Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Fe(III)-Catalyzed Hydroallylation of Unactivated Alkenes with Morita−Baylis−Hillman Adducts

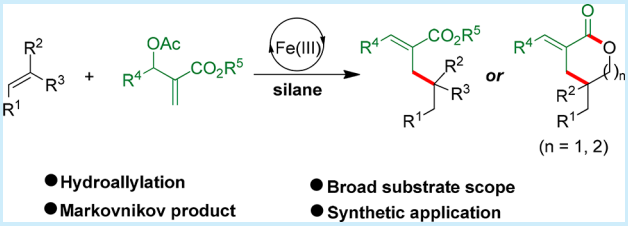
Jifeng Qi,[†] Jing Zheng,[†] and Sunliang Cui*[,†,‡]

[†]Institute of Drug Discovery and Design, College of Pharmaceutical Sciences, Zhejiang University, 866 Yuhangtang Road, Hangzhou 310058, Zhejiang, China

[‡]State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China

Supporting Information

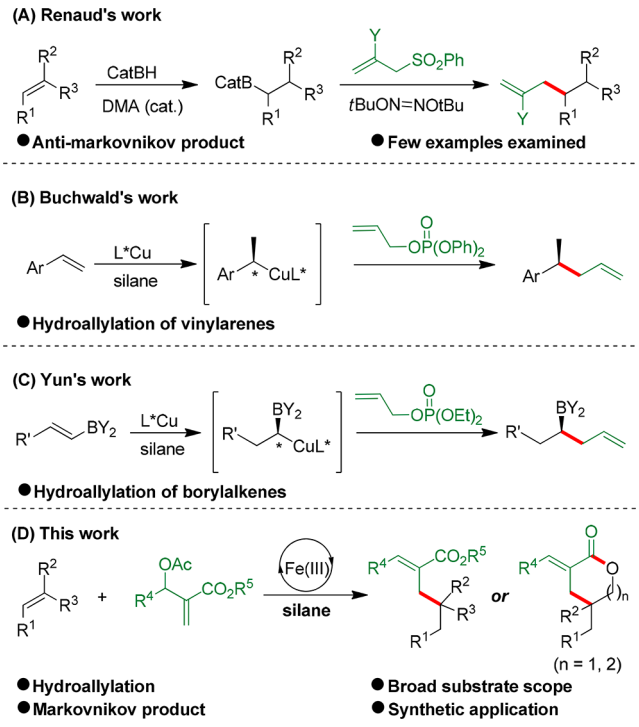
ABSTRACT: An Fe(III)-catalyzed hydroallylation of unactivated alkenes with Morita−Baylis−Hillman adducts via an Fe-catalyzed process is described. A variety of alkenes, including mono-, di-, and trisubstituted alkenes, could all smoothly convert to structural diversified cinnamates in this protocol. Interestingly, when the hydroxyl-containing alkenes were used, various lactones could be rapidly assembled. Moreover, this protocol could be applied to late-stage functionalization of natural products.



Alkenes are readily available fundamental feedstock in academia and industry. Therefore, the functionalization of alkenes for access to structural differential molecules has become an interesting and challenging task in organic synthesis.[1] Among these, the transition-metal-catalyzed hydrofunctionalization of unactivated alkenes has grown as a powerful approach for C−C and C−X (N, O, F, Cl) bond formation toward the construction of diverse molecules.[2] For example, Halpern first revealed the convincing evidence of radical mechanism for Mn(III)-catalyzed hydrogenation of α-methylstyrene and found that hydrogen atom transfer (HAT) was involved in the process.[3] Recently, Shenvi elucidated the HAT mechanism more clearly and applied this to synergistic catalysis.[4] In addition, Mukaiyama,[5] Carreira,[6] Baran,[7] Boger,[8] and Herzon[9] have also made great progress in this area with the achievement of practical and efficient alkene transformation. In those hydrofunctionalization processes, the silanes were used as reductants and the alkyl radical intermediates were in situ generated. On the other hand, Buchwald and co-workers have established Cu-catalyzed unactivated alkenes hydrofunctionalization with good enantioselectivity and regioselectivity.[10] In contrast, these processes invoked alkyl-copper species rather than the radical intermediates.[11] Despite these advances, the hydrofunctionalization of unactivated alkenes toward C−C bond formation remains continuous interesting.

Typically, the hydroallylation of unactivated alkenes represents a carbon chain prolonging approach and demonstrates valuable synthetic utility. For example, Renaud reported an anti-Markovnikov hydroallylation of unactivated alkenes (Scheme 1A).[12] In this protocol, the alkenes undergo hydroboration to be organoboranes and then transfer to alkyl radicals which are sequentially trapped by allyl sulfones to constitute hydroallylation process.[13] Buchwald established an elegant work of Cu-catalyzed enantioselective hydroallylation of vinylarenes with allylic phosphates (Scheme 1B).[10d] More recently, Yun also applied this to constitute hydroallylation of borylalkenes (Scheme 1C).[14] By contrast, the hydroallylation especially the hydro(cinnamyl)methylation of unactivated

Scheme 1. Hydroallylation of Unactivated Alkenes



Received: January 10, 2018

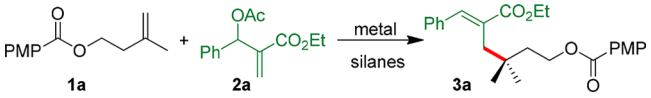
© XXXX American Chemical Society

DOI: 10.1021/acs.orglett.8b00108
Org. Lett. XXXX, XXX, XXX−XXX

alkenes receives much less attention. In the course of our research on alkene hydrofunctionalization,[15] we hypothesized that this could be realized by combination of HAT with suitable cinnamylmethylation reagents. Herein, we report an Fe(III)-catalyzed hydroallylation of unactivated alkenes with Morita–Baylis–Hillman adducts (Scheme 1D).

We commenced our study by using alkene **1a** as a model substrate and the Morita–Baylis–Hillman adduct **2a** as cinnamylation source.[16] Morita–Baylis–Hillman adducts could be easily accessed by the well-known Morita–Baylis–Hillman reaction from aldehydes, thus exhibiting sufficient structural diversity.[17] Initially, we tested the reaction using 30 mol % $Fe(acac)_3$ as catalyst and ethanol as solvent (Table 1, entry 1). To our delight, a new compound **3a** was observed as the main product. The standard identification showed that **3a** was a cinnamate compound, indicating a hydrocinnamylation process was occurring. A NOESY experiment was carried out to confirm that the phenyl ring and the ester group were substituted as the *E*-form. When the solvent was changed to THF and a 2 equiv amount of ethanol was used as additive, the yield was significantly improved to 80% (entry 2). We also tried to decrease the amount of $Fe(acac)_3$ to 10 mol % and found the yield was lower (entry 3). A survey of silanes was also conducted, and Et_3SiH was found to be inferior in shutting down the reactivity (entry 4), while the utilization of $(EtO)_3SiH$ led to a low yield (entry 5, 43%). In addition, reducing the temperature to 25 °C also resulted in a lower yield (entry 6). Moreover, various transition metals such as $Mn(acac)_3$, $Co(acac)_2$, and $Ni(acac)_2$ were also screened. When the $Mn(acac)_3$ was used, **3a** was formed in 61% yield (enrty 7). In contrast, the utilization of $Co(acac)_2$ and $Ni(acac)_2$ did not afford any product (entries 8 and 9).

Table 1. Reaction Optimization[a]

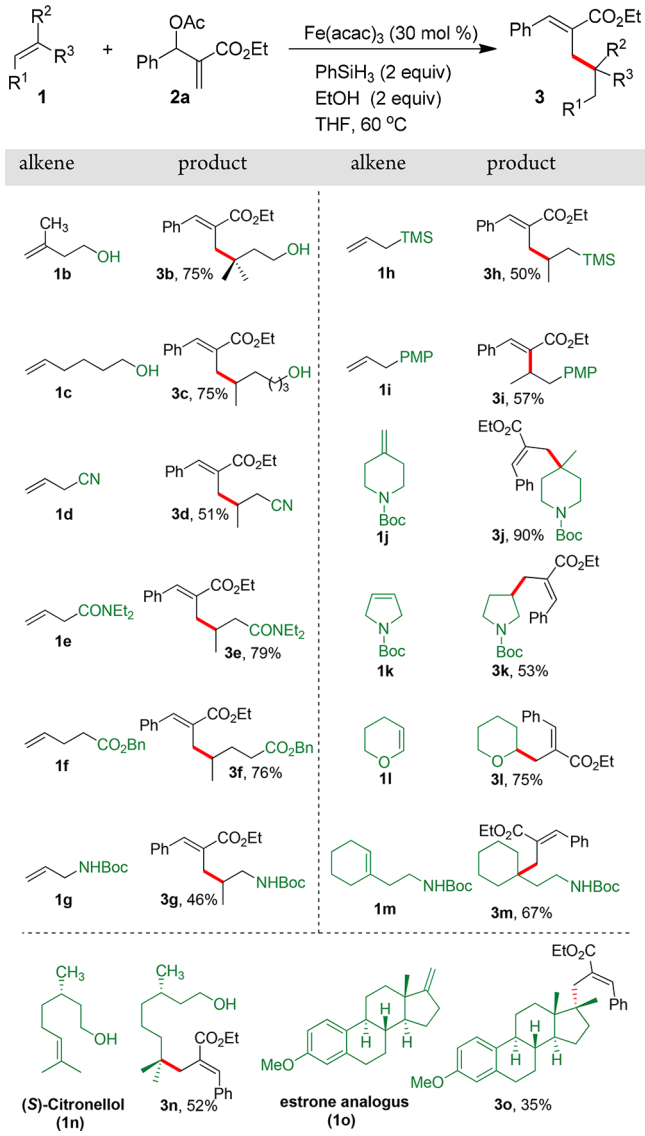


entry	catalysis	silanes	solvent	T (°C)	yield[b] (%)
1	$Fe(acac)_3$	$PhSiH_3$	EtOH	60	63
2[b]	$Fe(acac)_3$	$PhSiH_3$	THF	60	80
3[b,c]	$Fe(acac)_3$	$PhSiH_3$	THF	60	51
4[b]	$Fe(acac)_3$	Et_3SiH	THF	60	0
5[b]	$Fe(acac)_3$	$(EtO)_3SiH$	THF	60	43
6[b]	$Fe(acac)_3$	$PhSiH_3$	THF	25	19
7[b]	$Mn(acac)_3$	$PhSiH_3$	THF	60	61
8[b]	$Co(acac)_2$	$PhSiH_3$	THF	60	0
9[b]	$Ni(acac)_2$	$PhSiH_3$	THF	60	0

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), catalyst (30 mol %), silanes (1 equiv), solvent (2 mL), 2 h; yield refers to isolated product. [b]EtOH (2 equiv) was used as additive. [c]$Fe(acac)_3$ (10 mol %) was used.

With the optimized reaction conditions in hand, we next set out to explore the generality of this method (Table 2). Therefore, a series of alkenes with significant structural diversity, including mono-, di-, and trisubstituted alkenes, were subjected to this process. For example, the 3-methylbut-3-en-1-ol (**1b**) participated in the process smoothly to afford cinnamate **3b** in 75% yield. The terminal monosubstituted alkenes, such as hex-5-en-1-ol (**1c**), allyl cyanide (**1d**), allyl carboxamide (**1e**), benzyl pent-4-enoate (**1f**), *N*-Boc allyamine (**1g**), allyl silane (**1h**), and 1-allyl-4-methoxybenzene (**1i**), engaged in this process to afford the products in moderate to good yields (**3b–i**) and therefore offer ample opportunity for further functionalization. The piperidine-functionalized alkene **1j**, a type of disubstituted terminal alkene, proceeded well in this process to deliver the cinnamyl piperidine **3j** in good yield. With respect to disubstituted internal alkenes, the cyclic *N*-Boc-2,5-dihydro-1*H*-pyrrole **1k** and dihydropyran **1l** were well amenable to this protocol to furnish the products in good yields. Notably, the hydrocinnamylation of dihydropyran **1l** regioselectively occurred at the 2-position. The trisubstituted alkene-like cyclohexene tethered amine **1m** was also applied to this protocol to furnish the cinnamate **3m** in moderate yield. Furthermore, this protocol could be applied to late-stage functionalization of natural products and their derivatives. For example, the (*S*)-citronellol (**1n**) could be easily accessed to its cinnamate derivative **3n** upon use of this method. Meanwhile, the estrone analogue **1o** could couple with Morita–Baylis–Hillman adduct **2a** to deliver a single diastereomer **3o**, albeit in a slightly low yield. Therefore, this method provides a simple

Table 2. Scope of Alkenes[a]



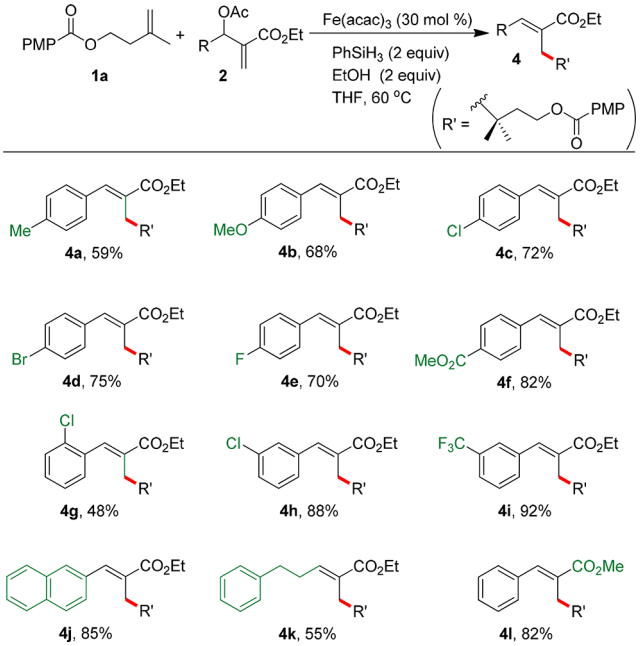
[a]Reaction conditions: **1** (0.3 mmol), **2a** (0.2 mmol), $Fe(acac)_3$ (30 mol %), $PhSiH_3$ (0.2 mmol), EtOH (0.4 mmol), THF (2 mL), 60 °C, 2 h; yields refer to isolated products.

DOI: 10.1021/acs.orglett.8b00108
Org. Lett. XXXX, XXX, XXX–XXX

and distinct approach for alkenes transformation and late-stage functionalization of natural products.

Next, the scope of Morita–Baylis–Hillman adducts was also investigated. As depicted in Scheme 2, a series of *para*-

Scheme 2. Scope of Morita–Baylis–Hillman Adducts[a]



[a]Reaction conditions: **1a** (0.3 mmol), **2** (0.2 mmol), $Fe(acac)_3$ (30 mol %), $PhSiH_3$ (0.2 mmol), EtOH (0.4 mmol), THF (2 mL), 60 °C, 2 h; yields refer to isolated products.

substituted Morita–Baylis–Hillman adducts **2**, regardless of the electron-donating or electron-withdrawing substitution, were subjected to this process and found well applicable. For example, groups like methyl, methoxy, fluoro, chloro, bromo, trifluoromethyl, and ester were tolerated in this hydrocinnamylation process and did not show significant effects in the yields. The *o*-chloro-substituted Morita–Baylis–Hillman adduct **2h** was also employed to furnish the product **4g** in moderate yields. On the other hand, the 3-Cl- and 3-CF_3-substituted adducts **2i** and **2j** could undergo the hydroallylation smoothly. Moreover, the 2-naphthyl- and the 2-phenylethyl-substituted adducts were also amenable in this process. Considering the ready availability of Morita–Baylis–Hillman adducts **2**, this protocol provides a simple and direct access to functionalized cinnamates with the achievement of structural diversity and molecule complexity (Scheme 3).[18]

At this point, we hypothesized that the hydrocinnamylation could be applied to a cascade lactonization for the hydroxyl-containing alkenes (Table 3). For example, the 2-methylallyl alcohol **1p** could engage in the hydrocinnamylation/lactoniza-

Scheme 3. Representative Pharmaceuticals of Cinnamates

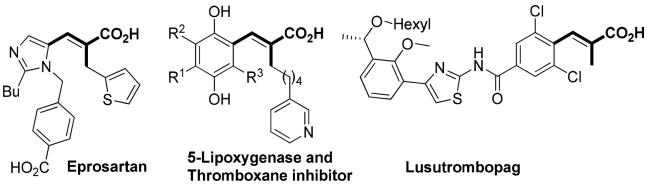
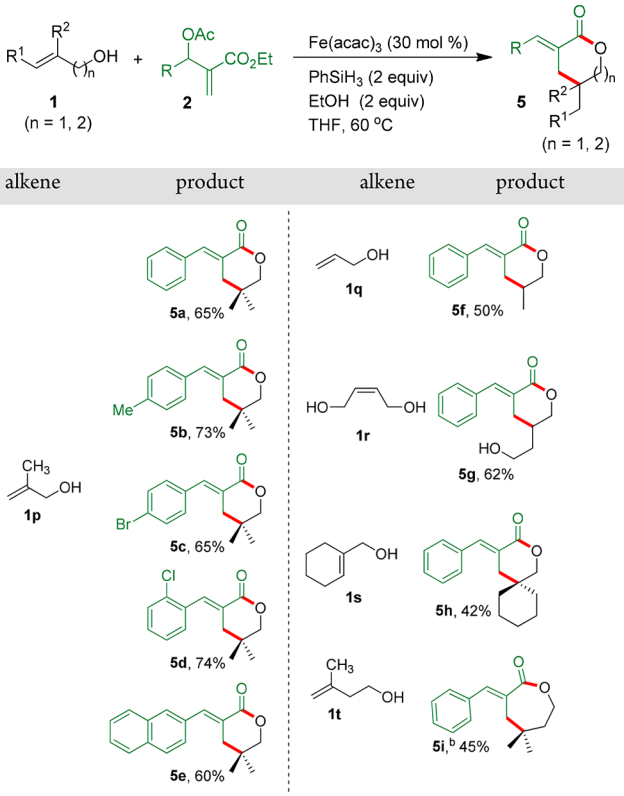


Table 3. Scope of Lactones[a]



[a]Reaction conditions: **1** (0.3 mmol), **2** (0.2 mmol), $Fe(acac)_3$ (30 mol %), $PhSiH_3$ (0.2 mmol), EtOH (0.4 mmol), THF (2 mL), 60 °C, 6 h; yields refer to isolated products. [b]Reaction was conducted for 6 h, then TsOH–H_2O (10 mol %) was added and the mixture refluxed for 1 h.

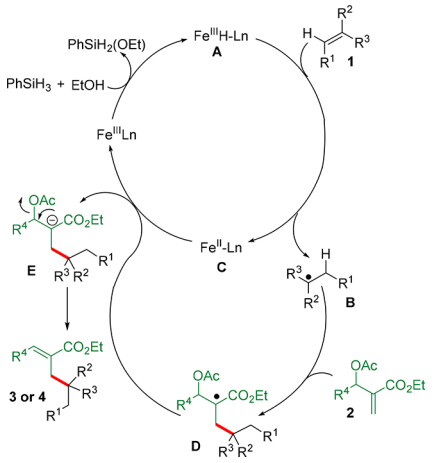
tion process with various Morita–Baylis–Hillman adducts upon standard conditions. This lactonization could afford the styrene-tethered six-membered lactones **5a–e** in good yields. The structure of **5c** was unambiguously confirmed by X-ray analysis. Meanwhile, the allyl alcohol **1q** and (*Z*)-but-2-ene-1,4-diol **1r** were amenable in this process to deliver the functionalized lactones. Interestingly, when the cyclohex-1-en-1-ylmethanol **1s** was utilized, a spiro lactone **5h** could be formed in 42% yields. Additionally, the 3-methylbut-3-en-1-ol **1t** was also found to be well applicable in this lactonization process to deliver the seven-membered oxepan-2-one **5i** in good yield when treated with 10 mol % of *p*-TsOH as additive. Thus, this method could be successfully applied to rapid assembly of lactones from easily available starting materials in a one-pot fashion.

On the basis of the results and literature reports,[5−9,15,16] a plausible reaction mechanism is proposed in Scheme 4. At the beginning, the Fe(III) catalyst is converted to Fe hydride species **A** in the presence of phenylsilane and ethanol. Then **A** undergoes HAT to alkene **2** to give alkyl radical **B** and Fe(II) **C**, and **B** was trapped by Morita–Baylis–Hillman adducts **2** to furnish intermediate **D**. The next single-electron transfer (SET) between **C** and **D** delivers anionic **E**, followed by an elimination to produce the cinnamates **3** or **4**. When the alkenes contain a hydroxyl group, a cascade intramolecular lactonization would occur to deliver the lactones.

In summary, a general and efficient Fe(III)-catalyzed hydroallylation of unactivated alkenes has been developed. The protocol features mild reaction conditions, broad substrate

DOI: 10.1021/acs.orglett.8b00108
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 4. Proposed Reaction Mechanism



scope, and sufficient structural diversity. Moreover, this method could also be applied to lactonization and late-stage functionalization of natural products, thus demonstrating valuable synthetic utility.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00108.

Full experimental procedures and spectra data (PDF)

Accession Codes

CCDC 1582722 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.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: slcui@zju.edu.cn.

ORCID

Sunliang Cui: 0000-0001-9407-5190

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for the financial support from National Natural Science Foundation of China (No. 21472163).

■ REFERENCES

(1) For reviews, see: (a) Willis, M. C. *Chem. Rev.* **2010**, *110*, 725. (b) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981.

(2) (a) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795. (b) Huang, L.; Arndt, M.; Gooßen, K.; Heydt, H.; Gooßen, L. J. *Chem. Rev.* **2015**, *115*, 2596. (c) Villa, M.; Jacobi von Wangelin, A. *Angew. Chem., Int. Ed.* **2015**, *54*, 11906. (d) Crossley, S. W. M. C.; Obradors; Martinez, R. M.; Shenvi, R. A. *Chem. Rev.* **2016**, *116*, 8912. (e) Greenhalgh, M. D.; Jones, A. S.; Thomas, S. P. *ChemCatChem* **2015**, *7*, 190.

(3) Sweany, R. L.; Halpern, J. *J. Am. Chem. Soc.* **1977**, *99*, 8335.

(4) (a) Green, S. A.; Matos, J. L. M.; Yagi, A.; Shenvi, R. A. *J. Am. Chem. Soc.* **2016**, *138*, 12779. (b) Iwasaki, K.; Wan, K. K.; Oppedisano, A.; Crossley, S. W. M.; Shenvi, R. A. *J. Am. Chem. Soc.* **2014**, *136*, 1300. (c) Crossley, S. W. M.; Barabé, F.; Shenvi, R. A. *J. Am. Chem. Soc.* **2014**, *136*, 16788.

(5) Kato, K.; Mukaiyama, T. *Chem. Lett.* **1992**, *21*, 1137.

(6) (a) Waser, J.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 5676. (b) Waser, J.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4099. (c) Waser, J.; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 8294. (d) Waser, J.; Gaspar, B.; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.* **2006**, *128*, 11693. (e) Gaspar, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 4519. (f) Gaspar, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 5758.

(7) (a) Gui, J.; Pan, C.-M.; Jin, Y.; Qin, T.; Lo, J. C.; Lee, B. J.; Spergel, S. H.; Mertzman, M. E.; Pitts, W. J.; Cruz, T. E. L.; Schmidt, M. A.; Natarajan, N. S. R.; Baran, P. S. *Science* **2015**, *348*, 886. (b) Lo, J. C.; Yabe, Y.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 1304. (c) Lo, J. C.; Gui, J.; Yabe, Y.; Pan, C.-M.; Baran, P. S. *Nature* **2014**, *516*, 343. (d) Dao, H. T.; Li, C.; Michaudel, Q.; Maxwell, B. D.; Baran, P. S. *J. Am. Chem. Soc.* **2015**, *137*, 8046.

(8) (a) Barker, T. J.; Boger, D. L. *J. Am. Chem. Soc.* **2012**, *134*, 13588. (b) Leggans, E. K.; Barker, T. J.; Duncan, K. K.; Boger, D. L. *Org. Lett.* **2012**, *14*, 1428.

(9) (a) Ma, X.; Herzon, S. B. *Chem. Sci.* **2015**, *6*, 6250. (b) Ma, X.; Herzon, S. B. *J. Org. Chem.* **2016**, *81*, 8673. (c) Ma, X.; Herzon, S. B. *J. Am. Chem. Soc.* **2016**, *138*, 8718. (d) Ma, X.; Dang, H.; Rose, J. A.; Rablen, P.; Herzon, S. B. *J. Am. Chem. Soc.* **2017**, *139*, 5998.

(10) For selected articles, see: (a) Zhu, S.; Niljianskul, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 15746. (b) Yang, Y.; Shi, S.-L.; Niu, D.; Liu, P.; Buchwald, S. L. *Science* **2015**, *349*, 62. (c) Zhu, S.; Niljianskul, N.; Buchwald, S. L. S. L. *Nat. Chem.* **2016**, *8*, 144. (d) Wang, Y.-M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2016**, *138*, 5024. (e) Zhou, Y.; Bandar, J. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **2017**, *139*, 8126. (f) Wang, H.; Yang, J. C.; Buchwald, S. L. *J. Am. Chem. Soc.* **2017**, *139*, 8428.

(11) For selected works from others, see: (a) Nishikawa, D.; Hirano, K.; Miura, M. *J. Am. Chem. Soc.* **2015**, *137*, 15620. (b) Gui, Y.-Y.; Hu, N.; Chen, X.-W.; Liao, L.-L.; Ju, T.; Ye, J.-H.; Zhang, Z.; Li, J.; Yu, D.-G. *J. Am. Chem. Soc.* **2017**, *139*, 17011. (c) Yu, S.; Sang, H. L.; Ge, S. *Angew. Chem.* **2017**, *129*, 16112.

(12) Schaffner, A. P.; Renaud, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 2658.

(13) For other allylations, see selected articles: (a) Charrier, N.; Zard, S. Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 9443. (b) Shu, W.; Genoux, A.; Li, Z.; Nevado, C. *Angew. Chem., Int. Ed.* **2017**, *56*, 10521. (c) Zhang, J.; Li, Y.; Xu, R.; Chen, Y. *Angew. Chem., Int. Ed.* **2017**, *56*, 12619. (d) Chen, H.; Jia, X.; Yu, Y.; Qian, Q.; Gong, H. *Angew. Chem., Int. Ed.* **2017**, *56*, 13103. (e) Xu, G.; Zhao, H.; Fu, B.; Cang, A.; Zhang, G.; Zhang, Q.; Xiong, T.; Zhang, Q. *Angew. Chem., Int. Ed.* **2017**, *56*, 13130.

(14) Han, J. T.; Jang, W. J.; Kim, N.; Yun, J. *J. Am. Chem. Soc.* **2016**, *138*, 15146.

(15) (a) Zheng, J.; Wang, D.; Cui, S. *Org. Lett.* **2015**, *17*, 4572. (b) Zheng, J.; Qi, J.; Cui, S. *Org. Lett.* **2016**, *18*, 128. (c) Deng, Z.; Chen, C.; Cui, S. *RSC Adv.* **2016**, *6*, 93753. (d) Shen, Y.; Qi, J.; Mao, Z.; Cui, S. *Org. Lett.* **2016**, *18*, 2722. (e) Shen, Y.; Huang, B.; Zheng, J.; Lin, C.; Liu, Y.; Cui, S. *Org. Lett.* **2017**, *19*, 1744.

(16) For Morita–Baylis–Hillman adducts used as cinnamylation sources, see: Mandal, S. K.; Paira, M.; Roy, S. C. *J. Org. Chem.* **2008**, *73*, 3823.

(17) For reviews, see: (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811. (b) Basavaiah, D.; Reddy, B. S.; Badsara, S. S. *Chem. Rev.* **2010**, *110*, 5447. (c) Wei, Y.; Shi, M. *Chem. Rev.* **2013**, *113*, 6659.

(18) (a) Ilson, B. *Am. J. Hypertens.* **1998**, *11*, 108A. (b) Hibi, S.; Okamoto, Y.; Tagami, K.; Numata, H.; Kobayashi, N.; Shinoda, M.; Kawahara, T.; Harada, K.; Miyamoto, K.; Yamatsu, I. *J. Med. Chem.* **1996**, *39*, 3148. (c) Kim, E. S. *Drugs* **2016**, *76*, 155.

DOI: 10.1021/acs.orglett.8b00108
Org. Lett. XXXX, XXX, XXX–XXX