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Cu-Catalyzed C−H Alkenylation of Benzoic Acid and Acrylic Acid Derivatives with Vinyl Boronates

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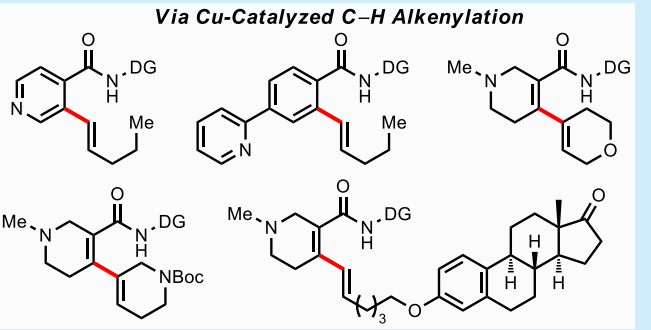
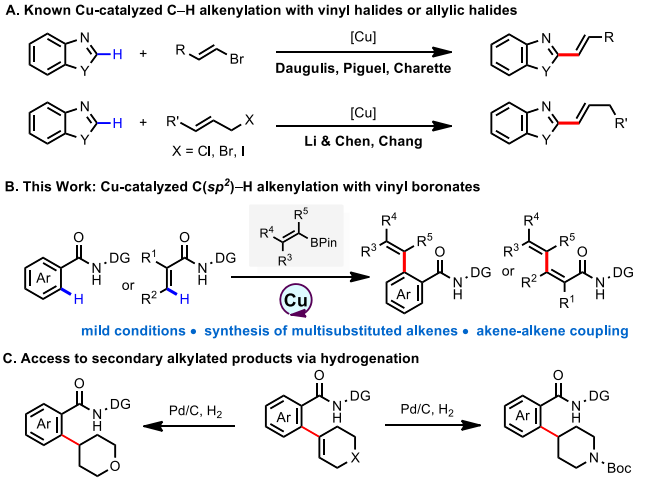
ABSTRACT: An efficient Cu-catalyzed C−H alkenylation with acyclic and cyclic vinyl boronates was realized for the first time under mild conditions. The scope of the vinyl borons and the compatibility with functional groups including heterocycles are superior than Pd-catalyzed C−H coupling with vinyl borons, providing a reliable access to multisubstituted alkenes and dienes. Subsequent hydrogenation of the product from the internal vinyl borons will lead to installation of secondary alkyls.



Cu-catalyzed or -mediated C−H functionalization has attracted great attention due to the abundance, low cost, and low toxicity of copper.[1−3] Since the early finding of its capability of functionalizing the aromatic C−H bonds,[1] a diverse range of C−H activation reactions has been developed,[2,3] thus providing a complementary approach to construct a carbon−carbon or carbon−heteroatom bond. It is worth noting that Cu(II) catalyst has been shown to catalyze transformations that are not successful with Pd catalysts. The exceptional tolerance of the heterocycle is also a practical advantage of Cu catalysts.[3a,c] However, development in this field is still at an early stage compared to the state of the art Pd-catalyzed C−H functionalizations.[4] Here we report a Cu(II)-catalyzed alkenylation of benzoic acid and acrylic acid derivatives with vinyl boronates for the first time. With the aid of an oxazoline-aniline directing group, a series of multisubstituted alkenes and dienes were constructed in high efficiency in the presence of cyclic and acyclic alkenyl boronates (Scheme 1B). Hydrogenation of the resulting internal alkenes could also provide the corresponding secondary alkylated arenes (Scheme 1C).

Substituted alkenes and dienes are ubiquitous motifs in natural products, pharmaceuticals, and organic materials.[5] In addition, they are widely used synthons participating in many reduction and oxidation processes.[6] C−H coupling with vinyl borons could provide an attractive route for this class of compounds.[7] Attempts to achieve this transformation using Pd catalysts have been largely unsuccessful due to the decomposition of vinylboronates in the presence of Pd(II) catalysts.[8] Our early finding of Cu-catalyzed C−H coupling with arylboronate[3d] prompted us to investigate the feasibility of using Cu catalysts to effect this transformation.

Scheme 1. Synopsis for Cu-Catalyzed C−H Alkenylation with Vinyl Boronates



Recently, Daugulis,[9a] Piguel,[9b] Charette,[9c] and others[9d] have demonstrated the direct alkenylation of acidic C−H in the presence of strong base with vinyl halides. Employing allylic halides via an allylation/isomerization sequence, Li, Chen,[10a] and Chang[10b] have achieved the C−H alkenylation of relatively

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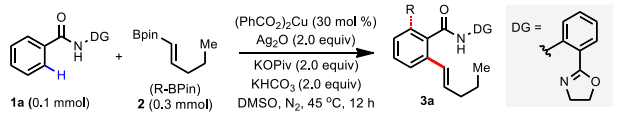
more acidic aryl C−H bonds (azoles or fluorinated benzenes, Scheme 1A). Despite this progress, Cu-catalyzed alkenylation of inert C−H bond remains a significant challenge. We envisioned Cu-catalyzed C−H coupling with alkenyl boronates could be an attractive approach owing to the availability of vinyl boronates.

In our initial screening using a readily removable oxazoline-aniline directing group, we found that cross-coupling of substrate **1a** with (*E*)-1-pentenylboronic acid pinacol ester (**2**) proceeded in 7% yield of monoalkenylated product along with 11% yield of a hydroxylation byproduct under our previous conditions (66% yield for arylation, see Supporting Information for more information). After systematically tuning the reaction parameters (Scheme 2), the yield of alkenylation

Scheme 2. Effects of Reaction Parameter[a,b]



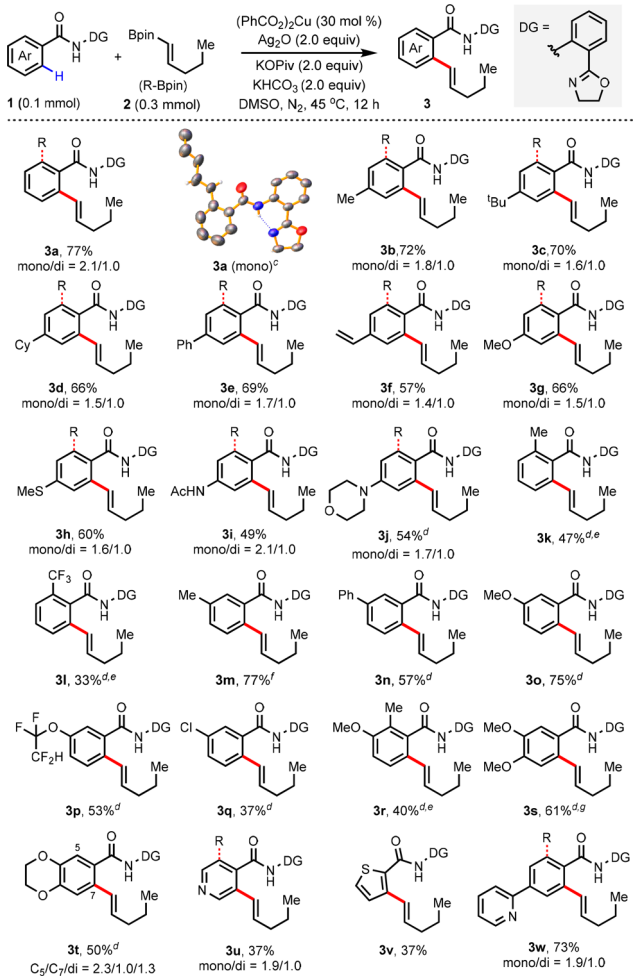
Entry	Deviation from optimal conditions	Yield (%) (mono/di)	Entry	Deviation from optimal conditions	Yield (%) (mono/di)
1	none	86 (2.1/1.0)	9	$Cu(OAc)_2$ was used	78 (2.4/1.0)
2	No $(PhCO_2)_2Cu$	N.D.	10	$Cu(OPiv)_2$ was used	83 (2.1/1.0)
3	No KOPiv	6 (6.0/0)	11	30 °C	68 (4.2/1.4)
4	No $KHCO_3$	66 (2.3/1.0)	12	50 °C	70 (2.0/1.0)
5	No bases	N.D.	13	60 °C	51 (1.0/1.0)
6	No Ag_2O	trace	14	DMF instead of DMSO	54 (5.8/1.0)
7	air instead of N_2	70 (2.6/1.0)	15	Dioxane instead of DMSO	N.D.
8	$(PhCO_2)_2Cu$ (20 mol%) was used	70 (4.4/1.0)	16	CH_3CN instead of DMSO	N.D.

[a]The yield was determined by ^1H NMR using dibromomethane as an internal standard. [b]Isolated yield.

products is improved to 86% as measured by NMR (77% isolated yield) with a mono/di selectivity of 2.1/1.0. The optimized conditions consist of copper(II) benzoate (30 mol %), Ag_2O (2.0 equiv), the potassium salt of pivalic acid (KOPiv) (2.0 equiv), $KHCO_3$ (2.0 equiv), and dimethyl sulfoxide (DMSO) (2.0 mL). The reaction is run under N_2 atmosphere at 45 °C. Control experiments demonstrated that the reaction cannot proceed in the absence of copper(II) benzoate and bases, while only trace amounts of the desired alkenylation products were observed without the use of Ag_2O (entry 6). Both KOPiv and $KHCO_3$ are crucial for maintaining the high efficiency (entries 3 and 4), in which KOPiv played a major role providing **3a** in 66% yield alone. It is noteworthy that the reaction can also be performed under air, albeit with lower yield and 6% of hydroxylated byproduct (entry 7). $Cu(OAc)_2$ and $Cu(OPiv)_2$ could also promote this C−H alkenylation reaction with a slightly lower yield in comparison with $(PhCO_2)_2Cu$ (entries 9 and 10). Notably, the reaction temperature is pivotal for suppressing the formation of the hydroxylation byproduct (entries 11−13). Higher temperature normally led to lower yield of desired alkenylation product and higher yield of hydroxylation byproduct (see Supporting Information for more information). Replacement of DMSO by other solvents, like MeOH, dioxane, MeCN, toluene, and dichloromethane, shut down the reaction, while dimethylformamide (DMF) provided the desired products in 54% yield (entries 14−16). In addition, reducing the loading of $(PhCO_2)_2Cu$ and tuning the concentration all led to inferior results.

Under the optimal conditions, we next evaluated the scope of the benzoic acids using (*E*)-1-pentenylboronic acid pinacol ester (**2**) as an alkenylating reagent (Scheme 3). Normally, the *ortho*-substituted substrates gave lower yields in comparison

Scheme 3. Evaluation of Benzoic Acids[a,b]



[a]Reaction conditions: **1** (0.1 mmol), **2** (0.3 mmol), $Cu(PhCO_2)_2$ (0.03 mmol), Ag_2O (0.2 mmol), KOPiv (0.2 mmol), $KHCO_3$ (0.2 mmol), DMSO (2.0 mL), N_2, 45 °C, 12 h. [b]Isolated yield. [c]Single-crystal X-ray structure of **3a** (mono) with thermal ellipsoids at 30% probability levels. [d]$Cu(OPiv)_2$ (0.03 mmol). [e]60 °C. [f]$Cu(PhCO_2)_2$ (0.035 mmol), 50 °C. [g]9 h.

with *meta*- and *para*-substituted benzoic acids (**3k** and **3l**). Both electron-rich and electron-deficient group-substituted benzoic acids are well-tolerated, giving the corresponding alkenylated arenes in moderate to good yields. The *para*-substituted substrates (**3b**−**3j** and **3w**) provided a mono- and diproducts mixture in high efficiency, while the monoalkenylation happened with *meta*-substituted substrates (**3m**−**3r**) due to the steric hindrance. This protocol features good functional group tolerance with alkyl, aryl, vinyl, amino, chloro, methoxyl, methylthio group, and trifluoromethyl groups, in which the compatibility with the vinyl group highlights the impressive mild conditions. Heterocyclic substrates (**3u**−**3w**) are also suitable substrates for this alkenylation, albeit lower yields were obtained. Not surprisingly, the C−H alkenylation proceeded at the *ortho*-position to oxazoline-aniline directing group rather than at the strong coordinating heterocycle site (**3w**).

Next, the generality of alkenyl boronates was evaluated using **1o** as model substrate. As depicted in Scheme 4, both *cis*- and

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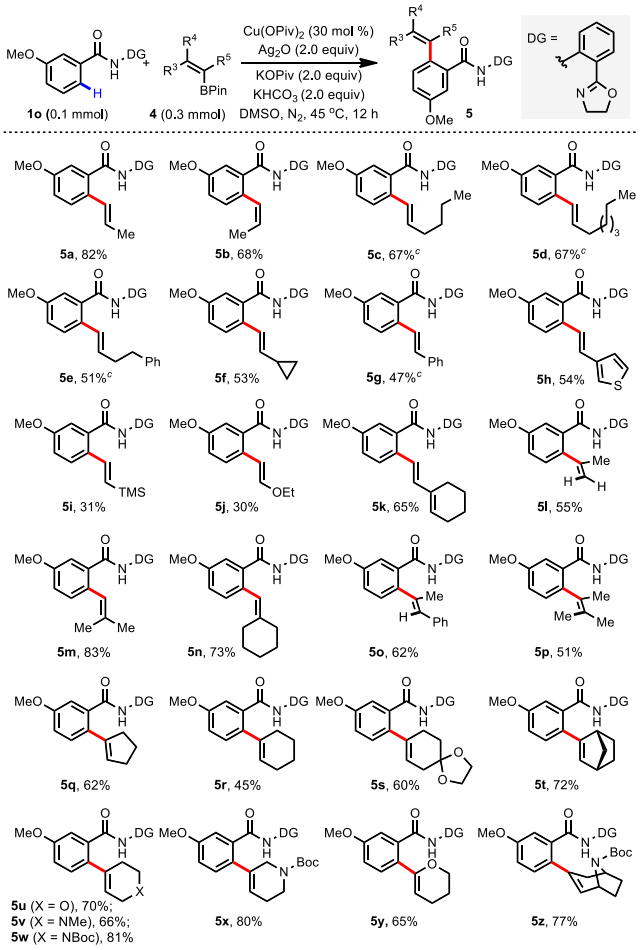
Scheme 4. Scope of Vinyl Boronates[a,b]

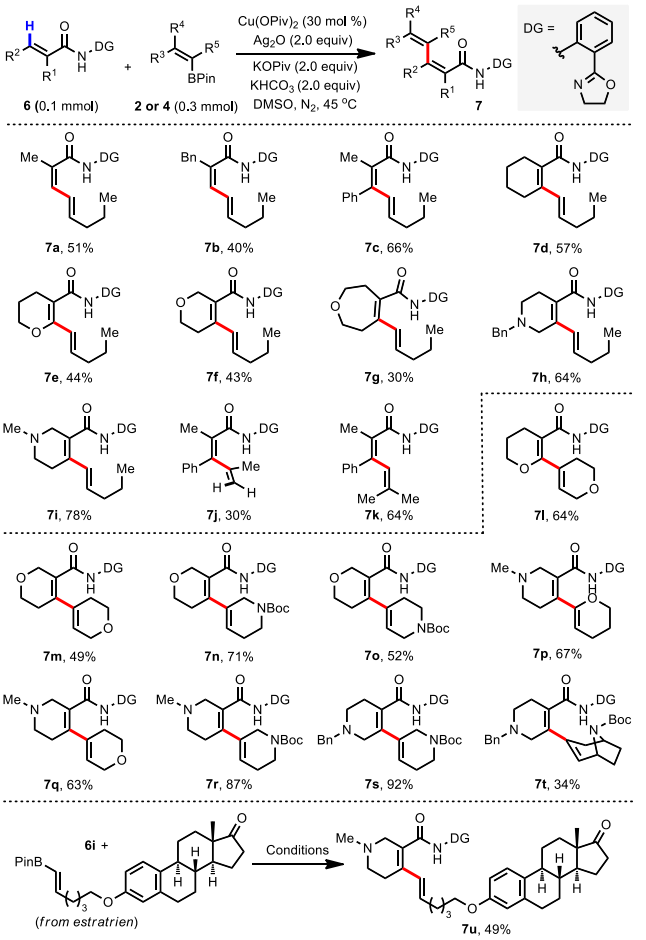


[a]Reaction conditions: **1o** (0.1 mmol), **4** (0.3 mmol), $Cu(OPiv)_2$ (0.03 mmol), Ag_2O (0.2 mmol), KOPiv (0.2 mmol), $KHCO_3$ (0.2 mmol), DMSO (2.0 mL), N_2, 45 °C, 12 h. [b]Isolated yield. [c]50 °C.

trans-vinyl boronates are compatible with this protocol, giving corresponding *cis* or *trans* alkenes in high yields (**5a** and **5b**). Alkyl vinyl boronates reacted with **1o** providing the desired products in 51−82% yields (**5a**−**5f**). Notably, the compatibility with the cyclopropanyl group indicated this C−H vinylation reaction through a cyclocupration intermediate rather than a radical process. Styrene- and heterostyrene-derived coupling partners are also tolerated under the mild conditions albeit with moderate yields (**5g** and **5h**). The mild reaction conditions also allowed the coupling with base- or acid-sensitive alkenylating reagents, like tetramethylsilane (TMS)-vinyl, vinyl ether, and diene, etc. (**5i**−**5k**). Isopropenylboronic acid pinacol ester gave the desired product in 55% yield (**5l**). In addition, disubstituted (**4m**−**4o**), trisubstituted (**4p**), and cyclic vinyl boronates (**4q**−**4t**) are all suitable coupling partners for this reaction. It is worth noting that a broad range of heterocyclic alkenyl boronates are compatible with this reaction, providing a diverse range of novel heteroalkenylated arenes (**5u**−**5z**).

Given the importance of dienes in organic synthesis and their population in bioactive molecules, we turned to investigate the direct coupling of a vinyl C−H bond with vinyl boronates. Because of the instability of dienes under oxidative conditions, the direct synthesis of dienes via C−H activation remains challenging. To our delight, various dienes were synthesized under our mild conditions (Scheme 5), given a variety types of dienes in 30−78% yields employing

Scheme 5. Alkene−Alkene Coupling[a,b]



[a]Reaction conditions: **6** (0.1 mmol), **2** or **4** (0.3 mmol), $Cu(OPiv)_2$ (0.03 mmol), Ag_2O (0.2 mmol), KOPiv (0.2 mmol), $KHCO_3$ (0.2 mmol), DMSO (2.0 mL), N_2, 45 °C, and see Supporting Information for detailed reaction time. [b]Isolated yield.

$Cu(OPiv)_2$ as the most efficient catalyst (**7a**−**7k**). Moreover, heterocyclic alkene substrates are also compatible providing a direct method for synthesis of alkenylated heterocycles in high yields (**7e**−**7i**). Notably, the incredible heteroatom tolerance allows the direct coupling of heterocyclic substrates with heterocyclic alkenyl boronates (**7l**−**7t**) in high efficiency. The direct coupling of **6i** with an estratrien-derived vinyl boronate demonstrated the versatility of this process for late-stage functionalization of complex bioactive molecules (**7u**).

The scalability of this process was examined by the direct coupling of **1o** (1.0 g, 3.4 mmol) with (*E*)-1-pentenylboronic acid pinacol ester (**2**), providing the desired alkenylated product **3o** in 77% yield (Scheme 6a). The directing group (**9**) could be readily removed in the presence of KOH, and it was recovered in 70% yield. The resulting alkenylated benzoic acid (**8**) is a significant intermediate in organic synthesis, which could be easily transformed to alkylated benzoic acid (**10**), lactone (**11**), and aldehyde (**12**) (Scheme 6b). It is noteworthy that hydrogenation of the heterocyclic alkene derivatives gave alkylated tetrahydropyran (**13**) and piperidine (**14**) in 81% and 95% yields, respectively (Scheme 6c). Because of the

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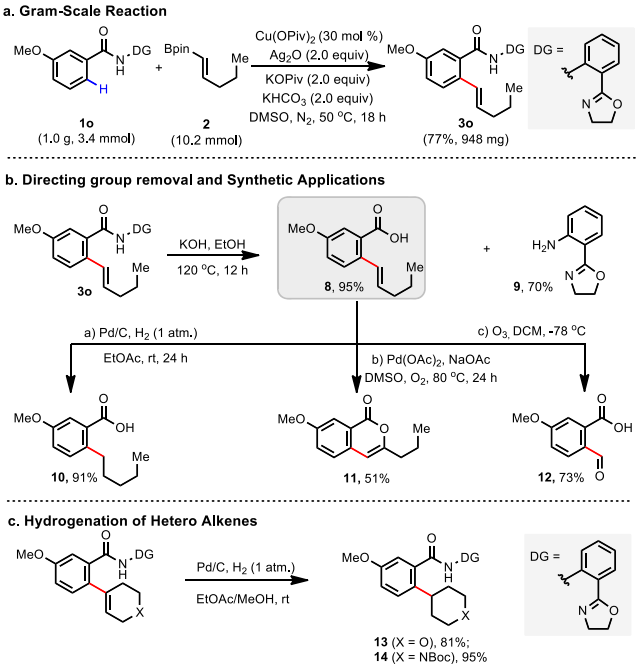
Scheme 6. Gram-Scale Reaction and Applications



difficulties in installing secondary alkyls via Pd-catalyzed C−H alkylation, this method provides a solution to this persistent problem. In addition, the direct synthesis of substituted piperidine or tetrahydropyran derivatives, highly valuable motifs in medicinal chemistry, is noteworthy.

In summary, a series of alkenes and dienes was synthesized via Cu-catalyzed C−H alkenylation with cyclic and acyclic vinyl boronates for the first time. The procedure features mild conditions, broad functional group, and heterocycle tolerance, filling a significant gap in directed C−H activation reaction development.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01469.

Experimental procedures, complete characterization data, copies of ^{1}H and ^{13}C NMR spectra, and X-ray crystallographic data (PDF)

Accession Codes

CCDC 1976936 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.
CCDC 1976936 corresponds to [**3a** (mono)] as described in this manuscript.

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■ REFERENCES

(1) (a) Chen, X.; Hao, X. S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790−6791. (b) Uemura, T.; Imoto, S.; Chatani, N. *Chem. Lett.* **2006**, *35*, 842−843.

(2) For selected reviews on Cu-catalyzed or -mediated C−H functionalization: (a) Rao, W.-H.; Shi, B.-F. *Org. Chem. Front.* **2016**, *3*, 1028−1047. (b) Guo, X.-X.; Gu, D.-W.; Wu, Z.-X.; Zhang, W.-B. *Chem. Rev.* **2015**, *115*, 1622−1651. (c) Hirano, K.; Miura, M. *Chem. Commun.* **2012**, *48*, 10704−10714. (d) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11062−11087. (e) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074−1086.

(3) For selected examples on Cu-catalyzed or -mediated C−H functionalization: (a) Yu, J.-F.; Li, J.-J.; Wang, P.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2019**, *58*, 18141−18145. (b) Kim, H.; Heo, J.; Kim, J.-H.; Baik, M.-H.; Chang, S. *J. Am. Chem. Soc.* **2018**, *140*, 14350−14356. (c) Shang, M.; Wang, M.-M.; Saint-Denis, T.-G.; Li, M.-H.; Dai, H.-X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2017**, *56*, 5317−5321. (d) Shang, M.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. *Org. Lett.* **2014**, *16*, 5666−5669. (e) Li, Q.; Zhang, S.-Y.; He, G.; Ai, Z.-Y.; Nack, W.-A.; Chen, G. *Org. Lett.* **2014**, *16*, 1764−1767. (f) Wang, Z.; Ni, J.-Z.; Kuninobu, Y.; Kanai, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 3496−3499. (g) Wu, X.-S.; Zhao, Y.; Zhang, G.-W.; Ge, H.-B. *Angew. Chem., Int. Ed.* **2014**, *53*, 3706−3710. (h) Shang, M.; Sun, S.-Z.; Wang, H.-L.; Laforteza, B. N.; Dai, H.-X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2014**, *53*, 10439−10442. (i) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593−1597. (j) Ban, I.; Sudo, T.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008**, *10*, 3607−3069. (k) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404−12405. (l) Gui, Q.-W.; Chen, X.; Hu, L.; Wang, D.-D.; Liu, J.-D.; Tan, Z. *Adv. Synth. Catal.* **2016**, *358*, 509−514.

(4) For selected reviews on Pd-catalyzed C−H functionalization: (a) He, G.; Wang, B.; Nack, W. A.; Chen, G. *Acc. Chem. Res.* **2016**, *49*, 635−645. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147−1169. (c) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094−5115.

(5) For selected examples: (a) Kaur, P.; Singh, K. *J. Mater. Chem. C* **2019**, *7*, 11361−11405. (b) Ben-Califa, N.; Bishara, A.; Neumann, D.; Kashman, Y. *Invest. New Drugs* **2012**, *30*, 98−104. (c) Zhou, X.-H.; Luo, J.-D.; Davies, J. A.; Huang, S.; Jen, A. K. Y. *J. Mater. Chem.* **2012**, *22*, 16390−16398. (d) Ruiz-Gaspa, S.; Nogues, X.; Enjuanes, A.; Monllau, J. C.; Blanch, J.; Carreras, R.; Mellibovsky, L.; Grinberg, D.; Balcells, S.; Diez-Perez, A.; Pedro-Botet, J. *J. Cell. Biochem.* **2007**, *101*, 1430−1438. (e) Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1995**, *117*, 8126−8131.

(6) (a) Patai, S. *The chemistry of double bonded functional groups;* Wiley: Chichester, U.K., 1997. (b) Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427−436.

(7) For recent selected examples on transition-metal-catalyzed C−H alkenylation: (a) Kozhushkov, S. I.; Ackermann, L. *Chem. Sci.* **2013**, *4*, 886−896. (b) Shang, X.-J.; Liu, Z.-Q. *Chem. Soc. Rev.* **2013**, *42*, 3253−3260. (c) Le Bras, J.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170−1214. (d) Rossi, R.; Bellina, F.; Lessi, M. *Synthesis* **2010**, *2010*, 4131−4153. (e) Jambu, S.l.; Tamizmani, M.; Jeganmohan, M. *Org. Lett.* **2018**, *20*, 1982−1986. (f) Wang, P.; Verma, P.; Xia, G.-Q.; Shi, J.; Qiao, J.-X.; Tao, S.-W.; Cheng, P. T.-W.; Poss, M.-A.; Farmer, M.-E.; Yeung, K.-S.; Yu, J.-Q. *Nature* **2017**, *551*, 489−493. (g) Shang, R.; Ilies, L.; Asako, S.; Nakamura, E. *J. Am. Chem. Soc.* **2014**, *136*, 14349−14352. (h) Deb, A.; Bag, S.; Kancherla, R.; Maiti, D. *J. Am. Chem. Soc.* **2014**, *136*, 13602−13605. (i) Meng, L.-K.; Kamada, Y.-K.; Muto, K.; Yamaguchi, J.; Itami, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 10048−10051. (j) Zhao, Y.-S.; He, G.; Nack, W.-A.; Chen, G. *Org. Lett.* **2012**, *14*, 2948−2951. (k) Mochida, S.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2011**, *76*, 3024−3033. (l) Park, S.-H.; Kim, J.-Y.; Chang, S. *Org. Lett.* **2011**, *13*, 2372−2375. (m) Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010**, *327*, 315−319. (n) Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9982−9983. (o) Xu, Y.-H.; Lu, J.; Loh, Y.-P. *J. Am. Chem. Soc.* **2009**, *131*, 1372−1373. (p) Jia, C. G.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 844−639. (q) Lu, M.-Z.; Chen, X.-R.; Xu, H.; Dai, H.-X.; Yu, J.-Q. *Chem. Sci.* **2018**, *9*, 1311−1316.

(8) Wasa, M.; Chan, K. S. L.; Yu, J.-Q. *Chem. Lett.* **2011**, *40*, 1004−1006.

(9) (a) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128−1129. (b) Besselièvre, F.; Piguel, S.; Mahuteau-Betzer, F.; Grierson, D.-S. *Org. Lett.* **2008**, *10*, 4029−4032. (c) Mousseau, J. J.; Bull, J. A.; Charette, A. B. *Angew. Chem., Int. Ed.* **2010**, *49*, 1115−1118. (d) Zhang, W.; Tian, Y.; Zhao, N.; Wang, Y.; Li, J.; Wang, Z. *Tetrahedron* **2014**, *70*, 6120−6126.

(10) (a) Li, D.; Wu, X.-X.; Gao, T.; Li, B.; Chen, S. *Org. Biomol. Chem.* **2017**, *15*, 7282−7285. (b) Xie, W.-L.; Chang, S. *Angew. Chem., Int. Ed.* **2016**, *55*, 1876−1880.

https://dx.doi.org/10.1021/acs.orglett.0c01469
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