Organic LETTERS

Letter

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

pubs.acs.org/OrgLett

A Total Synthesis of (−)-Hamigeran B and (−)-4-Bromohamigeran B

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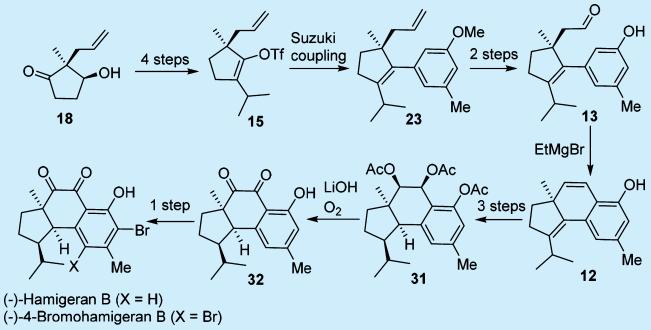
Supporting Information

ABSTRACT: A concise synthesis of (−)-hamigeran B and (−)-4-bromohamigeran B is presented. The key reactions include a Suzuki coupling of enol triflate **15** with arylboronic ester for efficient synthesis of the densely 1,2,3-trisubstituted cyclopentene **23**, a coordination-controlled intramolecular Friedel−Crafts cyclization of free phenol **13** for highly regioselective construction of tricyclic core **12**, and a LiOH/O_2-promoted hydrolysis and concomitant aerobic oxidation of **31** for atom- and step-economic accessing of diketone **32**. The application of these key transformations allowed for a rapid and efficient synthesis of (−)-hamigeran B and (−)-4-bromohamigeran B in 13 steps from the readily available chiral material **18**.



The hamigerans comprise a structurally diverse class of diterpenoids which feature the presence of a unique [5,6,6]- or [5,7,6]-tricarbocyclic core (Figure 1).[1] In addition, three or four stereogenic centers are arranged contiguously around a *cis* connected [4.3.0] or [5.3.0] bicyclic system. Generally, these natural products exhibit cytotoxicity against various tumor cells at a moderate level. Most interestingly, hamigeran B (**3**) displays strong antiviral activity against herpes and polio viruses with 100% inhibition without any significant cytotoxicity against host cells.[1a]

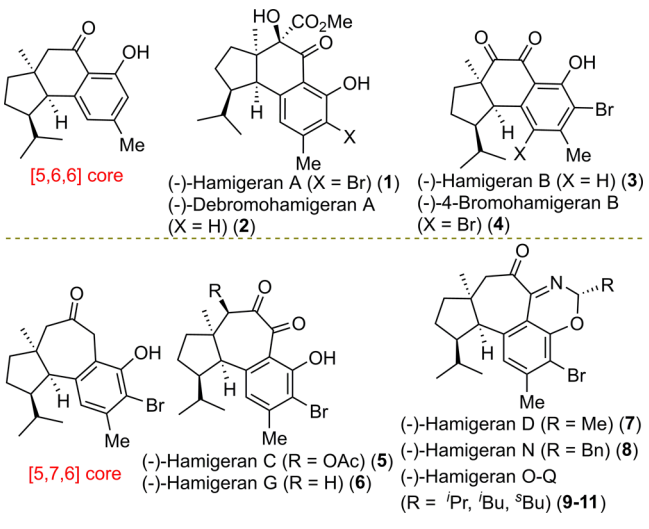


Figure 1. Selected structures of hamigerans.

Owing to their unique structural features and their biological properties, hamigerans have attracted much attention from the synthetic community. Since the first enantioselective synthesis of hamigerans **1**−**4** by the group of Nicolaou in 2001,[2] many synthetic endeavors have been devoted to the enantioselective synthesis of hammigeran B (**3**) and 4-bromohamigeran B (**4**). Chronologically, these have included the elegant works of Clive,[3] Trost,[4] Taber,[5] Stoltz,[6] Jiang,[7] Xie and Zhou,[8] and Sugai.[9] In addition, several racemic syntheses[10] and synthetic studies toward constructing the tricyclic core structures[11] have also been reported. In addition to the intensive synthetic efforts on **3** and **4**, very recently, Gao and co-workers disclosed their beautiful work on the synthesis of **6**−**11** in a divergent manner.[12]

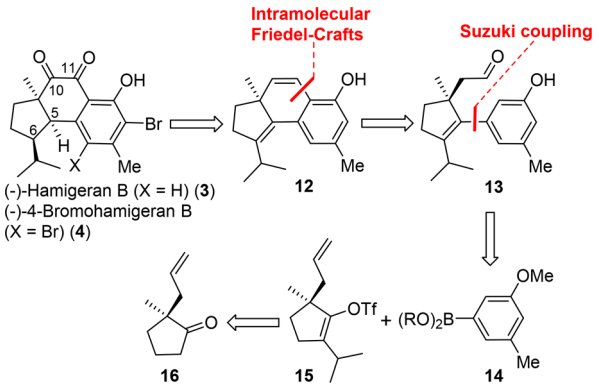
Despite the significant advances, the development of a more efficient route for the enantioselective synthesis of hamigerans, especially for the biologically important hamigeran B (**3**) and its derivatives, remains highly desired for in-depth biological studies. Herein, we present a concise synthesis of (−)-hamigeran B (**3**) and (−)-4-bromohamigeran B (**4**) via a 13-step sequence from a readily affordable material.

Our retrosynthetic analysis is illustrated in Scheme 1. We envisioned that the synthesis of hamigeran B (**3**) and 4-bromohamigeran B (**4**) could be achieved from the tricarbocyclic

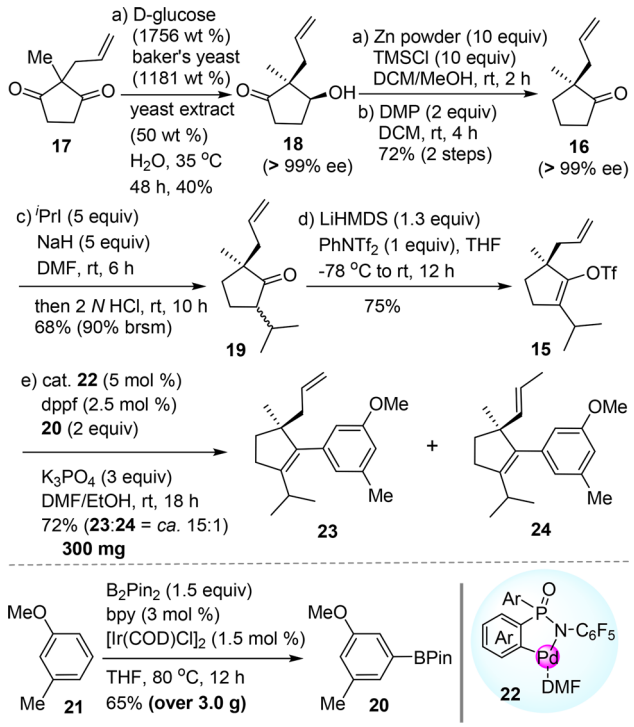
Received: May 11, 2018

DOI: 10.1021/acs.orglett.8b01490
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Retrosynthetic Analysis



Scheme 2. Synthesis of Cyclization Precursor 23



intermediate **12**. The key structural difference of this advanced intermediate as compared with those reported in literature[3,5,12] is the existence of an unmasked phenol. We assumed that the presence of a free phenol in **12** would be crucial for facile introduction of the diketone at C_{11} and C_{12} by means of aerobic oxidation of the corresponding vicinal diol,[13] and for, ultimately, providing a more atom- and step-economic way for the synthesis. The key intermediate **12** was envisioned as being constructed through an intramolecular Friedel−Crafts cyclization of **13** followed by dehydration. Disconnection of **13** revealed a couple of Suzuki coupling partners, viz., arylboronic compound **14** and heavily substituted nonactivated enol triflate **15**. Triflate **15** was to be derived from the known chiral ketone **16**.

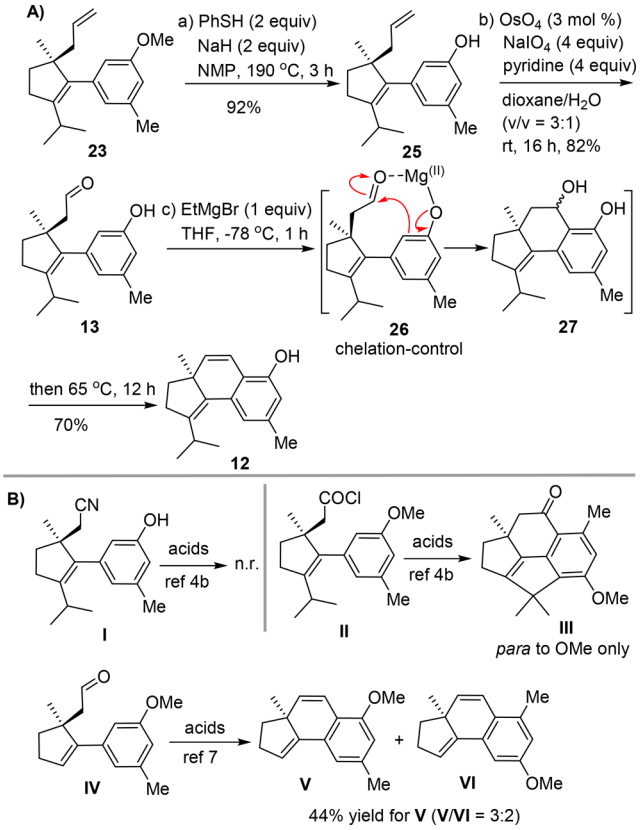
For the preparation of chiral cyclopentanone **16**, three different methods were examined. We first tried the Pd-catalyzed enantioselective decarboxylative allylic alkylation reported by Stoltz.[14] **16** was obtained in 80% yield and 84% ee (86% ee in literature). The imperfect enantioselectivity prompted us to investigate the desymmetric CBS reduction of 2,2-disubstituted 1,3-cyclopentanedione **17** which could be easily prepared from commercially available 2-methyl 1,3-cyclopentanedione by allylation[15] (Scheme 2). While good enantioselectivity of greater than 90% ee was provided for 3-*β*-hydroxy ketone **18**, the modest diastereoselectivity (dr = ca. 5−6:1) together with the problem for scaling up diminished its practicality. We then inspected the enzyme-catalyzed desymmetric enantioselective reduction of **17**.[16] Compound **18** could be obtained in about 65% yield with an excellent enantioselectivity of >99% ee and an improved diastereoselectivity (dr = ca. 8−9:1) as compared with the CBS reduction. The improvement on diastereoselectivity made it relatively easier to completely remove the undesired diastereoisomers of **18** by column chromatography. As a result, enantiomerically pure **18** could be obtained in 36−40% yield over two steps from the commercially available material [see Supporting Information (SI) for details]. Although the overall yield for the preparation of **18** was still not sufficiently high using the enzyme-catalyzed reduction, the reaction could be reliably performed on multigram scale. Clemmensen reduction[17] of **18** followed by Dess-Martin oxidation was performed on multigram scale to afford ketone **16** in 72% yield over two steps with >99% ee as determined by HPLC analysis with a chiral stationary phase (see Figure S18 in SI). Isopropylation of **16** proceeded smoothly to give the densely substituted ketone **19**, which was converted into the corresponding enol triflate **15** in high yield.

For the synthesis of 1,2,3-trisubstituted cyclopentene derivative **23**, we preferred to examine the Suzuki cross-coupling of **15** with pinacol boronate **20** instead of the corresponding boronic acid that was used previously in Trost's synthesis[4b] because, to compare with the somewhat tedious procedure for synthesizing the boronic acid, the boronic ester **20** could now be much more conveniently prepared in a single step on multigram scale over 60% yield via a modified Hartwig Ir-catalyzed direct C−H boronation of 3-methylanisole **21**.[18] Preliminary experiments showed that the coupling of **15** with **20** was less effective under the conditions reported by Trost for coupling with boronic acid [$Pd(PPh_3)_4$, KBr, K_3PO_4, dioxane, 80 °C to reflux].[4b] The coupled product **23** was obtained in lower than 40% yield. We therefore examined the catalytic efficiency of palladacycle **22**, which was developed by our group and has been demonstrated to possess high catalytic activity for the mild Suzuki coupling of arene (*pesudo*)halides with aryl boronic acids.[19] To our delight, after a brief optimization of reaction parameters, we found that the combination of **22** with a dppf ligand provided an effective catalyst system for the desired coupling. The product **23** could be obtained in 72% yield at room temperature accompanied by the formation of a small amount of double bond migrated side product **24** (**23**:**24** = ca. 15:1). The byproduct **24** could be easily separated during the late stage oxidation of olefin (*vide infra*).

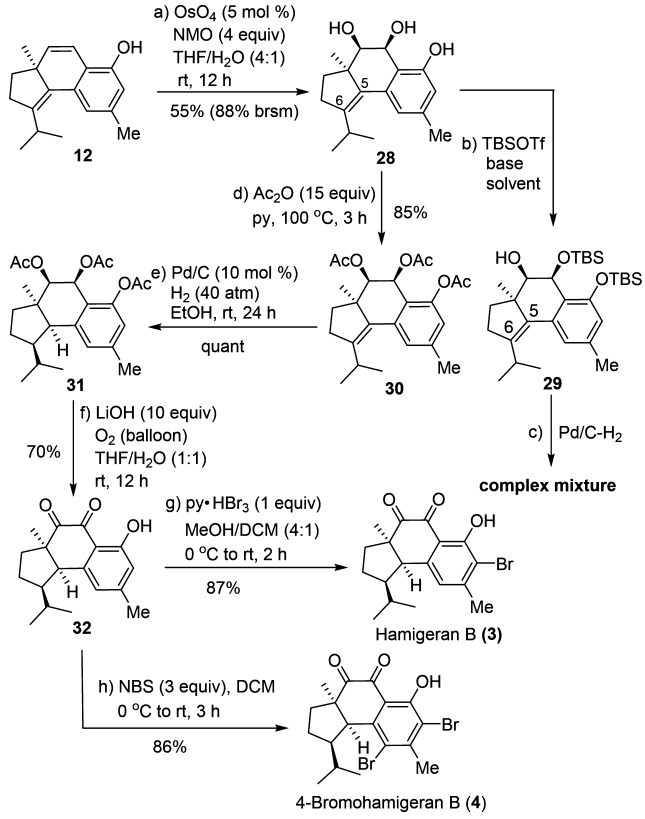
Next, we moved forward to the construction of the tricarbocyclic core **12** from **23** (Scheme 3A). Demethylation of **23** with PhSH afforded the free phenol **25** in 92% yield.[20] Oxidation of the olefinic functionality in **25** was affected by a combination of OsO_4 and $NaIO_4$ to give the aldehyde **13** in 80% yield. The small amount of demethylated byproduct formed from **24** could be easily separated at this stage. Subsequently, treatment of **13** with a slight excess of EtMgBr afforded the intramolecular Friedel−Crafts cyclization product **27**. This was found to undergo *in situ* dehydration at 65 °C to give the tricyclic core **12** as a single regioisomer in 70% yield with 99.8% ee (see Figure S19). The exclusively high regioselectivity may be attributed to the formation of a coordination intermediate **26**,[21] which fixes the nucleophilic site at the *ortho* position to the phenolic OH. It should be mentioned that the chelation-

DOI: 10.1021/acs.orglett.8b01490
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Construction of Tricarbocyclic Core 12



Scheme 4. Completion of the Synthesis of 3 and 4



controlled cyclization has been demonstrated to display a much higher efficiency than the acid-mediated approaches reported in prior literature[4b,7] (Scheme 3B). For instance, in a 2005 report, Trost and co-workers[4b] showed that the cyclization of **I** and **II** was ineffective in the presence of various acids. The reactions were either ineffective (for **I**) or provided solely the tetracyclic byproduct **III** with undesired regioselectivity *para* to methoxy group (for **II**). Recently, Jiang and co-worker[7] investigated the acid-promoted cyclization of **IV**, under the optimized conditions, the reaction proceeded in moderate yield and poor regioselectivity (**V**/**VI** = 3:2).

Having established an efficient method for constructing the tricyclic core **12**, we set out to complete the total synthesis of **3** and **4** (Scheme 4). Accordingly, the regioselective dihydroxylation of the double bond in the central ring of **12** with OsO_4 and NMO proceeded *anti* to the angular methyl group to give diol **28** in 55% yield (88% brsm). The regio- and stereochemistry of **28** was determined by NOESY correlations (see Figure S11). The somewhat low yield of the dihydroxylation is presumably due to the presence of free phenol in **12** which can interact with the OsO_4 and, therefore, retard the reactivity of the oxidation reaction.[22] Attempted improvement of the efficiency by addition of additives such as pyridine, DABCO, and sulfonamide compounds was ineffective. For the stereoselective hydrogenation of the C_5═C_6 double bond in **28**, we first tried to protect the three hydroxy groups in **28** with bulky TBS based on a related procedure reported by Clive.[3a] However, extensive trials showed that a simultaneous silylation of all three hydroxy groups was problematic presumably due to the steric hindrance of the TBS group as well as the presence of a quaternary carbon center at the ring junction. Under an array of conditions, a two-OH silylated product was afforded as major product which was tentatively assigned as **29** based on ^{1}H NMR and NOESY analysis, and D_2O exchange experiments, although rigorous structural proof was not carefully established. Attempted stereoselective hydrogenation of the C_5═C_6 double bond in **29** led to a complex mixture. Based on the ^{1}H NMR spectrum of the crude mixtures, this is most likely the result of partial desilylation and dehydroxylation of benzylic alcohol in addition to the hydrogenation of the double bond.

Encouraged by the method reported by Gao,[12] we then examined a less hindered protecting group. Thus, protection of the three hydroxy groups with acetyl gave triacetate **30** in 85% yield. Hydrogenation of **30** proceeded very efficiently at 40 atm to provide the hydrogenated product **31** as a single diastereoisomer in quantitative yield. The absolute configuration of C_5 and C_6 was determined by NOESY spectroscopic analysis (see Figure S14). According to our retrosynthetic analysis, we initially planned to synthesize **32** from **31** by executing a stepwise deprotection of the acetyl group followed by a base-mediated transition-metal catalyzed aerobic oxidation of the vicinal diol at C_{10} and C_{11}. However, we identified that a small amount of desired diketone **32** could be isolated during the hydrolysis of **31**. Inspired by this important clue, we subjected **31** to LiOH under an oxygen atmosphere. To our delight, hydrolysis and concomitant oxidation proceeded cleanly to produce **32** in 70% yield under metal-free conditions. This serendipitous finding provided a more atom- and step-economic method for the synthesis of **32**. Of note, the result also implied that the presence of a free phenol is crucial for promoting the aerobic oxidation since auto-oxidation was not observed in a previous study[12] wherein the phenolic OH was masked by the Me group. As a consequence, an extra step using Swern and Ley oxidation had to be implemented.[3,5] Finally, monobromination[12] and

DOI: 10.1021/acs.orglett.8b01490
Org. Lett. XXXX, XXX, XXX−XXX

dibromination[5] of **32** were carried out according to the known methods to deliver (−)-hamigeran B (**3**) and (−)-4-bromohamigeran B (**4**), respectively, in high yield. The NMR spectroscopic data and optical rotations of our synthesized (−)-hamigeran B ($[\alpha]_D^{20}$ −164.7 (*c* 0.15, CH_2Cl_2)) and (−)-4-bromohamigeran B ($[\alpha]_D^{20}$ −85.0 (*c* 0.37, CH_2Cl_2)) were close to those of the corresponding natural products ($[\alpha]_D^{25}$ −151.1 (*c* 0.15, CH_2Cl_2)) for hamigeran B and $[\alpha]_D^{25}$ −81.2 (*c* 0.37, CH_2Cl_2) for 4-bromohamigeran B,[1a] respectively.

In conclusion, we have established a concise route for the synthesis of (−)-hamigeran B (**3**) and (−)-4-bromohamigeran B (**4**) that proceeds via a 13-step sequence from the known chiral hydroxy ketone **18** (15 steps from commercially available 2-methyl 1,3-diketone). To the best of our knowledge, this synthetic route represents one of the very few that can accomplish the synthesis of hamigeran B and 4-bromohamigeran B within 15 steps either from a known compound or from commercial material. Moreover, most of the transformations employed herein could be performed on multigram scale. This makes our synthetic route highly useful for the large scale synthesis of both compounds, and, ultimately, for supplying sufficient samples for an in-depth investigation of their biological properties. Further optimization of the synthetic procedure toward a large scale synthesis is currently underway in our lab.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01490.

Detailed experimental procedures, characterization data, the copies of NMR spectra, and HPLC charts (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from NSFC (21602215, 21572215) and the Engineering Research Center of Marine Bioresources Comprehensive Utilization of SOA (MBRCU201604) is acknowledged.

■ REFERENCES

(1) (a) Wellington, K. D.; Cambie, R. C.; Rutledge, P. S.; Bergquist, P. R. *J. Nat. Prod.* **2000**, *63*, 79. (b) Cambie, R. C.; Rickard, C. E. F.; Rutledge, P. S.; Wellington, K. D. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **2001**, *57*, 958. (c) Singh, A. J.; Dattelbaum, J. D.; Field, J. J.; Smart, Z.; Woolly, E. F.; Barber, J. M.; Heathcott, R.; Miller, J. H.; Northcote, P. T. *Org. Biomol. Chem.* **2013**, *11*, 8041. (d) Miesch, M.; Welsch, T.; Rietsch, V.; Miesch, L. Total Syntheses of Hamigeran B. In *Strategies and Tactics in Organic Synthesis*; Harmata, M., Ed.; Elsevier: Oxford, 2013; Vol. 9, p 203. (e) Dattelbaum, J. D.; Singh, A. J.; Field, J. J.; Miller, J. H.; Northcote, P. T. *J. Org. Chem.* **2015**, *80*, 304.

(2) (a) Nicolaou, K. C.; Gray, D.; Tae, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 3675. (b) Nicolaou, K. C.; Gray, D.; Tae, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 3679. (c) Nicolaou, K. C.; Gray, D. L. F.; Tae, J. *J. Am. Chem. Soc.* **2004**, *126*, 613.

(3) (a) Clive, D. L. J.; Wang, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 3406. (b) Clive, D. L. J.; Wang, J. *Tetrahedron Lett.* **2003**, *44*, 7731. (c) Clive, D. L. J.; Wang, J. *J. Org. Chem.* **2004**, *69*, 2773.

(4) (a) Trost, B. M.; Pissot-Soldermann, C.; Chen, I.; Schroeder, G. M. *J. Am. Chem. Soc.* **2004**, *126*, 4480. (b) Trost, B. M.; Pissot-Soldermann, C.; Chen, I. *Chem. - Eur. J.* **2005**, *11*, 951.

(5) Taber, D. F.; Tian, W. *J. Org. Chem.* **2008**, *73*, 7560.

(6) Mukherjee, H.; McDougal, N. T.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.* **2011**, *13*, 825.

(7) Jiang, B.; Li, M.-M.; Xing, P.; Huang, Z.-G. *Org. Lett.* **2013**, *15*, 871.

(8) Lin, H.; Xiao, L.-J.; Zhou, M.-J.; Yu, H.-M.; Xie, J.-H.; Zhou, Q.-L. *Org. Lett.* **2016**, *18*, 1434.

(9) Kuwata, K.; Fujita, R.; Hanaya, K.; Higashibayashi, S.; Sugai, T. *Tetrahedron* **2018**, *74*, 740.

(10) (a) Lau, S. Y. W. *Org. Lett.* **2011**, *13*, 347. (b) Miesch, L.; Welsch, T.; Rietsch, V.; Miesch, M. *Chem. - Eur. J.* **2009**, *15*, 4394.

(11) (a) Zhou, N.; Liu, J.; Yan, Z.; Wu, Z.; Zhang, H.; Li, W.; Zhu, C. *Chem. Commun.* **2017**, *53*, 2036. (b) Zhu, H.; Nie, X.; Huang, Q.; Zhu, G. *Tetrahedron Lett.* **2016**, *57*, 2331. (c) Cai, Z.; Harmata, M. *Org. Lett.* **2010**, *12*, 5668. (d) Arnáiz, E.; Blanco-Urgoiti, J.; Abdi, D.; Domínguez, G.; Castells, J. P. *J. Organomet. Chem.* **2008**, *693*, 2431. (e) Madu, C. E.; Lovely, C. J. *Org. Lett.* **2007**, *9*, 4697. (f) Harmata, M.; Zheng, P.; Schreiner, P. R.; Navarro-Vázquez, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1966. (g) Sperry, J. B.; Wright, D. L. *Tetrahedron Lett.* **2005**, *46*, 411. (h) Mehta, G.; Shinde, H. M. *Tetrahedron Lett.* **2003**, *44*, 7049.

(12) Li, X.; Xue, D.; Wang, C.; Gao, S. *Angew. Chem., Int. Ed.* **2016**, *55*, 9942.

(13) (a) Zhang, S.; Wan, C.; Wang, Q.; Zhang, B.; Gao, L.; Zha, Z.; Wang, Z. *Eur. J. Org. Chem.* **2013**, *2013*, 2080. (b) Wan, C.; Fan, J.; Zhang, J.; Wang, Z. *Chin. Sci. Bull.* **2010**, *55*, 2817.

(14) Craig, R. A., II; Loskot, S. A.; Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Org. Lett.* **2015**, *17*, 5160 and references cited therein.

(15) (a) Shimizu, M.; Yamada, S.; Fujita, Y.; Kobayashi, F. *Tetrahedron: Asymmetry* **2000**, *11*, 3883. (b) Liu, L. L.; Chiu, P. *Chem. Commun.* **2011**, *47*, 3416.

(16) Brooks, D. W.; Mazdiyasni, H.; Grothaus, P. G. *J. Org. Chem.* **1987**, *52*, 3223.

(17) Xu, S.; Toyama, T.; Nakamura, J.; Arimoto, H. *Tetrahedron Lett.* **2010**, *51*, 4534.

(18) (a) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390. (b) Boller, T. M.; Murphy, J. M.; Hapke, M.; Ishiyama, T.; Miyaura, N.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 14263. (c) Murphy, J. M.; Tzschucke, C. C.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 757. (d) Murphy, J. M.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 15434.

(19) (a) Guan, J.; Wu, G.-J.; Han, F.-S. *Chem. - Eur. J.* **2014**, *20*, 3301. (b) Du, Z.-J.; Guan, J.; Wu, G.-J.; Xu, P.; Gao, L.-X.; Han, F.-S. *J. Am. Chem. Soc.* **2015**, *137*, 632. (c) Wu, G.-J.; Han, F.-S.; Zhao, Y.-L. *RSC Adv.* **2015**, *5*, 69776. (d) Wu, G.-J.; Zhang, Y.-H.; Tan, D.-X.; Han, F.-S. *Nat. Commun.* **2018**, *9*, 2148.

(20) (a) Nayak, M. K.; Chakraborti, A. K. *Tetrahedron Lett.* **1997**, *38*, 8749. (b) Hansson, C.; Wickberg, B. *Synthesis* **1976**, *1976*, 191.

(21) Casnati, G.; Pochini, A.; Terenghi, M. G.; Ungaro, R. *J. Org. Chem.* **1983**, *48*, 3783.

(22) Pilgrim, B. S.; Donohoe, T. J. *J. Org. Chem.* **2013**, *78*, 2149 and references cited therein.

DOI: 10.1021/acs.orglett.8b01490
Org. Lett. XXXX, XXX, XXX−XXX