JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Synthesis of Highly Functionalized Tri- and Tetrasubstituted Alkenes via Pd-Catalyzed 1,2-Hydrovinylation of Terminal 1,3-Dienes

Vaneet Saini, Mark O'Dair, and Matthew S. Sigman*

Department of Chemistry, University of Utah, 315 South 1400 East, Salt Lake City, Utah 84112-0085, United States

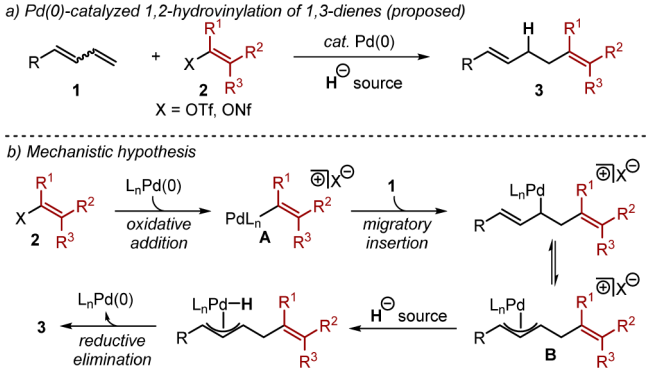
Supporting Information

ABSTRACT: An efficient method for the construction of Csp^2-Csp^3 bond in a regio- and stereoselective fashion involving 1,3-terminal dienes, enol triflates/nonaflates, and sodium formate under Pd(0)-catalysis is described. The three component assembly allows trapping of a π-allyl intermediate, after the initial migratory insertion of the diene, by a hydride source that leads to structurally complex and synthetically challenging tri- and tetrasubstituted alkene building blocks.

Tri- and tetrasubstituted alkenes are important synthetic targets since they are a common structural motifs in many biologically active molecules[1,2] and natural products[3−5] as well as substrates for complexity generating reactions.[6−12] However, the synthesis of such alkenes in a well-defined manner remains a great challenge. As our group is interested in accessing substrates of this type in another context,[13] we reflected on the methods available to access tri- and tetrasubstituted alkenes. The most general methods, which we have deployed, involve carbometalation of alkynes using pyrophoric organometallic reagents (i.e., trialkylaluminium, lithium dialkylcopper, and alkyl lithium), followed by trapping of the resultant alkenyl−metal bond with various different processes such as addition of electrophiles, cross-coupling, or oxidative coupling.[14] Despite significant advances in these protocols, the reactions often suffer from major drawbacks limiting their utility including poor functional group tolerance as a result of the use of highly nucleophilic organometallic reagents and difficult to control regioselective carbometalation of disubstituted alkynes.[14,15]

On the basis of our desire to access more diverse, stereodefined alkenes, we envisioned an alternative strategy for their synthesis by performing a Pd-catalyzed 1,2-hydrovinylation of a 1,3-diene (Scheme 1a) with a vinyl electrophile. Recent progress in the synthesis of well-defined vinyl electrophiles, mainly the access to triflate derivatives, may allow for a compellingly broad scope.[16−19] Specifically, we hypothesized that initiating catalysis by oxidative addition of a well-defined vinyl triflate **2** would allow for subsequent migratory insertion of a 1,3-diene **1** into the cationic vinyl Pd-intermediate **A** to yield a π-allyl intermediate **B** (Scheme 1b). Introduction of a hydride source would allow for reduction of this intermediate, likely site-selectivity based on an incorporated steric and electronic bias on the 1,3-diene.[20,21a] By utilizing a cationic Pd-system, migratory insertion should be significantly faster than direct reduction of **A** with a hydride[21,22] or β-hydride elimination[23] in the case of acyclic electrophiles to form allenes. The reductive coupling of a vinyl triflate with a diene could be considered a reductive Heck-type reaction installing a Csp^2-Csp^3 bond. It should be noted that in practice reductive intermolecular Heck-type reactions have been limited to norbornene-like alkenes preventing the complexity incurred through β-hydrogen elimination processes. Furthermore, reductive Heck approaches using vinyl electrophiles have mainly been explored in an intramolecular fashion.[24,25] Herein, we present a Pd-catalyzed intermolecular 1,2-hydrovinylation of 1,3-dienes[26] and vinyl triflates with sodium formate as the reductant, wherein mild conditions are applied to the synthesis of a vast array of well-defined, highly functionalized tri- and tetrasubstituted alkenes.

Scheme 1. Proposed Pd(0)-Catalyzed 1,2-Hydrovinylation of 1,3-Dienes with Enol Triflates/Nonaflates and a Hydride Source



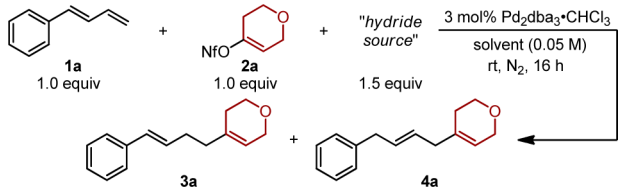
Optimization was initiated using a simplified goal of accessing trisubstituted alkenes by employing a cyclic vinyl electrophile coupling partner. The reaction system of *trans*-1-phenyl-1,3-butadiene (**1a**), 3,6-dihydro-2*H*-pyran-4-yl nonaflate (**2a**), and ammonium formate was subjected to conditions similar to those reported by our group for the vinylarylation of dienes (Table 1, entry 1).[21a] Low yield of the hydrovinylation product was obtained with 47% of the enol nonaflate remaining. The probable reason for the higher levels of conversion as compared to the product yield could be attributed to the direct reduction of **2a**. Evaluation of various other metal formates revealed that simply employing sodium formate, which is sparingly soluble, afforded the product in good yield and excellent selectivity (entries 2−4). Introducing silanes gave the desired product in modest yields and lower regioselectivity (entries 5 and 6). Therefore, sodium formate was selected for further optimization due to the

Received: November 12, 2014
Published: January 2, 2015

ACS Publications © 2015 American Chemical Society

DOI: 10.1021/ja511640g
J. Am. Chem. Soc. 2015, 137, 608−611

Table 1. Optimization for the 1,2-Hydrovinylation of 1,3-Diene with a Cyclic Enol Nonaflate



entry	solvent	hydride source	% conv. **2a**[a]	% yield (**3a**/**4a**)[a,b]
1	DMA	HCO_2NH_4	53	5 (nd)
2[c]	DMA	$(HCO_2)_2Zn$	69	52 (15.4:1)
3	DMA	$HCO_2Li{\cdot}H_2O$	57	46 (16:1)
4	DMA	HCO_2Na	>95	62 (16:1)
5	DMA	Et_3SiH	93	59 (9.6:1)
6	DMA	$(EtO)_3SiH$	84	27 (8.8:1)
7	THF	HCO_2Na	28	4 (nd)
8	*t*-AmOH	HCO_2Na	48	10 (>20:1)
9[d]	DMA	HCO_2Na	>95	79 (15:1)
10[d,e]	DMA	HCO_2Na	>95	78 (15:1)

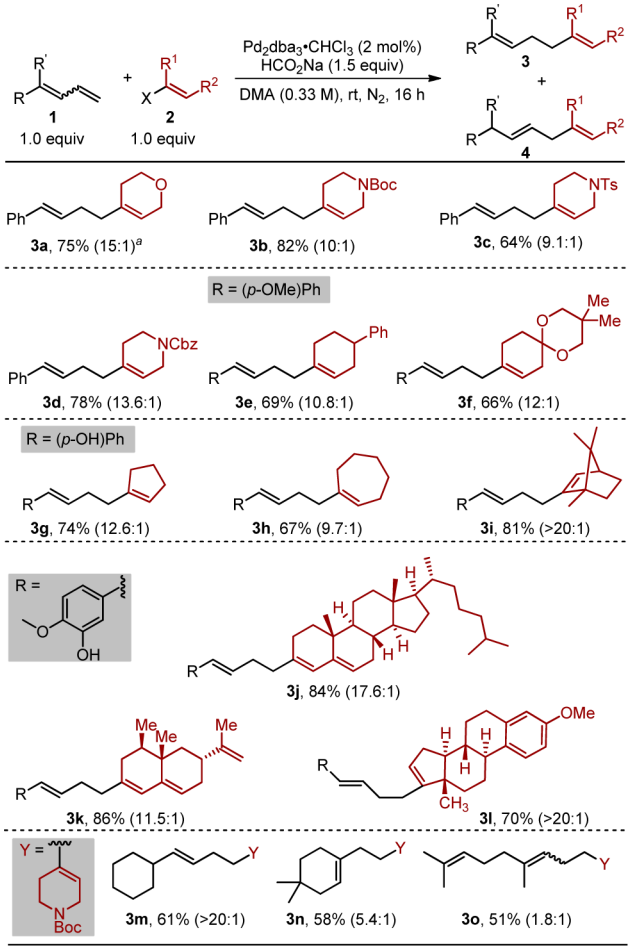
[a]Determined by NMR using an internal standard on 0.2 mmol scale. [b]Yields are a combination of both **3a** and **4a**. [c]Reaction performed with 0.75 equiv of zinc formate. [d]Reaction performed in a concentration of 0.33 M **2a**. [e]Reaction performed using 2 mol % $Pd_2dba_3{\cdot}CHCl_3$. Reaction performed on 0.5 mmol scale gave 75% yield (both **3a** and **4a**) and 15:1 regioselectivity (**3a**/**4a**).

promising results and clear economic advantages. Changing the solvents to either ethereal or alcoholic solvents, such as THF and *tert*-amyl alcohol, afforded lower yields of **3a** (entries 7 and 8). Further improvement was obtained by increasing the concentration of **2a** to 0.33 M (entry 9). Comparable results were obtained when the catalyst loading was reduced to 2 mol % of $Pd_2dba_3{\cdot}CHCl_3$ (entry 10).

The scope of cyclic enol nonaflates and triflates with various aryl dienes were explored (Table 2). Besides the dihydropyran derived nonaflate used to optimize the reaction (**3a**), various protected tetrahydropyridine nonaflates gave the desired product in good yields and generally high selectivity for the styrenyl products (**3b**−**3d**). Six-membered carbocyclic electrophiles with substitution at the 4-position, such as a phenyl (**3e**) and ketal (**3f**) group, were equally compatible. Additionally, simple cyclic enol nonaflates with different ring sizes were successfully incorporated (**3g** and **3h**). Next, we turned our attention toward the functionalization of natural product derived vinyl triflates. For example, enol triflates obtained from (1*S*)-(−)-camphor and cholesterol yielded **3i** and **3j**, respectively, in excellent yields and selectivity. Furthermore, the 1,1-disubstituted alkene in a (+)-nootkatone derivative remained intact and gave the 1,2-hydrovinylated product **3k** in 86% yield with good site selectivity. The insensitivity of this reaction to the nature of the vinyl electrophile was highlighted by the use of a sterically hindered and biologically relevant estrone derivative, which gave the desired compound **3l** in 70% yield.

To explore the effect of the diene coupling partner, three aliphatic 1,3-dienes were subjected to the reaction. A simple cyclohexyl-substituted substrate performed well in the reaction with high site selectivity in the reduction resulting in >20:1 of the 1,2-hydrovinylated product (**3m**). However, using a substrate derived from 4,4-dimethyl-1-vinylcyclohexene gave modest site selectivity and yield (**3n**). The origin of this observation may be attributed to the preferential formation of thermodynamically more stable internal alkene product. Finally, a geraniol derived

Table 2. Scope of the Pd(0)-Catalyzed 1,2-Hydrovinylation of 1,3-Dienes with Cyclic Enol Electrophiles

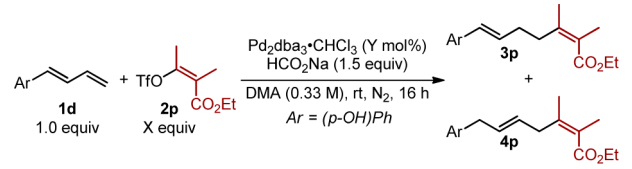


[a]The bracket represents the ratios of **3**:**4**. All yields are a combination of both **3** and **4**. All yields represent an average of two experiments. Note: For **3a**−**3h** and **3m**−**3o**, enol nonaflates were used; for **3i**−**3l**, enol triflates were used.

diene lead to significantly lower site selectivity (**3o**). While the cause of this latter result is unclear at this time, a general observation is that a steric bias is required for high selectivity.

After proof of concept, we wished to expand the system to synthetically more diverse electrophiles by investigating the use of acyclic enol triflates derived from *β*-keto esters (Table 3). The stereoselective synthesis of these enol triflates has been

Table 3. Optimization for the 1,2-Hydrovinylation of 1,3-Diene with *β*-Keto Ester Derived Enol Triflate

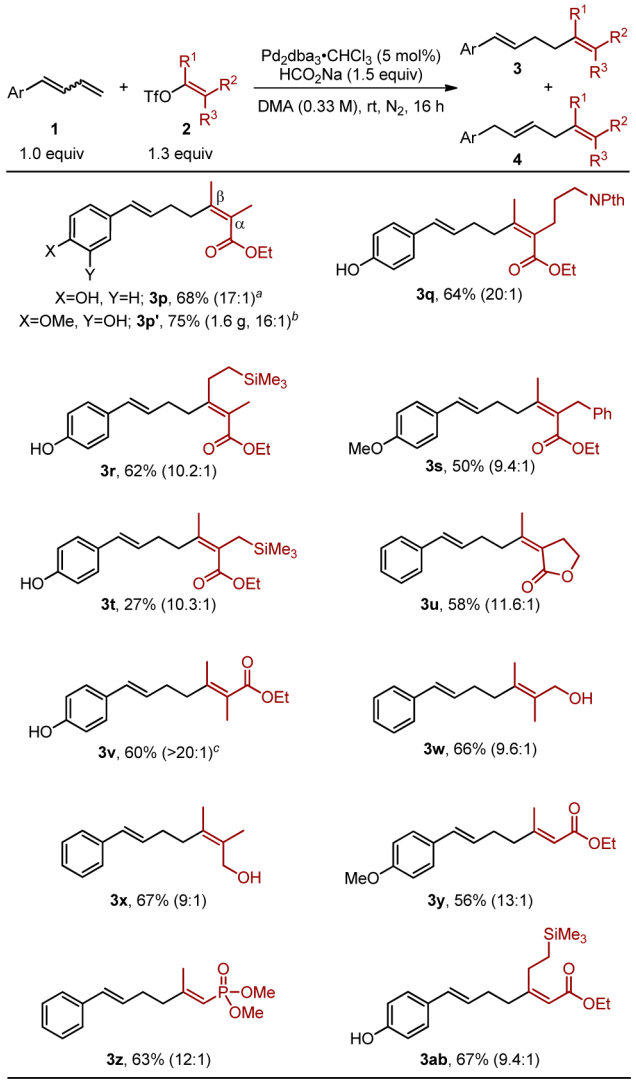


entry	*X*	*Y*	% conv. **1d**	% yield (**3p**/**4p**)[a]
1	1.0	2	80	45 (>20:1)
2	1.3	2	83	55 (>20:1)
3	1.3	5	95	68 (17:1)

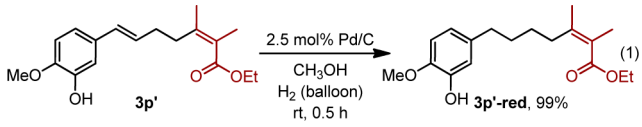
[a]Determined by NMR using an internal standard on 0.2 mmol scale. Yields are a combination of both **3p** and **4p**.

DOI: 10.1021/ja511640g
J. Am. Chem. Soc. 2015, 137, 608−611

Table 4. Scope of the Pd(0)-Catalyzed 1,2-Hydrovinylation of 1,3-Dienes with β-Keto Ester Derived Enol Triflates



[a]The bracket represents the ratios of **3**/**4**. All yields are a combination of both **3** and **4**. All yields represent an average of two experiments. [b]The reaction was performed on 7.0 mmol scale and 1.0 M conc. of diene. [c]Mixture of (*E*) and (*Z*) isomers were observed (**3v**/**3p**, 6.6:1).



extensively reported.[16−18] Recently, Frantz and co-workers have developed a practical approach that allows access to di- and trisubstituted enol triflates in a highly stereodefined and scalable fashion.[19] On the basis of the effective formation of **3l** from the oxidative addition of a sterically congested vinyl electrophile, we were hopeful that the use of this type of triflate to access tetrasubstituted alkenes would be successful. However, the use of acyclic electrophiles of this sort was anticipated to be particularly challenging, especially under Pd(0)-catalysis, since they have the inherent ability to undergo β-hydride elimination after the initial oxidative addition, to form allenes as demonstrated in the synthesis of various useful compounds such as dienes,[27] heteroaromatics,[28] and chiral allenes.[23] Also, E_2 elimination of acyclic enol triflates in the presence of a base is an established method for alkynyl ester synthesis.[29] Therefore, we were initially concerned that these issues may impede our ability to develop reactions using these reagents.

Submitting (*Z*)-enol triflate (**2p**) to the previous reaction conditions furnished the desired (*Z*)-tetrasubstituted alkene **3p** in 45% yield without measurable degradation of alkene stereochemical integrity (Table 3, entry 1). Slight adjustments to the reaction conditions, such as increasing the catalyst loading and stoichiometry of the vinyl triflate, improved the yield (entries 2 and 3). We hypothesize that the mild reaction conditions employed, such as the absence of basic coordinating ligands and strong exogenous bases, leads to a faster rate of migratory insertion relative to β-hydride elimination avoiding previously reported deleterious processes.

As many configurationally defined (*Z*)-enol triflates are readily synthesized from cheap and easily accessible β-keto esters, the scope is broad (Table 4). The reaction was successfully scaled to 7.0 mmol (**3p′**) allowing access to these compounds on a gram scale. Installation of various functional groups, which provide handles for further elaboration, is highlighted by the successful incorporation of an *N*-phthalimide protected amine (**3q**) and an alkyl silane at the β-position (**3r**). Substitution at the α-position, such as a benzyl group (**3s**) and an alkyl silane (**3t**), underwent hydrovinylation albeit in lower yields. An enol triflate bearing a lactone reacted smoothly under the reaction conditions (**3u**). Unfortunately, the reaction with (*E*)-enol triflate yielded a mixture of (*E*)- and (*Z*)-tetrasubstituted alkenes (**3v**). The reactivity difference between (*E*)- and (*Z*)-enol triflates has previously been observed, but the exact reason for this result is unclear at this time.[28] However, the reaction of the reduced variant produced by treatment with DIBAL-H[16] lead to (*E*)-tetrasubstituted alkene (**3w**) with no loss of stereochemical integrity. Similarly, the use of (*Z*)-hydroxymethylene enol triflate gave 67% yield of a single stereoisomer as determined by comparing the ^{1}H and ^{13}C NMR of both the stereoisomers (i.e., **3w** and **3x**), whereas the (*E*)- and (*Z*)-stereochemistry was confirmed using NOE experiments. Conversely, (*E*)-enol triflates containing hydrogen at the α-position afforded (*E*)-trisubstituted alkenes as illustrated in the successful synthesis of **3y**−**3ab**. Finally, the disubstituted alkene present in **3p′** can be reduced selectively in the presence of the electron-deficient tetrasubstituted alkene using 2.5 mol % of Pd/C to give quantitative yield (eq 1). Thus, this reductive Heck approach can also be considered as a two-step alkylation of stereodefined trisubstituted enol triflates.

In conclusion, we have developed a simple and mild reductive Heck approach for the coupling of terminal 1,3-dienes with cyclic as well as acyclic enol triflates and nonaflates. This method allows rapid access to a variety of structurally diverse and functionalized alkenes including stereodefined (*E*)- and (*Z*)-tri- and tetrasubstituted alkenes starting from easily accessible β-keto ester derived enol triflates. These alkenes will be versatile building blocks for applications in enantioselective relay Heck reactions under study in our lab.[13] Additional studies are also directed toward the expansion of this reductive Heck approach to other dienes and terminal alkenes.

■ 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.

DOI: 10.1021/ja511640g
J. Am. Chem. Soc. 2015, 137, 608−611

AUTHOR INFORMATION

Corresponding Author

*sigman@chem.utah.edu

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The work was supported by the National Institutes of Health (NIGMS R01GM063540).

REFERENCES

(1) Levenson, A. S.; Jordan, V. C. *Eur. J. Cancer* **1999**, *35*, 1628.

(2) Prasit, P.; Wang, Z.; Brideau, C.; Chan, C. C.; Charleson, S.; Cromlish, W.; Ethier, D.; Evans, J. F.; Ford-Hutchinson, A. W.; Gauthier, J. Y.; Gordon, R.; Guay, J.; Gresser, M.; Kargman, S.; Kennedy, B.; Leblanc, Y.; Léger, S.; Mancini, J.; O'Neill, G. P.; Ouellet, M.; Percival, M. D.; Perrier, H.; Riendeau, D.; Rodger, I.; Tagari, P.; Thérien, M.; Vickers, P.; Wong, E.; Xu, L. J.; Young, R. N.; Zamboni, R.; Boyce, S.; Rupniak, N.; Forrest, M.; Visco, D.; Patrick, D. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1773.

(3) Williams, R. B.; Norris, A.; Slebodnick, C.; Merola, J.; Miller, J. S.; Andriantsiferana, R.; Rasamison, V. E.; Kingston, D. G. I. *J. Nat. Prod.* **2005**, *68*, 1371.

(4) Rychlet Elliott, M.; Dhimane, A.-L.; Malacria, M. *J. Am. Chem. Soc.* **1997**, *119*, 3427.

(5) Arnone, A.; Brambilla, U.; Nasini, G.; de Pava, O. V. *Tetrahedron* **1995**, *51*, 13357.

(6) Such as asymmetric epoxidation, dihydroxylation, hydrogenation, polymerization, and materials research. See refs 7−12.

(7) For a review on asymmetric epoxidation, see: Xia, Q. H.; Ge, H. Q.; Ye, C. P.; Liu, Z. M.; Su, K. X. *Chem. Rev.* **2005**, *105*, 1603.

(8) For a review on dihydroxylation, see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(9) For a recent report on dihydroxylation, see: Döbler, C.; Mehltretter, G. M.; Sundermeier, U.; Beller, M. *J. Am. Chem. Soc.* **2000**, *122*, 10289.

(10) For reports on asymmetric hydrogenation, see: (a) Tang, W.; Wu, S.; Zhang, X. *J. Am. Chem. Soc.* **2003**, *125*, 9570. (b) Blackmond, D. G.; Lightfoot, A.; Pfaltz, A.; Rosner, T.; Schnider, P.; Zimmermann, N. *Chirality* **2000**, *12*, 442.

(11) For a report on polymerization, see: Hall, H. K. *Angew. Chem., Int. Ed.* **1983**, *22*, 440.

(12) For a report on materials research, see: Chiappe, C.; Detert, H.; Lenoir, D.; Pomelli, C. S.; Ruasse, M. F. *J. Am. Chem. Soc.* **2003**, *125*, 2864.

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

(14) For a review on the synthesis of tetrasubstituted alkenes, see: Flynn, A. B.; Ogilvie, W. W. *Chem. Rev.* **2007**, *107*, 4698.

(15) You, W.; Li, Y.; Brown, M. K. *Org. Lett.* **2013**, *15*, 1610.

(16) Crisp, G. T.; Meyer, A. G. *J. Org. Chem.* **1992**, *57*, 6972.

(17) Ritter, K. *Synthesis* **1993**, *1993*, 735.

(18) Specklin, S.; Bertus, P.; Weibel, J. M.; Pale, P. *J. Org. Chem.* **2008**, *73*, 7845.

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

(20) Liao, L.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 10209.

(21) (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) Saini, V.; Liao, L.; Wang, Q.; Jana, R.; Sigman, M. S. *Org. Lett.* **2013**, *15*, 5008.

(22) Cacchi, S.; Morera, E.; Ortar, G. *Org. Synth.* **2011**, *88*, 260.

(23) Crouch, I. T.; Neff, R. K.; Frantz, D. E. *J. Am. Chem. Soc.* **2013**, *135*, 4970.

(24) For a recent review on advancements in the reductive Heck reactions, see: Yang, X.; Ma, S.; Du, Y.; Tao, Y. *Chin. J. Org. Chem.* **2013**, *33*, 2325.

(25) (a) Lee, K.; Cha, J. K. *J. Am. Chem. Soc.* **2001**, *123*, 5590. (b) Gao, P.; Cook, S. P. *Org. Lett.* **2012**, *14*, 3340 and references therein.

(26) Zhang, A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2006**, *128*, 54.

(27) Crouch, I. T.; Dreier, T.; Frantz, D. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 6128.

(28) Babinski, D. J.; Aguilar, H. R.; Still, R.; Frantz, D. E. *J. Org. Chem.* **2011**, *76*, 5915.

(29) Maity, P.; Lepore, S. D. *J. Org. Chem.* **2009**, *74*, 158.

DOI: 10.1021/ja511640g
J. Am. Chem. Soc. 2015, 137, 608−611