JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

Palladium-Catalyzed Enantioselective Intermolecular Coupling of Phenols and Allylic Alcohols

Nicholas J. Race, Cristiane S. Schwalm, Takayuki Nakamuro, and Matthew S. Sigman*

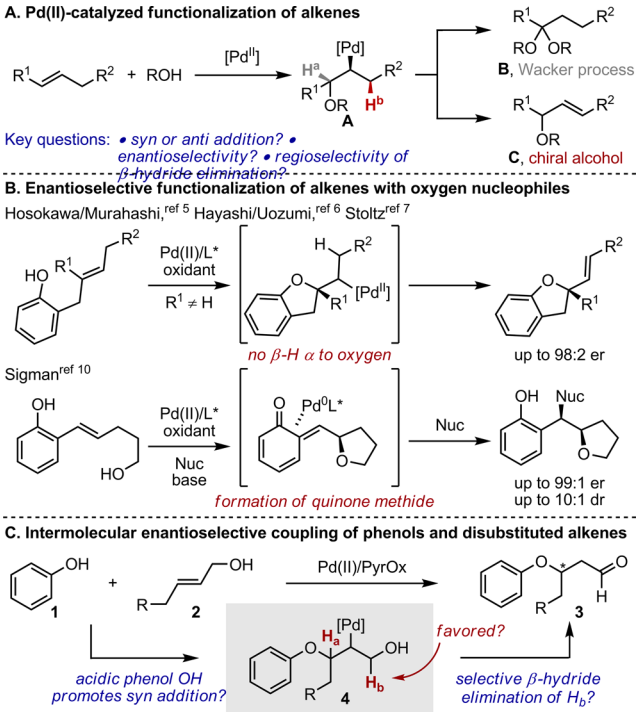
Department of Chemistry, University of Utah, 315 S 1400 E, Salt Lake City, Utah 84112, United States

Supporting Information

ABSTRACT: An enantioselective intermolecular coupling of oxygen nucleophiles and allylic alcohols to give β-aryloxycarbonyl compounds is disclosed using a chiral pyridine oxazoline-ligated palladium catalyst under mild conditions. As opposed to the formation of traditional Wacker-type products, enantioselective migratory insertion is followed by β-hydride elimination toward the adjacent alcohol. Deuterium labeling experiments suggest a *syn*-migratory insertion of the alkene into the Pd−O bond. A broad scope of phenols, various allylic alcohols, and an alkyl hydroperoxide are viable coupling partners in this process.

The addition of heteroatom nucleophiles to alkenes is an area of great interest to the synthetic community.[1] Perhaps the most extensively investigated process of this type is the Pd(II)-catalyzed coupling of water and alkenes, known as the Wacker reaction.[2] In general, addition of oxygen nucleophiles to alkenes can proceed through either nucleophilic addition (*anti*) or migratory insertion (*syn*) to deliver a Pd−alkyl intermediate (**A**). Despite recent advances in Pd(II)-catalyzed alkene functionalization reactions, the enantioselective coupling of oxygen nucleophiles and alkenes remains underdeveloped, especially in an intermolecular setting.[3,4] This is because at the stage of **A** β-hydride elimination of H_a occurs to ultimately deliver an achiral product (**B**, Scheme 1A).[2] To circumvent this innate selectivity, several strategies have been reported in which the stereochemical information generated after nucleophilic addition is retained in the product (Scheme 1B). The first, described by Hosokawa and Murahashi, is an enantioselective Wacker-type cyclization of *ortho*-(trisubstituted)allyl phenol derivatives.[5] Chiral dihydrofurans are generated in this reaction as the Pd−alkyl intermediate, generated upon cyclization, cannot undergo β-hydride elimination toward the oxygen by virtue of no available C−H bonds. The enantioselectivity of this reaction was significantly improved by both Hayashi and Uozumi[6] as well as Stoltz and co-workers who also applied aerobic reaction conditions.[7−9] A second, distinctly different, approach has been reported by our group in the enantioselective difunctionalization of styrenes containing an *ortho*-phenol.[10] This reaction is also initiated by enantioselective nucleopalladation wherein the resulting Pd−alkyl intermediate readily undergoes decomposition to an *ortho*-quinone methide in lieu of β-hydride elimination. Diastereoselective intermolecular addition of a second nucleophile then occurs to deliver the product.

Scheme 1. Wacker-Type Alkene Functionalization



In all, the two approaches described above utilize designed substrates to avoid the propensity of the Pd intermediate to eliminate the C−H bond at the site of nucleopalladation in intermediate **A**. To the best of our knowledge, there have been no reports of processes, after initial oxypalladation, where β-hydride elimination of H_b occurs in the presence of H_a. Thus, we questioned whether it would be possible to develop an enantioselective Pd-catalyzed intermolecular addition of an appropriate oxygen nucleophile to a simple disubstituted alkene, which avoids deleterious β-hydride elimination of H_a and provides an enantioenriched product (**C**, Scheme 1A).[11]

At the outset of this study, we were cognizant of two underlying mechanistic challenges: (1) how can a site selective, mechanistically distinct oxypalladation step be facilitated, and as articulated above, (2) can the resultant Pd-intermediate avoid β-hydride elimination at the newly established C−O stereocenter? In terms of the first question, the use of a disubstituted allylic alcohol should proceed under the requisite reaction

Received: November 4, 2016
Published: November 23, 2016

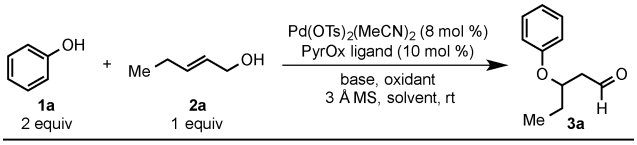
DOI: 10.1021/jacs.6b11486
J. Am. Chem. Soc. 2016, 138, 15881−15884

conditions in high site selectivity as established in both the Wacker[12] and Heck literature.[13] Likely of more importance is whether the oxy-palladation occurs via either a *syn* (Heck-type) or *anti* (Wacker-type) addition. If both mechanisms are operative, it is difficult to imagine that a chiral ligand can impart enantioselectivity during the key C−O forming step. Both Stoltz[7a] and Hayashi[14] have shown that their respective cyclization reactions occur via *syn* insertion of the alkene into the Pd−O bond. However, it should be noted that these are both intramolecular processes and most intermolecular additions of oxygen nucleophiles are thought to proceed through a Wacker-type *anti* addition.[2] Therefore, in our initial evaluation of oxygen nucleophiles, we focused on more acidic variants to bias the system toward a possible *syn*-oxypalladation.

Concerning the second challenge, assuming the C−O bond formation could be rendered enantioselective, it was reasoned that the direction of β-hydride elimination could be again influenced by the use of an allylic alcohol as the alkene coupling partner. Specifically, after oxy-palladation, intermediate **4** should be formed (Scheme 1C). We hypothesized that the terminal OH should render H_b in **4** more hydridic than H_a, since the phenol oxygen's lone pair is in conjugation with the aromatic ring. β-Hydride elimination should, therefore, occur preferentially with H_b akin to our efforts in relay Heck-type reactions.[15] Herein, we report the successful development of the addition of phenols and an alkylperoxide to allylic alcohols to form β-alkoxyaldehyde and ketone derivatives.

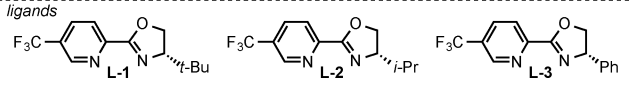
To initiate our studies, phenol (**1a**) and *cis*-2-penten-1-ol (not shown) were selected as model substrates for reaction discovery and optimization. Employing reaction conditions similar to our previously reported oxidative relay-Heck reaction ($Pd(OTs)_2(MeCN)_2$, pyridine oxazoline (PyrOx) ligand **L-1**, $Cu(OTf)_2$, O_2 and DMF)[15c] gave trace product (<1%). Additionally, the use of other polar solvents provided <5% of the desired product. A significant increase to 20% yield occurred when the solvent was changed to 1,2-dichloroethane and benzoquinone (BQ) was employed as the terminal oxidant. Further improvements were found upon switching from *cis*- to *trans*-2-penten-1-ol (**2a**), leading to desired product **3a** in 41% yield and 60:40 er (entry 1, Table 1). Surprisingly, a significant increase in enantioselectivity occurred (87:13 er) when the less bulky 2-*i*-PrPyrOx **L-2** was employed (entry 2) in contrast to our previous reports.[15d] A variety of bases and oxidants were then examined to presumably enhance the formation of the Pd-phenoxide complex required for a Heck-type addition (entries 2−5). As a result, $Ca(OH)_2$ and BQ were selected for further ligand optimization. A range of differentially substituted PyrOx ligands were examined, which ultimately revealed 2-PhPyrOx (**L-3**) furnishing product **3a** in 68% yield and 93:7 er (entry 6). Decreasing the reaction temperature resulted in a significantly reduced yield (34%) without a commensurate increase in enantioselectivity (entry 7). Ultimately, changing the solvent to trifluorotoluene led to an improved 76% isolated yield and 94:6 er (entry 8).

Table 1. Reaction Optimization[a]



entry	ligand	base (equiv)	oxidant (equiv)	solvent	yield (%)	er
1	**L-1**	DTBMP (2)	BQ (3)	$(CH_2Cl)_2$	41	60:40
2	**L-2**	DTBMP (2)	BQ (3)	$(CH_2Cl)_2$	53	87:13
3[b]	**L-2**	DTBMP (2)	$Cu(OTf)_2/O_2$	$(CH_2Cl)_2$	40	84:16
4	**L-2**	$Ca(OH)_2$ (1)	DDQ (3)	$(CH_2Cl)_2$	0	- -
5	**L-2**	$Ca(OH)_2$ (1)	BQ (3)	$(CH_2Cl)_2$	50	87:13
6	**L-3**	$Ca(OH)_2$ (1)	BQ (3)	$(CH_2Cl)_2$	68	93:7
7[c]	**L-3**	$Ca(OH)_2$ (1)	BQ (3)	$(CH_2Cl)_2$	34	93.5:6.5
8	**L-3**	$Ca(OH)_2$ (1)	BQ (3)	$PhCF_3$	79 (76)[d]	94:6

ligands



[a]Reaction optimization was performed on 0.2 mmol scale. Yields were determined by ^1H NMR using an internal standard. Er values were determined by HPLC after reduction to the corresponding alcohol. [b]50 °C. [c]10 °C. [d]Isolated yield in parentheses.

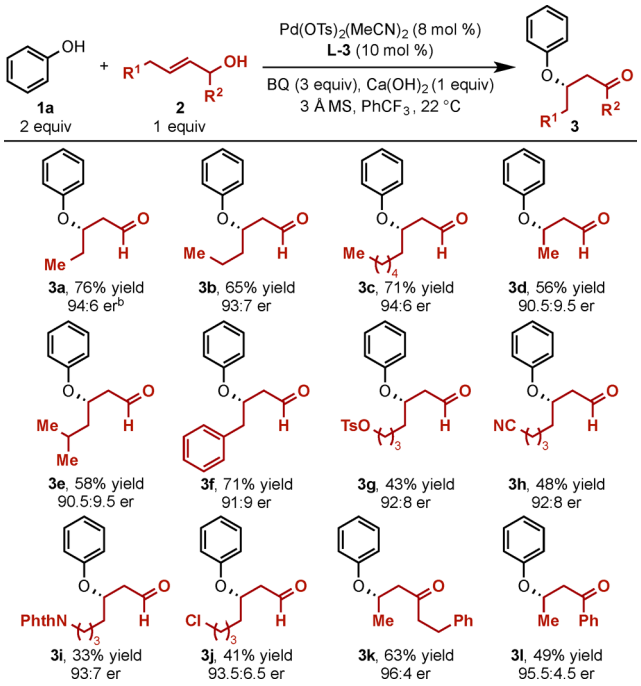
With the optimal reaction conditions in hand, the scope of allylic alcohols using phenol as the standard nucleophile was examined. Increasing the length of the alkyl group did not significantly alter the yield and er of the corresponding aldehyde (**3b-c**). However, when *trans*-crotyl alcohol (**2d**) was subjected to the reaction conditions, a decrease in er was observed (**3d**, 90.5:9.5 er). Methyl branching and incorporation of a phenyl group on the alkyl chain resulted in a decrease in enantioselectivity (**3e** and **3f**, respectively). Functional groups such as a tosyl-protected alcohol (**3g**), nitrile (**3h**), phthalimide (**3i**) and primary chloride (**3j**) are tolerated in this reaction and provide the desired aldehydes in modest yield and good er. Two secondary allylic alcohols were also subjected to the reaction and afforded the corresponding β-phenoxyketones **3k** and **3l** in good yield and excellent er (96:4 and 95.5:4.5, respectively). Unfortunately, the analogous homoallylic alcohols do not react effectively under these conditions and only recovered phenol was observed.

The enantioselectivity of this reaction is, for the most part, unaffected by differentially substituted phenols, containing both electron-withdrawing and donating groups. Fluoride-, chloride- and bromide-substituted phenols afford the corresponding aldehydes (**3n−p**) in good yield (57−75%) and enantioselectivity (94:6 er). Additionally, electron-deficient 4-(CF_3)-phenol (**1q**) delivered aldehyde **3p** in 61% yield and 93:7 er, whereas 4-(OCF_3)-phenol (**1r**) produced aldehyde **3r** in 94:6 er, albeit in 38% yield. Electron-donating 4-benzyl ether **1s** also works well under these reaction conditions, providing product **3s** in 76% yield and 93:7 er. The reaction endures *ortho*-substituted phenols (**1t**) with a moderate decrease in yield and enantioselectivity (**3t**, 41% yield, 91:9 er). A variety of differentially alkyl substituted phenols were also evaluated and afforded the desired products in excellent yields and er (**3u−w**). Finally, 3-acetylphenol (**1x**) furnished product **3x** in 55% yield and 90:10 er. It should be noted that phenols that were not soluble in trifluorotoluene (**1s**, **1v**, **1x**) performed well in 1,2-dichloroethane. The hydroquinone byproduct generated in these reactions was not observed to undergo competive addition to the allylic alcohols for the reactions reported in Tables 2 and 3.

Unlike Heck arylations and alkenylations, which undergo *syn*-migratory insertion, the mechanism by which oxygen nucleophiles add is highly dependent on the reaction conditions employed.[1] To establish the mode of insertion (*syn* or *anti*), deuterated alkenol **2a-d_2** was prepared and subjected to the standard reaction conditions (Scheme 2). Assuming the alkene does not dissociate during the reaction, the initially generated Pd−C stereocenter is retained in the migration sequence.[15a,b] As a result, the relative stereochemistry

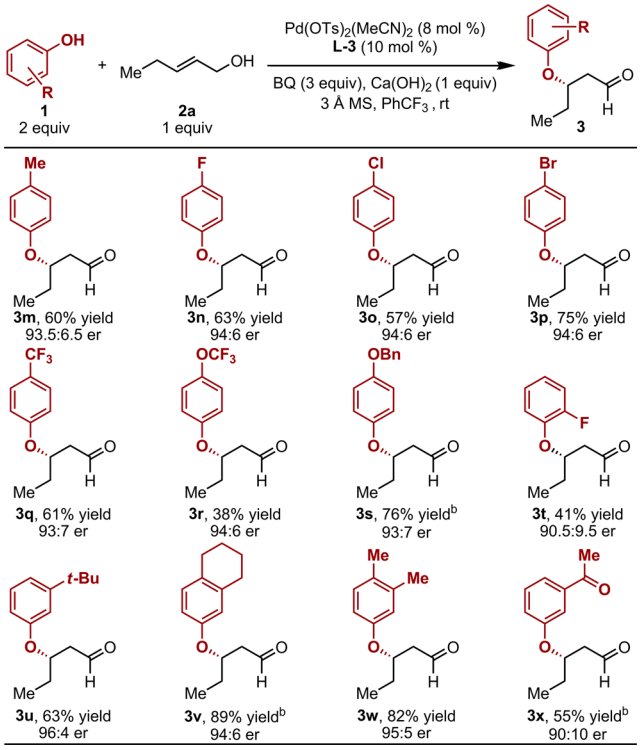
DOI: 10.1021/jacs.6b11486
J. Am. Chem. Soc. 2016, 138, 15881−15884

Table 2. Evaluation of Allylic Alcohols[a]



[a]Each entry represents the isolated yield on 0.25 mmol scale. The er values were determined by SFC and HPLC after aldehyde reduction. [b]2 mmol: 50% yield, 94:6 er.

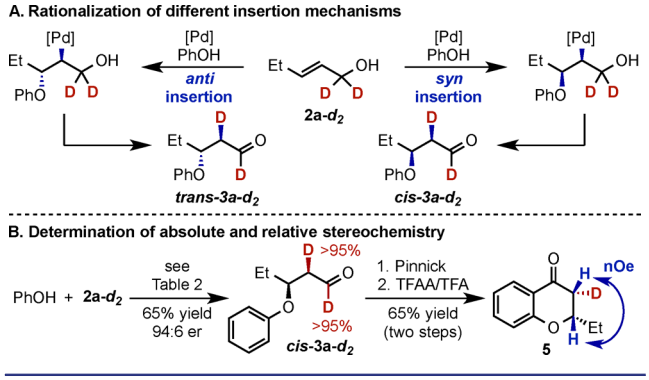
Table 3. Evaluation of Phenols[a]



[a]Each entry represents the isolated yield on 0.25 mmol scale. The er values were determined by SFC and HPLC after aldehyde reduction. [b]1,2-Dichloroethane as solvent.

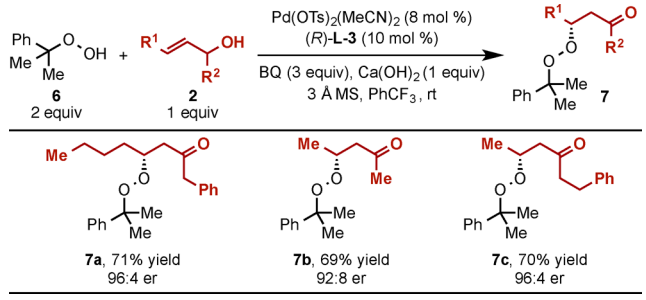
between the site of phenol addition and the α-deuterium in the aldehyde product would allow the insertion mechanism to be rationalized as either *syn* (*cis* relationship) or *anti* (*trans* relationship, Scheme 2A). In the event, aldehyde **3a-d_2** was isolated with complete diastereoselective migration of one deuterium atom to the α-carbon (Scheme 2B). To determine the relative stereochemistry between the phenol and the α-deuterium, aldehyde **3a-d_2** was converted to chromanone **5**, a common pharmacophore, through a Pinnick oxidation/Friedel–Crafts sequence.[16] Subsequent 1D nOe experiments confirmed a *cis* relationship, as shown on the structure **5** in Scheme 1B. This provides strong evidence for a *syn* migratory insertion pathway occurring in this reaction. Direct evidence for *syn* migratory insertion into Pd–O bonds has been reported by several groups for intramolecular processes.[7a,14,17] However, such evidence is comparatively lacking for intermolecular processes. The mechanistic features of this reaction closely resemble those of an oxidative Heck reaction but with an oxygen nucleophile. The absolute stereochemistry of **5** was determined to be (*S*) through $[\alpha]_D$ comparison with the reported non-deuterated analogue (see Supporting Information). This is consistent with the stereochemical models proposed in our previously reported redox-relay Heck reaction.[15b]

Scheme 2. Mechanistic Analysis



As alluded to in the introduction, the pK_a of the oxygen nucleophile would likely be critical for effective *syn* oxypalladation of internal alkenes. Indeed, simple aliphatic alcohols do not undergo this reaction, but on the basis of our previously reported use of alkyl peroxides in Wacker oxidations,[18] we reasoned that such nucleophiles would be applicable to this reaction manifold. Indeed, cumene hydroperoxide **6** was found to participate effectively, allowing access to β-peroxycarbonyl products (Table 4).[19,20] The scope was briefly examined, using (*R*)-**L-3** as ligand, and **7a–c** were afforded in good yield and enantioselectivity. Unfortunately, use of primary allylic alcohols with cumene hydroperoxide resulted in low product yields,

Table 4. Evaluation of Cumene Hydroperoxide[a]



[a]Each entry represents the isolated yield on 0.20 mmol scale. Er values were determined by SFC.

DOI: 10.1021/jacs.6b11486
J. Am. Chem. Soc. 2016, 138, 15881–15884

potentially due to decomposition of the aldehyde product in the presence of excess hydroperoxide. Lastly, it has previously been demonstrated that the O−O bond in these molecules can be reduced to afford formal cross-aldol products.[20]

In conclusion, we have developed the first enantioselective, intermolecular "oxa-Heck" reaction between commercially available oxygen nucleophiles (phenols and cumene hydroperoxide) and allylic alcohols. Mechanistic studies provide evidence for a *syn* migratory insertion in the C−O bond forming event; a mechanism that is underdeveloped in intermolecular, asymmetric processes. The strategic use of allylic alcohols promotes the direction of β-hydride elimination "away" from the newly formed C−O stereocenter to deliver ultimately β-aryloxy- and β-peroxycarbonyl products. The carbonyls formed from this reaction are formal conjugate addition adducts. However, there are few reports of enantioselective oxa-Michael reaction of phenols with α,β-unsaturated coupling partners.[21] This new methodology thus provides a complementary approach for the synthesis of these products. Future studies in our laboratory will focus on expanding the scope of this new reaction by exploring new heteroatom nucleophiles compatible with this strategy.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b11486.

Experimental procedures and characterization data for new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*sigman@chem.utah.edu

ORCID

Matthew S. Sigman: 0000-0002-5746-8830

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The work was supported by National Institute of Health (NIGMS R01GM063540). We thank Dr. Peter Flynn (D.M. Grant NMR Center) for assistance with NMR experimentation. C.S.S. acknowledges CNPq for a postdoctoral fellowship. T.N. acknowledges the JSPS fellowship for young scientists.

■ REFERENCES

(1) (a) Kočovský, P.; Bäckvall, J.-E. *Chem. - Eur. J.* **2015**, *21*, 36. (b) Doháňošová, J.; Gracza, T. *Molecules* **2013**, *18*, 6173. (c) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981.

(2) Michel, B. M.; Steffens, L. D.; Sigman, M. S. The Wacker Oxidation. In *Organic Reactions*; Vol. *84*; Denmark, S. E., Ed.; John Wiley & Sons, Inc., 2014; pp 75−414.

(3) Kawamura, Y.; Kawano, Y.; Matsuda, T.; Ishitobi, Y.; Hosokawa, T. *J. Org. Chem.* **2009**, *74*, 3048.

(4) (a) El-Qisairi, A.; Henry, P. M. *J. Organomet. Chem.* **2000**, *603*, 50. This process has been reinvestigated and revealed to exhibit no enantioselectivity, see: (b) Denmark, S. E.; Carson, N. *Org. Lett.* **2015**, *17*, 5728.

(5) Hosokawa, T.; Uno, T.; Inui, S.; Murahashi, S. *J. Am. Chem. Soc.* **1981**, *103*, 2318.

(6) Uozumi, Y.; Kato, K.; Hayashi, T. *J. Am. Chem. Soc.* **1997**, *119*, 5063.

(7) (a) Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 17778. (b) Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2892.

(8) (a) Takenaka, K.; Mohanta, S. C.; Patil, M. L.; Rao, C. V. L; Takizawa, S.; Suzuki, T.; Sasai, H. *Org. Lett.* **2010**, *12*, 3480. (b) Arai, M. A.; Kuraishi, M.; Arai, T.; Sasai, H. *J. Am. Chem. Soc.* **2001**, *123*, 2907.

(9) (a) Kapitán, P.; Gracza, T. *ARKIVOC* **2008**, *viii*, 8. (b) Tietze, L. F.; Zinnegrebe, J.; Spiegl, D. A.; Stecker, F. *Heterocycles* **2007**, *74*, 473. (c) Tietze, L. F.; Sommer, K. M.; Zinngrebe, J.; Stecker, F. *Angew. Chem., Int. Ed.* **2005**, *44*, 257.

(10) (a) Jensen, K. H.; Webb, J. D.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 17471. (b) Pathak, T. P.; Gligorich, K. M.; Welm, B. E.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 7870. (c) Jensen, K. H.; Pathak, T. P.; Zhang, Y.; Sigman, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 17074.

(11) For intermolecular (racemic) hydroetherification of alkenes with phenols, see: (a) Haibach, M. C.; Guan, C.; Wang, D. Y.; Li, B.; Lease, N.; Steffens, A. M.; Krogh-Jespersen, K.; Goldman, A. S. *J. Am. Chem. Soc.* **2013**, *135*, 15062. (b) Sevov, C. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 9303. (c) Li, Z.; Zhang, J.; Brouwer, C.; Yang, C.-G.; Reich, N. W.; He, C. *Org. Lett.* **2006**, *8*, 4175. (d) Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2005**, *127*, 6966. (e) Utsunomiya, M.; Kawatsura, M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 5865.

(12) DeLuca, R. J.; Edwards, J. L.; Steffens, L. D.; Michel, B. W.; Qiao, X.; Zhu, C.; Cook, S. P.; Sigman, M. S. *J. Org. Chem.* **2013**, *78*, 1682.

(13) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.

(14) Hayashi, T.; Yamasaki, K.; Mimura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3036.

(15) (a) Hilton, M. J.; Xu, L.-P.; Norrby, P.-O.; Wu, Y.-D.; Wiest, O.; Sigman, M. S. *J. Org. Chem.* **2014**, *79*, 11841. (b) 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. (c) Mei, T.-S.; Werner, E. W.; Burckle, A. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2013**, *135*, 6830. (d) Werner, E. W.; Mei, T.-S.; Burckle, A. J.; Sigman, M. S. *Science* **2012**, *338*, 1455.

(16) (a) Zhao, D.; Beiring, B.; Glorius, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 8454. (b) Vila, C.; Hornillos, V.; Fañanás-Mastral, M.; Feringa, B. L. *Chem. Commun.* **2013**, *49*, 5933.

(17) Hay, M. B.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 16468.

(18) Michel, B. W.; Steffens, L. D.; Sigman, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 8317.

(19) Harris, J. R.; Waetzig, S. R.; Woerpel, K. A. *Org. Lett.* **2009**, *11*, 3290.

(20) Lu, X.; Liu, Y.; Sun, B.; Cindric, B.; Deng, L. *J. Am. Chem. Soc.* **2008**, *130*, 8134.

(21) Nising, C. F.; Bräse, S. *Chem. Soc. Rev.* **2012**, *41*, 988.

DOI: 10.1021/jacs.6b11486
J. Am. Chem. Soc. 2016, 138, 15881−15884