chromatography equipped with a chiral column. Reaction performed on 0.5 mmol scale. [a]Using the *Z*-alkene, a 57% yield and er of 10:90 was observed.

Scheme 1. Processing of a Relay Heck Product To Resemble a Natural Product Core Structure



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alkenylative relay Heck and a diastereoselective intramolecular Diels–Alder reaction, to access these interesting structures.

In summary, we have successfully developed a method to install electron-deficient alkenyl groups in high enantioselectivity at various distances from a resultant carbonyl by using a redox-relay strategy. The success of this reaction is attributed to the use of electron-withdrawing alkenyl triflates, which leads to improved selectivity during the β-hydride elimination step to reinforce migration of the palladium catalyst toward the alcohol. This prevents trapping of the catalyst as a proposed π-allyl species. The relatively mild conditions and ability to remotely install alkenyl groups to the carbonyl set the stage for further synthetic applications of this method. Future work is aimed at this goal and further detailing the mechanistic underpinnings of this process.

■ ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim, 1996. (b) Nicolaou, K. C.; Snyder, S. A. *Classics in Total Synthesis II. More Targets, Strategies, Methods*; Wiley-VCH: Weinheim, 2003. (c) Saklani, A.; Kutty, S. K. *Drug Discovery Today* **2008**, *13*, 161. (d) Liu, K. K.-C.; Sakya, L. S. *Mini-Rev. Med. Chem.* **2004**, *4*, 1105.

(2) For reports on asymmetric conjugate additions, see: (a) Nakao, Y.; Chen, I. H.; Hiyama, T.; Ichikawa, I.; Duan, W.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 9137. (b) Oi, S.; Sato, T.; Inoue, Y. *Tetrahedron Lett.* **2004**, *45*, 5051. (c) Nicolaou, K. C.; Tang, W.; Dagneau, P.; Faraoni, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 3874. (d) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829.

(3) For reports on asymmetric allylic displacement, see: (a) Hamilton, J.; Sarlah, D.; Carreira, E. M. *J. Am. Chem. Soc.* **2013**, *135*, 994. (b) Akiyama, K.; Gao, F.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 419. (c) Gao, F.; McGrath, K. P.; Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 14315. (d) Gao, F.; Carr, J. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2012**, *51*, 6613. (e) Shintani, R.; Takatsu, K.; Takeda, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2011**, *50*, 8656. (f) Jung, B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 1490.

(4) Other methods for the enantioselective introduction of alkenyl groups: (a) Biradar, D. B.; Gau, H.-M. *Org. Lett.* **2009**, *11*, 499. (b) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757 and references therein. (c) Page, J. P.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2012**, *134*, 6556 and references therein. (d) Stevens, J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 11756 and references therein. (e) Cherney, A. H.; Reisman, S. E. *J. Am. Chem. Soc.* **2014**, *136*, 14365.

(5) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945 and references therein.

(6) (a) Ozawa, F.; Kobatake, Y.; Hayashi, T. *Tetrahedron Lett.* **1993**, *34*, 2505. (b) Kilroy, T. C.; Cozzi, P. G.; Nicole, E.; Patrick, J. *Synthesis* **2004**, *11*, 1879. (c) Loiseleur, O.; Hayashi, M.; Schmees, N.; Pflatz, A. *Synthesis* **1997**, *11*, 1338. (d) Loiseleur, O.; Meier, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 200. (e) Gilbertson, S. R.; Fu, Z. *Org. Lett.* **2001**, *3*, 161. (f) Gilbertson, S. R.; Denov, D. G.; Rheingold, A. L. *Org. Lett.* **2000**, *2*, 2885. (g) Kaukoranta, P.; Kallstrom, K.; Andersson, P. G. *Adv. Synth. Catal* **2007**, *349*, 2595. (h) Tietze, L. F.; Thede, K.; Sannicolo, F. *Chem. Commun.* **1999**, 1811. (i) Hennessy, A. J.; Malone, Y. M.; Guiry, P. J. *Tetrahedron Lett.* **2000**, *41*, 2261.

(7) (a) Werner, E. W.; Mei, T. S.; Burkle, A. J.; Sigman, M. S. *Science* **2012**, *338*, 1455. (b) Mei, T. S.; Werner, E. W.; Burkle, A. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2013**, *135*, 6830.

(8) Mei, T. S.; Patel, H. H.; Sigman, M. S. *Nature* **2014**, *508*, 340.

(9) Cartney, D. Mc.; Guiry, P. *Chem. Soc. Rev.* **2011**, *40*, 5122.

(10) (a) Shibasaki, M.; Vogl, E. M. *J. Organomet. Chem.* **1999**, *576*, 1. (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.

(11) Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371.

(12) Xu, L.; Hilton, M. J.; Zhang, X.; Norrby, P.-O.; Wu, Y.-D.; Sigman, M. S.; Wiest, O. *J. Am. Chem. Soc.* **2014**, *136*, 1960.

(13) (a) Liao, L.; Jana, R.; Urkalan, K. B.; Sigman, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 5784. (b) Saini, V.; Sigman, M. S. *J. Am. Chem. Soc.* **2012**, *134*, 11372. (c) McCammant, M. S.; Liao, L.; Sigman, M. S. *J. Am. Chem. Soc.* **2013**, *135*, 4167. (d) Stokes, B. J.; Bischoff, A. J.; Sigman, M. S. *Chem. Sci.* **2014**, *5*, 2336. (e) Stokes, B. J.; Opra, S. M.; Sigman, M. S. *J. Am. Chem. Soc.* **2012**, *134*, 11408.

(14) For examples of application of chiral pyrox ligands in Pd-catalyzed reactions, see: (a) Kikushima, K.; Holder, J. C.; Gatti, M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2011**, *133*, 6902. (b) McDonald, R. I.; White, P. B.; Weinstein, A. B.; Tam, C. P.; Stahl, S. S. *Org. Lett.* **2011**, *13*, 2830.

(15) Rauf, W.; Brown, J. M. *Chem. Commun.* **2013**, *49*, 8430.

(16) Werner, E. W.; Sigman, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 9692.

(17) Chassaing, S.; Specklin, S.; Weibel, J.-M.; Pale, P. *Tetrahedron* **2012**, *68*, 7245.

(18) The starting materials are generally consumed in the reactions. The remainder of the mass balance mainly consists of a mixture of alkene products that are derived from β-insertion into the alkenol.

(19) Babinski, D.; Soltani, O.; Frantz, D. E. *Org. Lett.* **2008**, *10*, 2901.

(20) (a) Paya, M.; Hoult, J. R. S. *Gen. Pharmac.* **1996**, *4*, 713. (b) Sendl, A.; Chen, J. L.; Jolad, S. D.; Stoddart, C.; Rozhon, E.; Kernan, M. *J. Nat. Prod.* **1996**, *59*, 808.

(21) Elisabethin: (a) Rodríguez, A. D.; González, E.; Huang, S. D. *J. Org. Chem.* **1998**, *63*, 7083. Elisapterosin: (b) Rodríguez, A. D.; Ramírez, C.; Rodríguez, I. I.; Barnes, C. L. *J. Org. Chem.* **2000**, *65*, 1390. Columbiasin: (c) Rodríguez, A. D.; Ramírez, C. *Org. Lett.* **2000**, *2*, 507.

(22) (a) Wang, Y.; West, F. G. *Synthesis* **2002**, *1*, 99. (b) Kraus, G. A.; Kim, J. *Org. Lett.* **2004**, *6*, 3115.

(23) Ross, A. G.; Li, X.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2012**, *134*, 16080.

DOI: 10.1021/ja5130836
J. Am. Chem. Soc. 2015, 137, 3462–3465