Organic Letters

Letter

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

pubs.acs.org/OrgLett

Switchable Decarboxylative Heck-Type Reaction and Oxo-alkylation of Styrenes with *N*-Hydroxyphthalimide Esters under Photocatalysis

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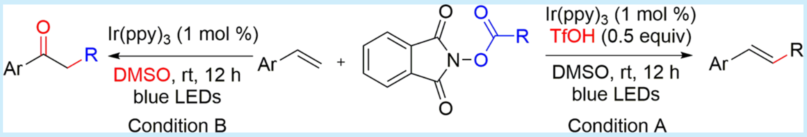
Supporting Information

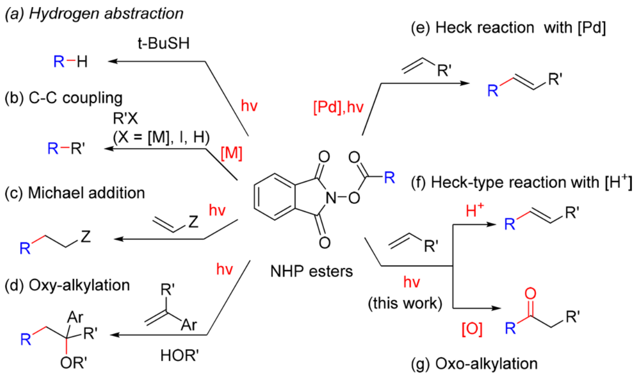


ABSTRACT: The switchable visible-light-mediated decarboxylative Heck-type reaction and oxo-alkylation reaction of *N*-hydroxyphthalimide esters under photocatalysis were developed. Disubstituted or trisubstituted alkenes were obtained in good yield with high *E*-selectivity in the presence of Brønsted acid as the additive, while ketones resulted in the absence of the acidic additive.

The Mizoroki−Heck reaction, which involves the metal-catalyzed coupling of olefins and aryl/vinyl (pseudo)-halides, is a powerful method for the synthesis of substituted alkenes.[1] Classically, this reaction utilizes aryl or vinyl electrophiles. Alkyl halides, especially tertiary alkyl halides, are challenging reagents, because of their slow oxidative addition rates, inherent instability of alkyl palladium species, and undesired premature β-hydrogen elimination process.[2] Since Fu's pioneering work on palladium-catalyzed Heck reactions of alkyl halides,[3] great effort has been devoted to the reaction with success.[4] In 2017, Fu[5] and Gevorgyan[6] independently reported the elegant photomediated Pd-catalyzed Heck reaction of alkyl halides at room temperature. This success relies on the alkyl radical-palladium(I) complex, which can suppress the undesired β-hydrogen elimination.

Being inexpensive, stable, and readily available, carboxylic acids are highly useful alternatives for organic halides in cross-coupling reactions.[7] In 2002, Myers et al. reported the first Pd-catalyzed decarboxylative Heck reactions utilizing aromatic carboxylic acids and alkenes as the substrates.[8] However, this transformation requires high temperature and only works for C(sp^2)−C(sp^2) couplings. As a carboxylic acid derivative, *N*-hydroxyphthalimide (NHP) esters can be easily reduced by photocatalysts or low-valent transition metals to generate alkyl radicals for various transformations (see Scheme 1). In 1988, Okada and Oda et al. reported the photomediated decarboxylation of NHP esters, following the abstraction of hydrogen to give hydrocarbon (Scheme 1, reaction a).[9] Recently, the C−C coupling of the generated radicals with organometallic compounds,[10] aryl iodides,[11] and C−H bond[12] has been well-established (Scheme 1, reaction b). In addition to the Michael addition of the alkyl radicals (Scheme 1, reaction c),[13] the interesting oxy-alkylation of styrenes was realized (Scheme 1, reaction d).[14] Very recently, Fu and Glorius independently reported the visible-light-mediated palladium-catalyzed decarboxylative Heck-type reaction of NHP esters (Scheme 1, reaction e).[15] During the preparation of this paper, the oxo-alkylation was also reported by Glorius et al.,[16] prompting us to report our results on the switchable Heck-type reaction in the presence of Brønsted acid, and the oxo-alkylation reaction to give ketones (Scheme 1, reactions f and g).

Scheme 1. Reactions of NHP Esters via Alkyl Radicals

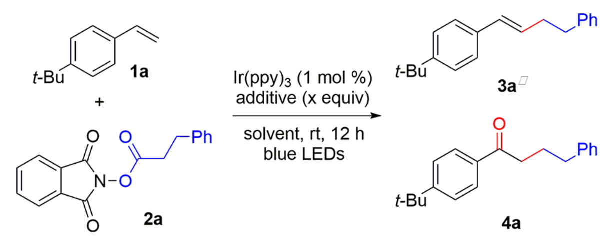


The model reaction of styrene **1a** and *N*-hydroxyphalimide **2a** was carried out using Ir(ppy)$_3$ (1 mol %) as the photocatalyst under irradiation with blue LEDs (see Table 1). Although it is disappointing that no desired alkene **3a** was formed when base was added (Table 1, entries 1 and 2), the reaction in the presence of 1.0 equiv of *p*-toluenesulfonic acid gave alkene **3a** in 46% yield (Table 1, entry 3). A series of acidic

Received: April 21, 2018

DOI: 10.1021/acs.orglett.8b01268
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Optimization of Reaction Conditions[a]



entry	additive (X equiv)	solvent	3a yield[b] (%)	4a yield[b] (%)
1	K_2CO_3 (1.0)	DMSO	0	0
2	Et_3N (1.0)	DMSO	0	0
3	TsOH (1.0)	DMSO	46[c]	0
4	TFA (1.0)	DMSO	48[c]	0
5	TfOH (1.0)	DMSO	53[c]	0
6	CH_3CO_2H (1.0)	DMSO	6[c]	0
7	$PhCO_2H$ (1.0)	DMSO	11[c]	0
8	TfOH (0.5)	DMSO	56[c]	0
9	TfOH (0.5)	DCM	0	0
10	TfOH (0.5)	MeCN	0	0
11	TfOH (0.5)	acetone	0	0
12		DMSO	0	66
13		MeCN	0	0

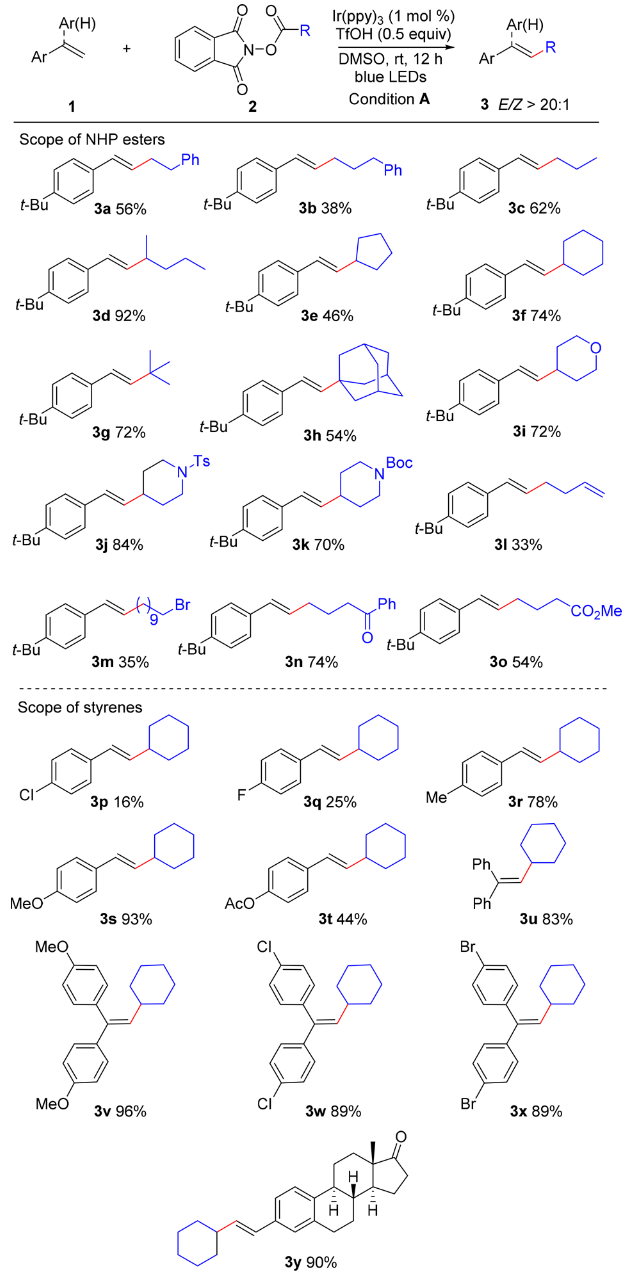
[a] General conditions: **1a** (0.4 mmol), **2a** (0.6 mmol), $Ir(ppy)_3$ (1 mol %), and additives in 2.0 mL of solvent, and irradiated under 12 W blue LEDs at room temperature for 12 h under nitrogen atmosphere. [b] Isolated yield. [c] $E/Z > 20:1$, determined by ^1H NMR spectroscopy of the crude reaction mixture. TFA = trifluoroacetic acid; TsOH = *p*-toluenesulfonic acid; TfOH = trifluoromethanesulfonic acid.

additives were then tested for the reaction (Table 1, entries 4–7), and trifluoromethanesulfonic acid (TfOH) turned out to be the best (Table 1, entry 5). Decreasing the loading of the acid to 0.5 equiv resulted in no loss of the yield (Table 1, entry 8). However, other solvents, such as DCM, MeCN, and acetone, were not suitable for this transformation (Table 1, entries 9–11). Investigation on the photocatalysts gave no better results (see Table S1 in the Supporting Information).

Interestingly, ketone **4a** was obtained in 66% without the formation of alkene **3a** when the reaction was carried out in the absence of the acidic additives (Table 1, entry 12). Control experiments revealed that no ketone was formed when other solvents were used instead of DMSO (Table 1, entry 13), which indicates that DMSO acts as both the solvent and the oxidant for the reaction.[17]

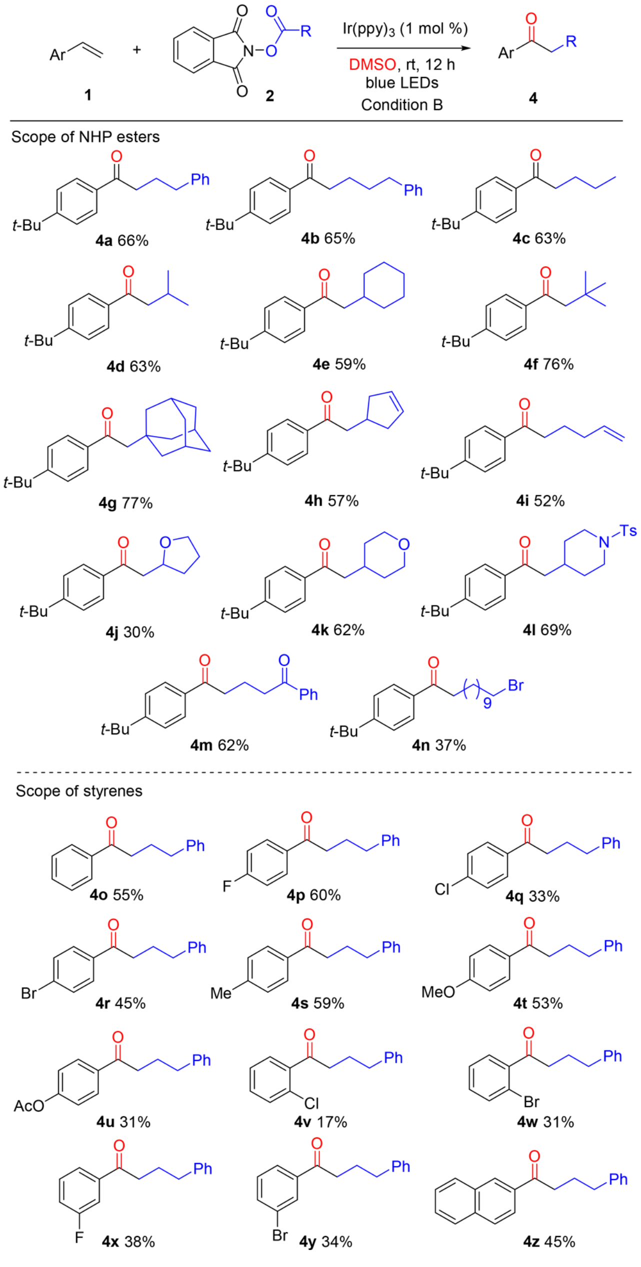
The scope of the Heck-type reaction of styrenes with *N*-hydroxyphthalimide esters was then investigated (Scheme 2). It was found that all the precursors of primary, secondary, and tertiary alkyl radicals worked for the reaction to give the desired alkenes in moderate to good yields (**3a**–**3h**). The reaction with *γ*-radicals of tetrahydropyran and piperidine gave the corresponding alkenes in good to high yields (**3i**–**3k**). The yield decreased when the esters containing a C–C double bond or bromine substituent were used (**3l** and **3m**), while keto and ester groups were well-tolerated in the substrate (**3n** and **3o**). Note that only *E*-alkenes were isolated and no *Z*-isomer was observed for all investigated cases. The styrenes with electron-withdrawing groups resulted in low yields (**3p** and **3q**), while those with electron-donating groups gave the desired products in much better yields (**3r** and **3s**). The reaction of 1,1-disubstituted alkenes worked very well (**3u**–**3x**). Notably, the reaction of estrone-derived alkene molecule afforded the corresponding product in 90% yield (**3y**). However, olefins other than styrenes, such as acrylates and enol ethers, did not work under current reaction condition.

Scheme 2. Heck-Type Reaction



Considering the wide applications of ketones in organic synthesis,[18] the oxo-alkylation of styrenes with NHP esters was also investigated (see Scheme 3). It was found that all the precursors of primary, secondary, and tertiary alkyl radicals worked well for the reaction to give the desired oxo-alkylation products (**4a**–**4g**) in good yields. A reaction of cyclic and acyclic alkyl radicals containing carbon–carbon double bond also went well (**4h** and **4i**). The reaction via *α*-radical of tetrahydrofuran afforded product (**4j**) in decreased yield, while those via *γ*-radical resulted in good yields (**4k** and **4l**). In addition, keto and bromine were also tolerated for the reaction (**4m** and **4n**). All styrenes with *para*-electron-withdrawing (Ar = 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4), and electron-donating groups (Ar = 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$AcOC_6H_4$) worked

Scheme 3. Oxo-alkylation Reaction

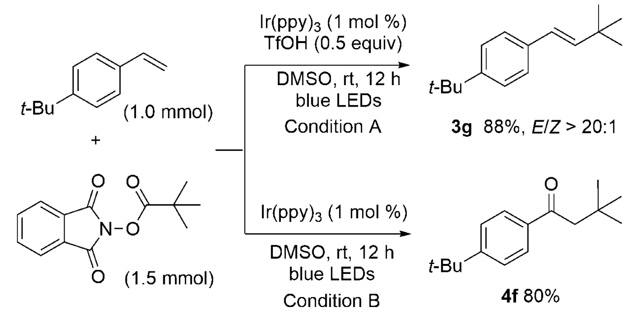


for the oxo-alkylation reaction (**4o**–**4u**). Styrenes with *meta*- and *ortho*- substituents and β-naphthyl resulted in low yields (**4v**–**4z**).

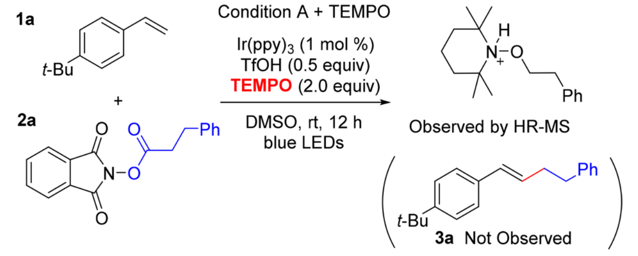
Both the Heck-type reaction and oxo-alkylation reaction could be carried out on 1 mmol scale (see Scheme 4).

Some control experiments were conducted to verify the involvement of the alkyl radical for the reaction. When the reaction was carried out under the standard conditions with the addition of 2.0 equiv of TEMPO, which is a typical radical scavenger, the formation of the adduct between TEMPO and the alkyl radical derived from decarboxylation of NHP ester **1a** was detected by high-resolution mass spectroscopy (HR-MS) (see the Supporting Information), while the corresponding product **3a** was not obtained (see Scheme 5).

Scheme 4. Reactions on 1 mmol Scale

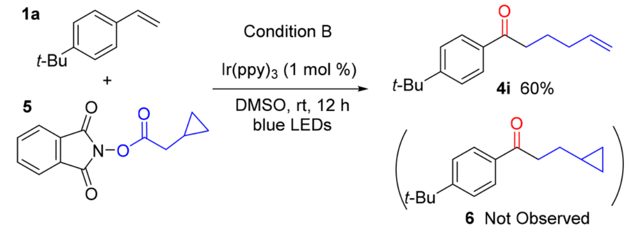


Scheme 5. Trapping of the Radical



The reaction with *N*-(2-cyclopropylacetyloxyl) phathimide **5** gave the corresponding product **4i** via ring-opening rearrangement of the cyclopropylmethyl radical in good yield (see Scheme 6).

Scheme 6. Rearrangement of the Radical



A plausible mechanism for the switchable reactions is depicted in Figure 1. Under visible-light irradiation, the catalyst $Ir(ppy)_3$ is excited and reduces the NHP ester to give alkyl radical via elimination of phthalimide anion and carbon dioxide. The addition of alkyl radical to styrene gives new alkyl radical intermediate **B**, which is oxidized to a carbocation intermediate **C** by Ir^{IV}. In the presence of acidic additive, the reaction goes by elimination of a β-proton to afford the substituted alkene **3** and regenerates the photocatalyst. In absence of acidic additive, the combination of carbocation **C** and DMSO affords the alkoxylsulfonium intermediate **D**, which is fragmented to give the ketone **4**, which is a process known as Kornblum oxidation.[17] The key difference between these two reactions may be the pH value of the reaction mixture in the presence or absence of acidic additive. The high concentration of protons may deter the depronation of alkoxylsulfonium intermediate **D**, thereby disfavoring the formation of ketone **4**.

In summary, we have developed a visible-light-mediated Heck-type olefination and oxo-alkylation of styrenes with *N*-hydroxyphthalimide esters as a mild radical precursor. The reaction gives alkenes in the presence of acidic additive, while ketones are obtained in the absence of acidic additive. The reaction features readily available starting materials, mild conditions and a broad scope of alkyl radicals, including primary, secondary, and tertiary ones. Detailed mechanistic

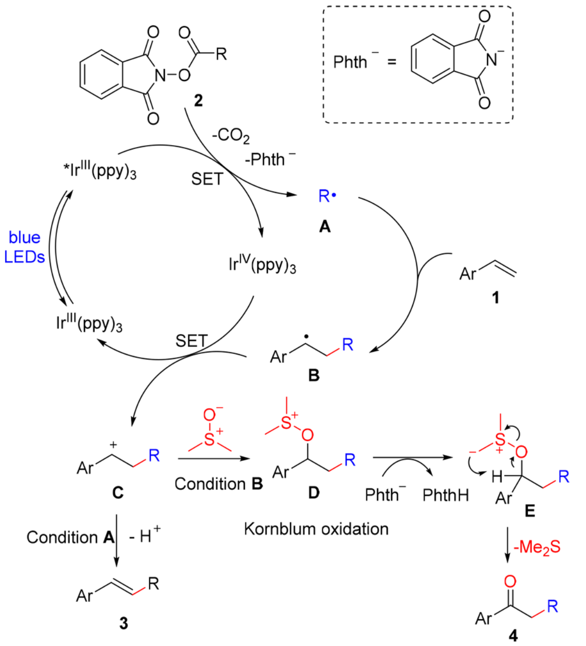


Figure 1. Possible mechanism.

studies and other photocatalyzed functionalization reactions of alkenes are currently underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01268.

Experimental details and NMR spectra for obtained compounds (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support from the National Natural Science Foundation of China (Nos. 21425207, 21521002, 21672216, 21702208), and the Chinese Academy of Sciences is greatly acknowledged.

REFERENCES

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

(2) (a) Collman, J. P. *Acc. Chem. Res.* **1975**, *8*, 342. (b) Ozawa, F.; Ito, T.; Yamamoto, A. *J. Am. Chem. Soc.* **1980**, *102*, 6457. (c) Pearson, R. G.; Figdore, P. E. *J. Am. Chem. Soc.* **1980**, *102*, 1541. (d) Ariafard, A.; Lin, Z. *Organometallics* **2006**, *25*, 4030. (e) Bissember, A. C.; Levina, A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 14232. (f) Zhou, H.; Ge, L.; Song, J.; Jian, W.; Li, Y.; Li, C.; Bao, H. *iScience* **2018**, *3*, 255.

(3) Firmansjah, L.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 11340.

(4) (a) Bloome, K. S.; Alexanian, E. J. *J. Am. Chem. Soc.* **2010**, *132*, 12823. (b) Bloome, K. S.; McMahen, R. L.; Alexanian, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 20146. (c) Matsubara, R.; Gutierrez, A. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2011**, *133*, 19020. (d) Weiss, M. E.; Kreis, L. M.; Lauber, A.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 11125. (e) Liu, C.; Tang, S.; Liu, D.; Yuan, J.; Zheng, L.; Meng, L.; Lei, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 3638. (f) Millán, A.; Álvarez de Cienfuegos, L.; Miguel, D.; Campaña, A. G.; Cuerva, J. M. *Org. Lett.* **2012**, *14*, 5984. (g) Liu, Q.; Yi, H.; Liu, J.; Yang, Y.; Zhang, X.; Zeng, Z.; Lei, A. *Chem. - Eur. J.* **2013**, *19*, 5120. (h) Nishikata, T.; Noda, Y.; Fujimoto, R.; Sakashita, T. *J. Am. Chem. Soc.* **2013**, *135*, 16372. (i) McMahon, C. M.; Alexanian, E. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 5974. (j) Parasram, M.; Iaroshenko, V. O.; Gevorgyan, V. *J. Am. Chem. Soc.* **2014**, *136*, 17926. (k) Zou, Y.; Zhou, J. *Chem. Commun.* **2014**, *50*, 3725. (l) Feng, Z.; Min, Q. Q.; Zhao, H. Y.; Gu, J. W.; Zhang, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 1270. (m) Dong, X.; Han, Y.; Yan, F.; Liu, Q.; Wang, P.; Chen, K.; Li, Y.; Zhao, Z.; Dong, Y.; Liu, H. *Org. Lett.* **2016**, *18*, 3774. (n) Xie, J.; Li, J.; Weingand, V.; Rudolph, M.; Hashmi, A. S. K. *Chem. - Eur. J.* **2016**, *22*, 12646. (o) Zhu, K.; Dunne, J.; Shaver, M. P.; Thomas, S. P. *ACS Catal.* **2017**, *7*, 2353.

(5) Wang, G.-Z.; Shang, R.; Cheng, W.-M.; Fu, Y. *J. Am. Chem. Soc.* **2017**, *139*, 18307.

(6) Kurandina, D.; Parasram, M.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2017**, *56*, 14212.

(7) (a) Gooßen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662. (b) You, S.-L.; Dai, L.-X. *Angew. Chem., Int. Ed.* **2006**, *45*, 5246. (c) Gooßen, L. J.; Rodríguez, N.; Gooßen, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3100. (d) Rodriguez, N.; Goossen, L. J. *Chem. Soc. Rev.* **2011**, *40*, 5030. (e) Weaver, J. D.; Recio, A.; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846. (f) Liu, Y.; Han, S.-J.; Liu, W.-B.; Stoltz, B. M. *Acc. Chem. Res.* **2015**, *48*, 740. (g) Shen, C.; Zhang, P.; Sun, Q.; Bai, S.; Hor, T. S. A.; Liu, X. *Chem. Soc. Rev.* **2015**, *44*, 291. (h) Xuan, J.; Zhang, Z.-G.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2015**, *54*, 15632.

(8) (a) Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 11250. (b) Tanaka, D.; Myers, A. G. *Org. Lett.* **2004**, *6*, 433.

(9) (a) Okada, K.; Okamoto, K.; Oda, M. *J. Am. Chem. Soc.* **1988**, *110*, 8736. (b) Okada, K.; Okubo, K.; Morita, N.; Oda, M. *Tetrahedron Lett.* **1992**, *33*, 7377. (c) Pratsch, G.; Lackner, G. L.; Overman, L. E. *J. Org. Chem.* **2015**, *80*, 6025.

(10) (a) Cornella, J.; Edwards, J. T.; Qin, T.; Kawamura, S.; Wang, J.; Pan, C.-M.; Gianatassio, R.; Schmidt, M.; Eastgate, M. D.; Baran, P. S. *J. Am. Chem. Soc.* **2016**, *138*, 2174. (b) Qin, T.; Cornella, J.; Li, C.; Malins, L. R.; Edwards, J. T.; Kawamura, S.; Maxwell, B. D.; Eastgate, M. D.; Baran, P. S. *Science* **2016**, *352*, 801. (c) Toriyama, F.; Cornella, J.; Wimmer, L.; Chen, T.-G.; Dixon, D. D.; Creech, G.; Baran, P. S. *J. Am. Chem. Soc.* **2016**, *138*, 11132. (d) Wang, J.; Qin, T.; Chen, T.-G.; Wimmer, L.; Edwards, J. T.; Cornella, J.; Vokits, B.; Shaw, S. A.; Baran, P. S. *Angew. Chem., Int. Ed.* **2016**, *55*, 9676.

(11) Huihui, K. M. M.; Caputo, J. A.; Melchor, Z.; Olivares, A. M.; Spiewak, A. M.; Johnson, K. A.; DiBenedetto, T. A.; Kim, S.; Ackerman, L. K. G.; Weix, D. J. *J. Am. Chem. Soc.* **2016**, *138*, 5016.

(12) Cheng, W.-M.; Shang, R.; Fu, M.-C.; Fu, Y. *Chem.-Eur. J.* **2017**, *23*, 2537.

(13) (a) Okada, K.; Okamoto, K.; Morita, N.; Okubo, K.; Oda, M. *J. Am. Chem. Soc.* **1991**, *113*, 9401. (b) Schnermann, M. J.; Overman, L. E. *Angew. Chem., Int. Ed.* **2012**, *51*, 9576.

(14) Tlahuext-Aca, A.; Garza-Sanchez, R. A.; Glorius, F. *Angew. Chem., Int. Ed.* **2017**, *56*, 3708.

(15) (a) Koy, M.; Sandfort, F.; Tlahuext-Aca, A.; Quach, L.; Daniliuc, C. G.; Glorius, F. *Chem. - Eur. J.* **2018**, *24*, 4552. (b) Wang, G.-Z.; Shang, R.; Fu, Y. *Org. Lett.* **2018**, *20*, 888.

(16) Tlahuext-Aca, A.; Garza-Sanchez, R. A.; Schafer, M.; Glorius, F. *Org. Lett.* **2018**, *20*, 1546.

(17) (a) Kornblum, N.; Powers, J. W.; Anderson, G. J.; Jones, W. J.; Larson, H. O.; Levand, O.; Weaver, W. M. *J. Am. Chem. Soc.* **1957**, *79*, 6562. (b) Tomita, R.; Yasu, Y.; Koike, T.; Akita, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 7144. (c) Liang, Y.-F.; Wu, K.; Song, S.; Li, X.; Huang, X.; Jiao, N. *Org. Lett.* **2015**, *17*, 876.

(18) Kong, W.; Yu, C.; An, H.; Song, Q. *Org. Lett.* **2018**, *20*, 349.