OL Organic Letters

Letter

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

pubs.acs.org/OrgLett

Alkynylboration Reaction Leading to Boron-Containing π-Extended *cis*-Stilbenes as a Highly Tunable Fluorophore

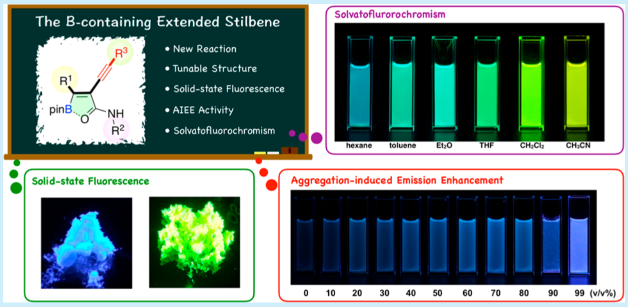
Marina Nogami,[†] Keiichi Hirano,[*,†] Kensuke Morimoto,[†] Masaru Tanioka,[†] Kazunori Miyamoto,[†] Atsuya Muranaka,[‡] and Masanobu Uchiyama[*,†,‡]

[†]Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

[‡]Cluster for Pioneering Research (CPR), Advanced Elements Chemistry Laboratory, RIKEN, 2-1 Hirosawa, Wako-shi, Saitama 351-0198, Japan

Supporting Information

ABSTRACT: An unprecedented boron-containing fluorophore, π-extended *cis*-stilbene, obtained via alkynylboration reaction of alkynamide is reported. Boron-containing π-extended *cis*-stilbenes emit fluorescence with high quantum yields in the solid state and exhibit aggregation-induced emission enhancement. The broad substrate scope of the alkynylboration reaction offers facile access to electronically diverse structures, enabling fine-tuning of light absorption/emission characteristics. The boron-containing π-extended *cis*-stilbene with a diphenylamino group displays solvatofluorochromism via an intramolecular charge-transfer transition.



Fluorescent organic molecules are widely used as imaging probes for medical diagnostics,[1] elements of organic light-emitting diodes (OLEDs),[2] functional dyes,[3] etc. Thus, there is great interest in novel and highly tunable fluorophores. Small organic compounds are especially useful due to their generally good solubility in organic/aqueous solvents and the ease of chemical elaboration of their molecular structures.[4]

We have extensively studied boration chemistry based on inter-/intramolecular Lewis basic activation of boron reagents,[5] and we recently developed a *trans*-alkynylboration reaction of propargylic alcohols **I** without the aid of transition-metal catalysts (Figure 1a).[5b,6] Notably, the "boron-containing π-extended *cis*-stilbene" products **II** emit very strong blue-violet fluorescence upon excitation with ultraviolet (UV) light, even in the solid state.[7] The high fluorescence quantum yield is considered to be due to the rigid structure[8] made by the boron-containing five-membered ring. Substituted stilbenes such as tri- and tetraarylethylenes enjoy a position as major players in the research field of aggregation-induced emission enhancement (AIEE),[9] which is a powerful tool for imaging of proteins causing physical disorders, such as Alzheimer's and Parkinson's diseases, as a result of aggregation.[10] Our boron-containing dye **II** is potentially of interest in this field, but a major drawback is the limitation of available substituents at the acetylenic terminus.[5b] Electron-rich aromatics can hardly be installed, so the electronic status of the π-system cannot be drastically modified. Here, in place of tertiary alkoxide used in our previous studies,[5b] we focused on surrogates of carboxylate[11] as an activator of alkynylboronates in order to boost the electrophilicity of the alkyne on the acceptor side and thus enable a much broader choice of the terminal substituent (Figure 1b).

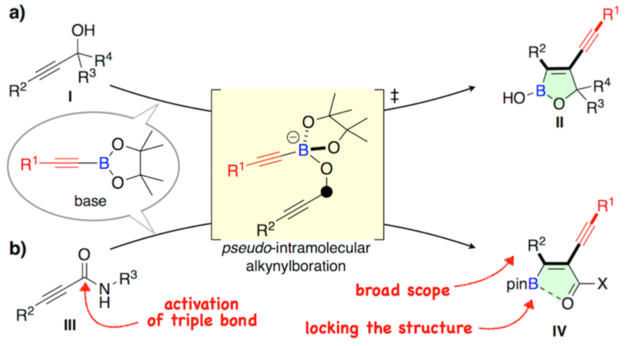


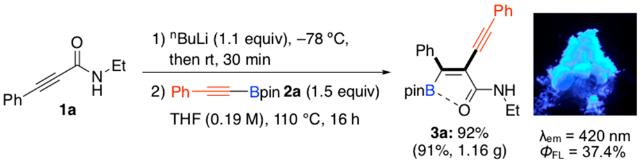
Figure 1. Synthesis of boron-containing π-extended *cis*-stilbenes: alkynylboration of alkyne via pseudo-intramolecular activation.

Our preliminary investigation with phenylpropiolic acid was not fruitful, as we had previously experienced in diboration reaction.[5d] After exhaustive screening, we found that our alkynylboration reaction was applicable to *N*-ethylpropiolamide (**1a**) to afford the desired boron-containing π-extended *cis*-stilbene **3a**, which showed a blue fluorescence emission with a good fluorescence quantum yield (λ_{em} = 420 nm, Φ_{FL} = 37.4%) upon irradiation with a UV lamp, as envisioned (Scheme 1). After a brief investigation of the reaction conditions,[12] **3a** was obtained in 92% yield. It is important to note that this

Received: March 31, 2019

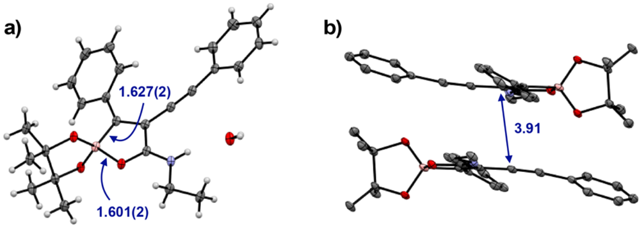
DOI: 10.1021/acs.orglett.9b01132
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Proof of Concept



transformation can easily be scaled up without loss of yield (1.16 g, 91%).

Figure 2. (a) Single-crystal X-ray diffraction analysis of **3a** with a molecule of water of crystallization (thermal ellipsoids at 50% probability). (b) Crystal packing (P−1 (No. 2) prepared from CH$_2$Cl$_2$/^{n}hexane) without hydrogens and water for clarity. Numbers indicate bond length or distance between atoms (Å).



The structure of **3a** was confirmed unequivocally by single-crystal X-ray analysis (Figure 2a). The boron center is significantly pyramidalized, and the bond lengths of B−Csp^2 (1.627(2) Å) and B−O$_{amide}$ (1.601(2) Å) indicate a strong interaction between boron and oxygen, judging from the sum of the covalent radii (B−Csp^2 1.57 Å; B−O 1.50 Å).[13] The ^{11}B NMR signal measured in CDCl$_3$ was observed at 15.2 ppm, and this value supports the sp^3-hybridized structure of the boron center.[11d,12] These observations indicate that the coordination of the oxygen atom of the amide moiety to boron efficiently rigidifies the molecular structure both in the solid state and in solution. The π-conjugated systems of two molecules in a grid are far apart (3.91 Å) owing to the repulsive interaction between them, which arises from the vertically positioned Bpin group. Electronic communication such as π−π stacking between molecules, which would result in fluorescence quenching, is thus avoided, and this should be one of the reasons why **3a** is highly fluorescent even in the solid state.

Compound **3a** also shows AIEE character (Figure 3). The emission spectra of **3a** dissolved in mixtures of THF and water in various ratios were measured. The emission intensity gradually increased as the water content was increased and increased sharply at around 80% water content. The emission wavelength (420 nm) is slightly shorter than that of the representative AIEE compound, tetraphenylethylene (430 nm).[14] Thus, the boron-containing π-extended *cis*-stilbene is expected to be an attractive platform for expanding the scope of AIEE compounds.

Available boron-containing π-extended *cis*-stilbene structures are summarized in Schemes 2 and 3. Various *N*-substituents of the amide moiety are tolerated (Scheme 2). The products with *N*-alkyl (**3a**−**g**, **3i**−**l**) and -aryl groups (**3n**−**q**) are generally obtained in high yields. The siloxyethyl (**3i**), allyl (**3j**), and propargyl (**3k**) substituents are especially attractive with respect to further chemical transformations. Enantiopure (*R*)-phenethyl amide **1l** was converted to **3l** without loss of optical purity.[15]

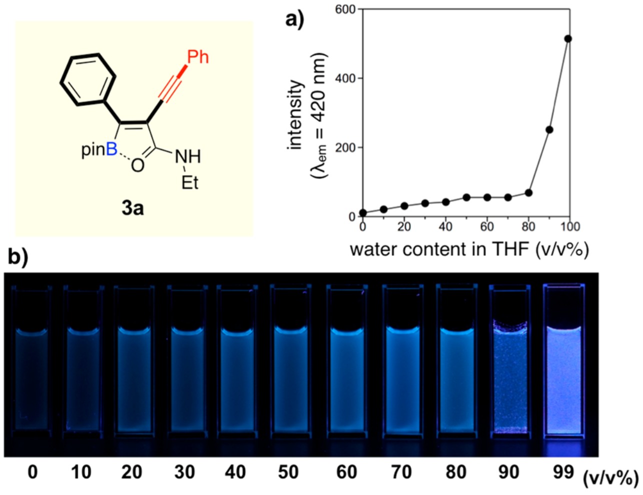
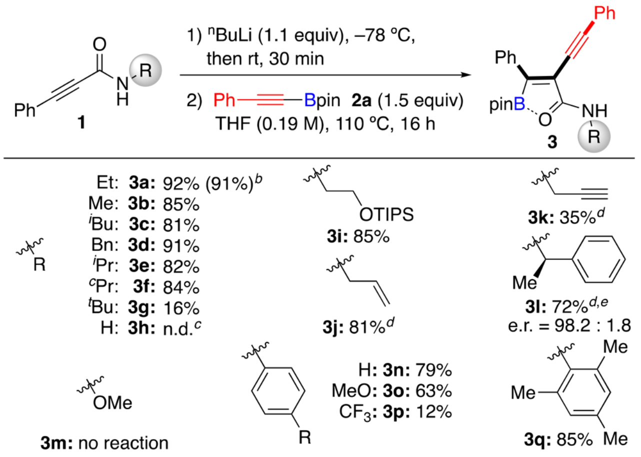


Figure 3. AIEE character of compound **3a** in mixtures of water and THF: (a) emission intensity; (b) transition of fluorescence.

Scheme 2. Generality of *N*-Substituents[a]

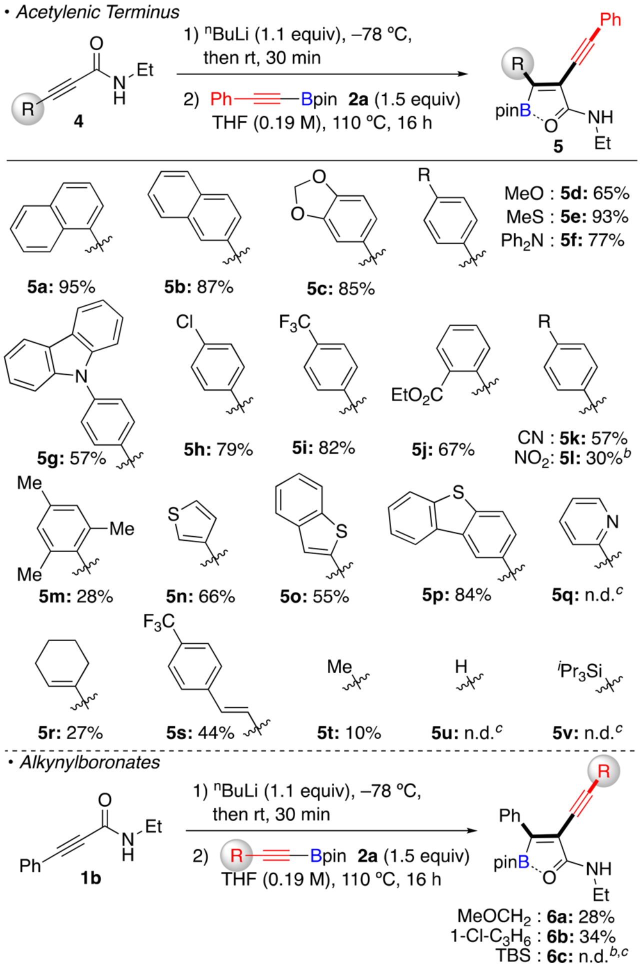


[a]Isolated yields. [b]3.2 mmol scale, 1.16 g. [c]Not detected. [d]1.0 equiv of ^{n}BuLi. [e]er of **1l**: 98.8:1.2.

A variety of aromatic groups can be installed on the π-extended *cis*-stilbene products **5a**−**m** as well (Scheme 3). The products containing thiophene-based electron-rich heterocycles were also obtained (**5n**−**p**), whereas an attempt to prepare the 2-pyridyl product **5q** failed, probably due to instability of the starting material **4q** under the reaction conditions. Enyne substrates can be used in this reaction (**5r**, **5s**). Efficient conversion of methyl-, hydrogen-, and silyl-substituted alkynes (**4t**−**v**) requires further improvement of the reaction system. Simple enyne products without an aryl substituent at the vinylic position such as **5t** do not emit strong fluorescence in the solution or in the solid state.[12] This fact clearly indicates the importance of the "π-extended *cis*-stilbene" structure as a fluorophore. Alkynylboronates with an alkyl substituent are also applicable (**6a**, **6b**), whereas the silyl substrate was not productive (**6c**).

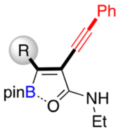
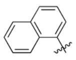
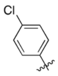
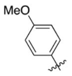
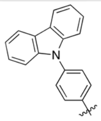
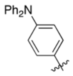
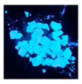
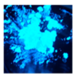
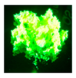
The absorption−emission properties of representative compounds are shown in Table 1. The products exhibit large Stokes shifts (ca. 5000−10000 cm^{-1}) and emit visible fluorescence with good to excellent fluorescence quantum yields (Φ_{FL}). Moreover, the emission wavelength can be fine-tuned by the appropriate choice of substituent at the acetylenic terminus. Quantum yields in the solid state are generally much higher than those in the solution state due to suppression of the twisting

Scheme 3. Wide Spectrum of Products[a]



[a]Isolated yields. [b]1.0 equiv of ^{n}BuLi. [c]Not detected.

Table 1. Absorption–Emission Properties of Compound 5

	5a	5h	5d	5g	5f
					
λ_{abs} (nm)[a]	312 [308]	314 [332]	328 [353]	320 [371]	421 [425]
λ_{em} (nm)[a]	432 [390]	431 [450]	450 [470]	478 [499]	528 [540]
Φ_{FL} (%)[b]	31 [5]	51 [2]	24 [2]	37 [40]	86 [46]
Photograph[c]					

[a]Wavelengths in the solid state. Those in CH_2Cl_2 are in square brackets. [b]Value of the samples in the solid state. Those in CH_2Cl_2 are in square brackets. [c]Photographs were taken under UV irradiation at 365 nm.

motion of the aryl rings. Compound **5g** exceptionally shows the opposite character, which may be attributed to π–π stacking in the solid state caused by a rigid and planar π-system of the carbazole unit.

The boron-containing π-extended *cis*-stilbene **5f** with the highest fluorescence quantum yield was further investigated in solution. The fluorescence wavelength is largely dependent on the solvent, and a vivid color change from blue to yellow was observed as the solvent polarity was increased (Figure 4a). DFT calculations revealed that the HOMO is mainly localized over the triarylamine moiety and the LUMO covers the ene–yne–amide unit (Figure 4b). Detailed analysis by means of time-dependent DFT calculations characterized the absorption band at 425 nm (see Scheme 3, **5f**) as being the intramolecular charge-transfer (ICT) transition from the HOMO to the LUMO, and this result is in good accordance with the solvatofluorochromism displayed by **5f**. Environmental stimulus-dependent fluorescent materials can be used as molecular sensors[16] and for bioimaging, and we anticipate that our modular boron-containing π-extended *cis*-stilbenes will find versatile applications in these fields.

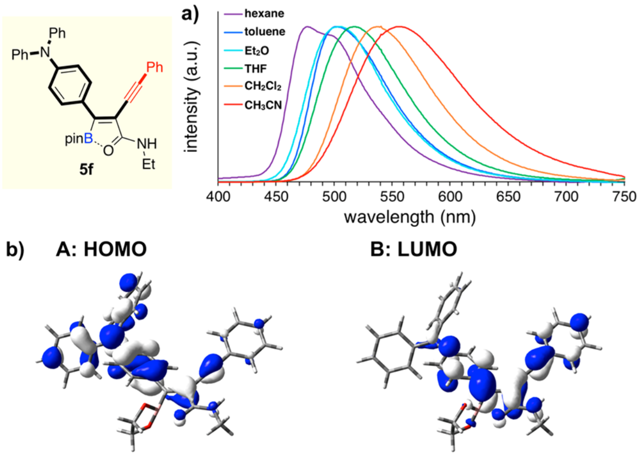
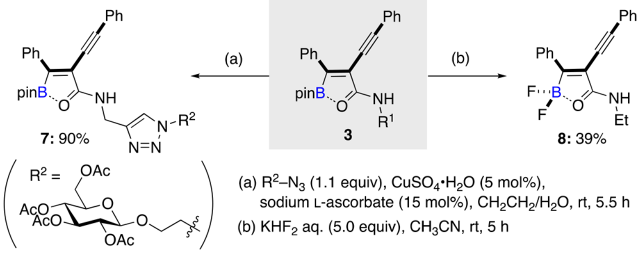


Figure 4. (a) Solvatofluorochromism of **5f** (λ_{ex} = 300 nm), *Y*-axis was normalized at the maximum fluorescence intensity. (b) Frontier molecular orbitals of **5f** computed at the level of B3LYP/6-31G*.

Finally, we examined chemical transformations of the π-extended *cis*-stilbene **3** (Scheme 4). In view of the potential future applications of **3** for molecular sensors and bioimaging, their suitability for ligation reactions is an important consideration. We found that the Huisgen cycloaddition reaction of **3k** successfully afforded the triazole product **7** in 90% yield with the boron-containing π-extended *cis*-stilbene moiety remaining intact.[17] In addition, a BODIPY-like product **8** was obtained by adopting the protocol for preparation of Molander's trifluoroborates.[18] Strong coordination of the amide

Scheme 4. Transformations



(a) R^2–N_3 (1.1 equiv), $CuSO_4$•H_2O (5 mol%), sodium L-ascorbate (15 mol%), CH_2CH_2/H_2O, rt, 5.5 h
(b) KHF_2 aq. (5.0 equiv), CH_3CN, rt, 5 h

function to boron presumably inhibits the third C−F bond formation.

In summary, we designed an alkynylboration reaction leading to an unprecedended boron-containing π-extended *cis*-stilbene possessing enormous potential as a luminophore. A wide variety of these compounds can be easily accessed by the alkynylboration of alkynamides via pseudo-intramolecular activation. The fluorescence emission wavelength in the solid state depends on the substituent at the acetylenic terminus, and aryl substituents endow the enyne compound with high fluorescence quantum yield and AIEE character. Detailed studies on the properties of the boron-containing π-extended *cis*-stilbenes, focusing on applications as molecular sensors and bioimaging, are ongoing 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.9b01132.

> Experimental procedures, characterization data, and computational details (PDF)

Accession Codes

CCDC 1886119 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 Authors

*E-mail: k1hirano@mol.f.u-tokyo.ac.jp.
*E-mail: uchiyama@mol.f.u-tokyo.ac.jp.

ORCID

Keiichi Hirano: 0000-0002-2702-9183
Masaru Tanioka: 0000-0003-4714-061X
Kazunori Miyamoto: 0000-0003-1423-6287
Atsuya Muranaka: 0000-0002-3246-6003
Masanobu Uchiyama: 0000-0001-6385-5944

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was partly supported by JSPS KAKENHI (S) (No. 24229011), The Asahi Glass Foundation, Foundation NAGASE Science Technology Development, and Sumitomo Foundation (to M.U.), JSPS Grant-in-Aid for Young Scientists (A) (No. 16H06214) (to K.H.) and Challenging Research (Exploratory) (No. 18K19390) (to K.H.). The calculations were performed on the RIKEN HOKUSAI GreatWave and BigWaterfall. We thank the Advanced Center for Computing and Communication (RIKEN) for providing computational resources.

■ REFERENCES

(1) (a) Koch, M.; Ntziachristos, V. *Annu. Rev. Med.* **2016**, *67*, 153. (b) Ueno, T.; Nagano, T. *Nat. Methods* **2011**, *8*, 642. (c) Kobayashi, H.; Ogawa, M.; Alford, R.; Choyke, P. L.; Urano, Y. *Chem. Rev.* **2010**, *110*, 2620.

(2) (a) Jung, H.; Kang, S.; Lee, H.; Yu, Y.-J.; Jeong, J. H.; Song, J.; Jeon, Y.; Park, J. *ACS Appl. Mater. Interfaces* **2018**, *10*, 30022. (b) Ahn, D. H.; Jeong, J. H.; Song, J.; Lee, J. Y.; Kwon, J. H. *ACS Appl. Mater. Interfaces* **2018**, *10*, 10246. (c) Uoyama, H.; Goushi, K.; Shizu, K.; Nomura, H.; Adachi, C. *Nature* **2012**, *492*, 234. (d) Noda, M.; Kobayashi, N.; Katsuhara, M.; Yumoto, A.; Ushikura, S.; Yasuda, R.; Hirai, N.; Yukawa, G.; Yagi, I.; Nomoto, K.; Urabe, T. *J. Soc. Inf. Disp.* **2011**, *19*, 316.

(3) For an excellent review on mechanofluorochromic materials, see: Chi, Z.; Zhang, X.; Xu, B.; Zhou, X.; Ma, C.; Zhang, Y.; Liu, S.; Xu, J. *Chem. Soc. Rev.* **2012**, *41*, 3878.

(4) Single benzene ring based luminophores: (a) Beppu, T.; Tomiguchi, K.; Masuhara, A.; Pu, Y.-J.; Katagiri, H. *Angew. Chem., Int. Ed.* **2015**, *54*, 7332. (b) Shimizu, M.; Takeda, Y.; Higashi, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 3653.

(5) (a) Nagashima, Y.; Yukimori, D.; Wang, C.; Uchiyama, M. *Angew. Chem., Int. Ed.* **2018**, *57*, 8053. (b) Nogami, M.; Hirano, K.; Kanai, M.; Wang, C.; Saito, T.; Miyamoto, K.; Muranaka, A.; Uchiyama, M. *J. Am. Chem. Soc.* **2017**, *139*, 12358. (c) Harada, K.; Nogami, M.; Hirano, K.; Kurauchi, D.; Kato, H.; Miyamoto, K.; Saito, T.; Uchiyama, M. *Org. Chem. Front.* **2016**, *3*, 565. (d) Nagashima, Y.; Hirano, K.; Takita, R.; Uchiyama, M. *J. Am. Chem. Soc.* **2014**, *136*, 8532. (e) Nagashima, Y.; Takita, R.; Yoshida, K.; Hirano, K.; Uchiyama, M. *J. Am. Chem. Soc.* **2013**, *135*, 18730.

(6) Excellent reviews on transition-metal-free and -catalyzed boration: (a) Cuenca, A. B.; Shishido, R.; Ito, H.; Fernández, E. *Chem. Soc. Rev.* **2017**, *46*, 415. (b) Yoshida, H. *ACS Catal.* **2016**, *6*, 1799.

(7) For a comprehensive review on photoluminescence of organic compounds in the solid state, see: Shimizu, M.; Hiyama, T. *Chem. - Asian J.* **2010**, *5*, 1516.

(8) DeBoer, C. D.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1968**, *90*, 803.

(9) (a) Kwok, R. T. K.; Leung, C. W.; Lam, J. W. Y.; Tang, B. Z. *Chem. Soc. Rev.* **2015**, *44*, 4228. (b) Hong, Y.; Lam, J. W. Y.; Tang, B. Z. *Chem. Soc. Rev.* **2011**, *40*, 5361. (c) Hong, Y.; Lam, J. W. Y.; Tang, B. Z. *Chem. Commun.* **2009**, 4332.

(10) (a) Wang, Y.-L.; Fan, C.; Xin, B.; Zhang, J.-P.; Luo, T.; Chen, Z.-Q.; Zhou, Q.-Y.; Yu, Q.; Li, X.-N.; Huang, Z.-L.; Li, C.; Zhu, M.-Q.; Tang, B. Z. *Mater. Chem. Front.* **2018**, *2*, 1554. (b) Kumar, M.; Hong, Y.; Thorn, D. C.; Ecroyd, H.; Carver, J. A. *Anal. Chem.* **2017**, *89*, 9322. (c) Pradhan, N.; Jana, D.; Ghorai, B. K.; Jana, N. R. *ACS Appl. Mater. Interfaces* **2015**, *7*, 25813. (d) Hong, Y.; Meng, L.; Chen, S.; Leung, C. W. T.; Da, L.-T.; Faisal, M.; Silva, D.-A.; Liu, J.; Lam, J. W. Y.; Huang, X.; Tang, B. Z. *J. Am. Chem. Soc.* **2012**, *134*, 1680.

(11) For transition-metal-free boration of propiolic acid derivatives, see: (a) Fritzemeier, R.; Gates, A.; Guo, X.; Lin, Z.; Santos, W. L. *J. Org. Chem.* **2018**, *83*, 10436. (b) Nagao, K.; Yamazaki, A.; Ohmiya, H.; Sawamura, M. *Org. Lett.* **2018**, *20*, 1861. (c) Yamazaki, A.; Nagao, K.; Iwai, T.; Ohmiya, H.; Sawamura, M. *Angew. Chem., Int. Ed.* **2018**, *57*, 3196. (d) Fritzemeier, R.; Santos, W. L. *Chem. - Eur. J.* **2017**, *23*, 15534. (e) Verma, A.; Snead, R. F.; Dai, Y.; Slebodnick, C.; Yang, Y.; Yu, H.; Yao, F.; Santos, W. L. *Angew. Chem., Int. Ed.* **2017**, *56*, 5111. (f) Nagao, K.; Ohmiya, H.; Sawamura, M. *Org. Lett.* **2015**, *17*, 1304. (g) Nagao, K.; Ohmiya, H.; Sawamura, M. *J. Am. Chem. Soc.* **2014**, *136*, 10605.

(12) See the Supporting Information.

(13) Cordero, B.; Gómez, V.; Platero-Prats, A. E.; Revés, M.; Echeverría, J.; Cremades, E.; Barragán, F.; Alvarez, S. *Dalton Trans.* **2008**, 2832.

(14) Shustova, N. B.; Ong, T.-C.; Cozzolino, A. F.; Michaelis, V. K.; Griffin, R. G.; Dincǎ, M. *J. Am. Chem. Soc.* **2012**, *134*, 15061.

(15) Burchat, A. F.; Chong, J. M.; Nielsen, N. *J. Organomet. Chem.* **1997**, *542*, 281.

(16) (a) Lin, V. S.; Chen, W.; Xian, M.; Chang, C. *Chem. Soc. Rev.* **2015**, *44*, 4596. (b) Cotruvo, J. A., Jr.; Aron, A. T.; Ramos-Torres, K. M.; Chang, C. *Chem. Soc. Rev.* **2015**, *44*, 4400. (c) Lee, M. H.; Kim, J. S.; Sessler, J. L. *Chem. Soc. Rev.* **2015**, *44*, 4185. (d) Wang, F.; Wang, L.; Chen, X.; Yoon, J. *Chem. Soc. Rev.* **2014**, *43*, 4312. (e) Thomas, S. W., III; Joly, G. D.; Swager, T. M. *Chem. Rev.* **2007**, *107*, 1339.

(17) Lee, B.-Y.; Park, S. R.; Jeon, H. B.; Kim, K. S. *Tetrahedron Lett.* **2006**, *47*, 5105.

(18) Molander, G. A.; Yun, C.-S.; Ribagorda, M.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 5534.