JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Cite This: J. Am. Chem. Soc. XXXX, XXX, XXX−XXX
Communication
pubs.acs.org/JACS

11-Step Total Synthesis of Teleocidins B-1−B-4

Hugh Nakamura, Kosuke Yasui, Yuzuru Kanda, and Phil S. Baran*

Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, United States

Supporting Information

ABSTRACT: A unified and modular approach to the teleocidin B family of natural products is presented that proceeds in 11 steps and features an array of interesting strategies and methods. Indolactam V, the known biosynthetic precursor to this family, was accessed through electrochemical amination, Cu-mediated aziridine opening, and a remarkable base-induced macrolactamization. Guided by a desire to minimize concession steps, the tactical combination of C−H borylation and a Sigman−Heck transform enabled the convergent, stereocontrolled synthesis of the teleocidins.

The discovery of teleocidins B-1, B-2, B-3, and B-4 (**1**−**4**, Figure 1) from a bacterial strain (*Streptomyces mecliocidius*) dates back to a report in 1960 by the Sakai group.[1] The structures of these intriguing indole-alkaloids were first elucidated shortly thereafter with the aid of X-ray crystallography.[2] Although they were regarded as general toxins early on,[1] it was later discovered that they exhibit potent protein kinase-C (PKC) activation, similar to that of phorbol and related natural products.[3] Early studies revealed indolactam V (**5**),[4] itself a popular target for synthesis,[5] as the biosynthetic precursor to **1**−**4**, with the terpenoid portion arriving from a late-stage geranylation at C-22, followed by Friedel−Crafts cyclization to forge the C-19 aryl bond.[6] Nature appears to indiscriminately produce **1**−**4** without stereocontrol, as indicated by reports of mixtures from isolation. A stereocontrolled pathway is clearly a vexing problem, as the distal nature of the amino acid macrocycle and dual quaternary-center flanked terpene fragment make any chirality relay[7] approach unworkable. Numerous studies toward the teleocidins have been reported over the years.[8] Thus far, two syntheses of **3** and **4** have been reported that proceed in 17−28 steps without stereocontrol at three of the four chiral centers (see the Supporting Information (SI) for a full summary).[9] This Communication discloses a simple 11-step route to **1**−**4**, traversing through **5**, and featuring strategic uses of electrochemical aryl amination, Cu-mediated tryptophol construction, C−H borylation, and stereocontrolled quaternary center formation via a Sigman−Heck reaction.

Our retrosynthetic analysis (Figure 1) was guided by a desire to minimize concession steps[10] and to controllably access **1**−**4** via indolactam (**5**). As such, C−H functionalization logic[11] was employed to disconnect the quaternary centers at C-19−C-6 and C-22−C-7. In a forward sense, the chirality of the C-19−C-6 bond could be controlled by adding different ligands via a Sigman−Heck reaction[12] onto olefin **6**, whereas the C-22−C-7 bond could be addressed through screening of Brönsted acids

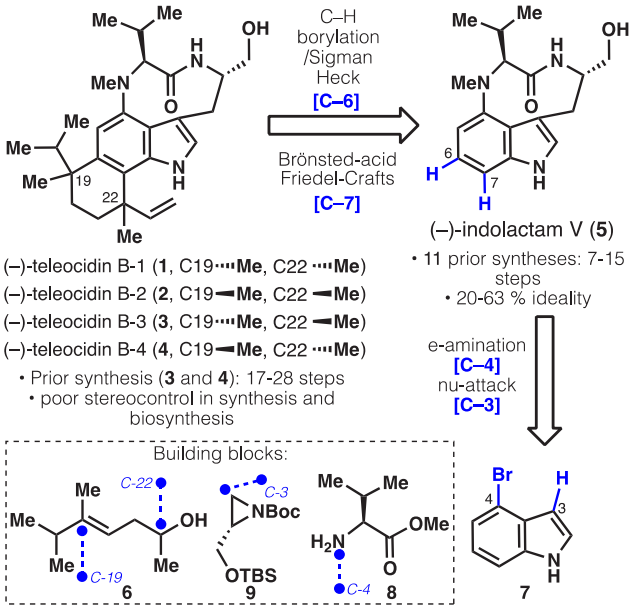


Figure 1. Unified approach to the teleocidins (**1**−**4**) through the tactical combination of modern transforms.

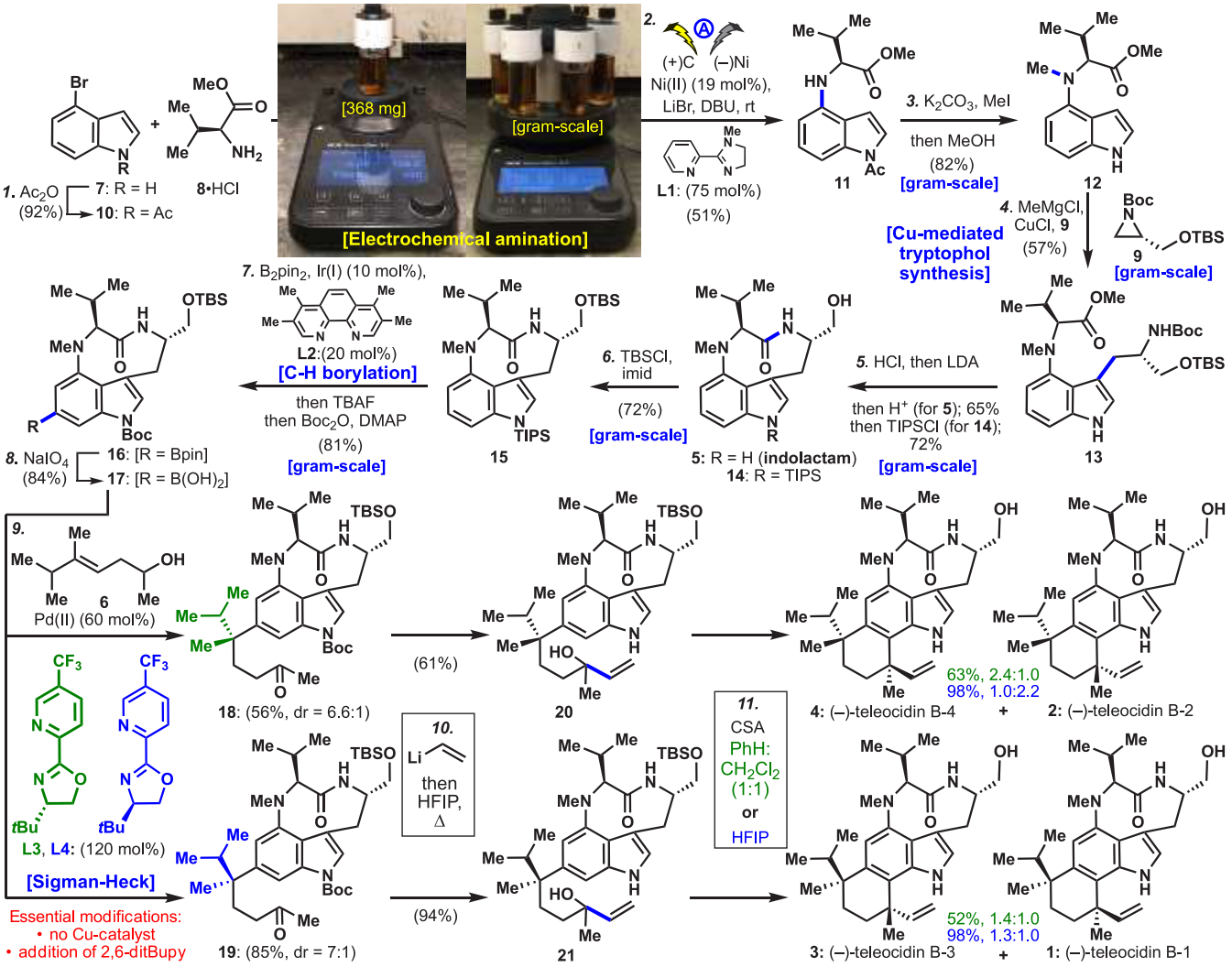
for a Friedel−Crafts reaction. This order of events is notably opposite to that employed by nature[6] and prior synthetic approaches.[8] The simple indole alkaloid **5** has been the subject of numerous synthetic studies, culminating in 11 total syntheses (7−15 steps, 20−63% ideality). It was envisaged that a simplified approach could commence from 4-bromoindole (**7**) by enlisting electrochemically assisted Ni-catalyzed amination[13] (at C-4 with **8**) followed by Cu-assisted nucleophilic aziridine opening (at C-3 with **9**) and base-induced macrocyclization.

The 11-step route to **1**−**4**, outlined in Scheme 1, commences with acetylation of commercial 4-bromoindole (**7**, ca. $4/gram) to furnish **10** (92% yield). The ensuing C−N coupling with valine at C-4 has precedent from both the Tokuyama[5m] and Billingsley[5n] groups using Ullmann (Cu-based) conditions. In those studies, an N-Ts group was required on the indole nitrogen. To avoid the Ts deprotection step, an Ac group was chosen as it is easily removed upon simple basic workup conditions. As Ullmann conditions were unsuccessful on **10**, an electrochemical (e) approach for amination[13] was evaluated. Under the originally reported conditions, only a low yield of adduct **11** was obtained. A series

Received: December 22, 2018
Published: January 13, 2019

DOI: 10.1021/jacs.8b13697
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Scheme 1. Total Synthesis of the Teleocidins 1–4[a]



[a]Reagents and conditions: (**1**) Ac_2O (1.5 equiv), Et_3N (4.1 equiv), DMAP (1 mol%), CH_2Cl_2, rt, 3 h. (**2**) $NiBr_2$·glyme (19 mol%), **L1** (75 mol%), LiBr (8.0 equiv), DBU (4.0 equiv), DMA, rt, 7 h. (**3**) K_2CO_3 (10.8 equiv), MeI (108 equiv), DMF, 60 °C, 58 h then MeOH, rt, 1.5 h. (**4**) MeMgCl (2.5 equiv), toluene, −78 °C, 20 min then **9** (3.0 equiv), CuCl (4.0 equiv), rt, 2.5 h. (**5**) MeOH/CH_2Cl_2/TMSCl (1:1:1), rt, 3 h then LDA (7.5 equiv), THF, rt, 1 h then aqueous workup (for **5**) or TIPSCl (1.05 equiv), rt, 2 h (for **14**). (**6**) TBSCl (1.2 equiv), imid. (2.6 equiv), DMF, rt, 0.5 h. (**7**) $[Ir(cod)OMe]_2$ (10 mol%), **L2** (20 mol%), B_2pin_2 (4.0 equiv), octane/THF (2:1), 80 °C, 6 h then TBAF in THF (1.0 equiv), rt, 2 h then Boc_2O (12.0 equiv) and DMAP (3.0 equiv), rt, 1 h. (**8**) $NaIO_4$ (11.0 equiv), NH_4OAc (23.0 equiv), aq. acetone, rt, 9 h. (**9**) **6** (4.5 equiv), $Pd(MeCN)_2(OTs)_2$ (60 mol%), **L3** or **L4** (120 mol%) 2,6-di-*t*Bu-py (2.4 equiv), 3 Å MS, THF/MeOH (2:1), rt, 12 h then 50 °C, 6 h. (**10**) Tributyl(vinyl)stannane (21 equiv), *n*-BuLi (18 equiv), −78 °C, 1 h, then HFIP, 110 °C, 5 h. (**11**) CSA (2.1 equiv), PhH/CH_2Cl_2 (1:1) 0 °C, 6 h then rt, 6 h or HFIP, 0 °C, 1 h then MeOH. Abbreviations: DMAP = *N*,*N*-dimethyl-4-aminopyridine; DBU = 1,8-diazobicyclo[5.4.0]undec-7-ene; DMA = *N*,*N*-dimethylacetamide; DMF = *N*,*N*-dimethylformamide; LDA = lithium diisopropylamide; imid. = imidazole; cod = 1,5-cyclooctadiene; TBAF = tetrabutylammonium fluoride; HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol; CSA = camphorsulfonic acid.

of ligands were evaluated (see SI for a list), and **L1** emerged as optimum, along with DBU as a base. The e-amination could be easily conducted using a commercial potentiostat either on ca. 400 mg scale or employing a carousel assembly to easily process >1 g every 7 h (51% isolated yield; see inset photograph for setup). *N*-Methylation (K_2CO_3/MeI) followed by basic workup furnished the indole-valine **12** in 82% yield. Appending the tryptophol side chain onto C-3 of the indole in a scalable way required extensive experimentation (see SI for optimization) and was inspired by the pioneering studies of Tokuyama[5m] and Chung.[14] In prior studies it was demonstrated that aziridine opening could take place using **7** directly rather than a fully elaborated system like **12** to avoid potential epimerization of the valine side chain. Under Tokuyama's optimized conditions without a Lewis acid additive, only ca. 30% yield of tryptophol **13** was obtained, along with significant amounts of a ketone byproduct arising from attack of the C-3 position onto the methyl ester side chain. It was found that addition of CuCl (4.0 equiv) was essential for both the reproducibility and scalability of this pivotal transformation (57%, gram-scale; yield could be improved to 67% by recycling recovered starting material). To complete the synthesis of indolactam (**5**), the Boc and TBS groups were removed using dry HCl followed by evaporation, re-dissolution, and addition of LDA (7.5 equiv) to effect direct macrolactamization. Of note, in this step, hydrolysis of the methyl ester in **13** was completely unworkable under a variety of conditions due to steric hindrance imposed after *N*-methylation (the N–H

DOI: 10.1021/jacs.8b13697
J. Am. Chem. Soc. XXXX, XXX, XXX–XXX

derivative is easily hydrolyzed). The ketone byproduct observed during optimization of the tryptophol-forming step (**12** → **13**) suggested that such a base-induced cyclization would proceed. Quenching the macrocyclization with acid led directly to **5** (65%), whereas use of TIPSCl delivered **14** (72%). The five-step synthesis of **5** represents the shortest and most ideal (80%) pathway yet reported to this simple alkaloid. With access to **14** in gram quantities, the primary alcohol was shielded with a TBS group to afford the borylation precursor **15**. In accord with prior work from this laboratory,[15] ligand **L2** proved ideal (even after a rescreening of ligands) for the regioselective C−H borylation of **15** to deliver **16** in 81% yield on gram scale. The only modification needed was the use of a mixed solvent system (octane/THF = 2:1) due to the limited solubility of **15** in pure octane.

The touchstone disconnection of our retrosynthetic strategy rested on the success of the ensuing stereocontrolled union of a terpene fragment onto the C-6 position followed by annulation to complete the core. The recently reported Sigman−Heck redox-relay transform appeared to be ideally suited to this task, as it has been reported to generate a wide variety of quaternary centers in a stereocontrolled fashion dictated by the ligand. In what is the most complex manifestation of this reaction, and the first in the context of natural product synthesis, boronic acid **17** (derived from oxidative cleavage of **16**) was subjected to a modified variant of Sigman's conditions to access either diastereomeric ketone **18** (6.6:1 dr, 56%) or **19** (7:1, 85%) using **L3** or **L4**, respectively. Several points are notable regarding the success of this crucial bond formation: (1) Cu-based co-catalysts that are normally employed were excluded due to significant amounts of proto-deborylation. (2) No reaction was observed using **16**; a free boronic acid was essential. (3) The addition of 2,6-di-*t*Bu-pyridine (2.4 equiv) also reduced proto-deborylation. (4) The use of a mixed solvent system (MeOH/THF = 2:1) emerged as ideal.

The final two carbon atoms needed to complete the synthesis of the teleocidin B family were introduced through the addition of vinyllithium, followed by addition of HFIP to remove the labile Boc group (61% yield of **20** from **18**; 94% yield of **21** from **19**). The final ring closures of these tertiary alcohols were accomplished using the simple Brönsted acid, CSA, to deliver all four teleocidin B natural products (**1**−**4**). An extensive screen (see SI) revealed that modest selectivity could be achieved for the remaining quaternary center in the case of **20** by simply changing solvents. Thus, a PhH/CH_2Cl_2 mixture (1:1) afforded a 2.4:1.0 mixture of **4**:**2** from **20** in 63% yield, whereas HFIP solvent inverted the ratio to 1.0:2.2 in 98% yield. For **21**, the major diastereomer was always **3** relative to **1** (ca. 1.4:1.0) for all conditions screened.

The syntheses described herein were enabled by reactions and strategies that have only emerged in the past decade. In pursuit of ideality,[10] key disconnections made to avoid concession steps resulted naturally in the use of C−H functionalization logic and a maximal use of innate functionality. The forcing function of such strategic constraints resulted in an 11-step route, of which 7 steps generated skeletal C−C and C−N bonds. Memorable in this regard are the Cu-mediated tryptophol synthesis, base-induced macrocyclization, regioselective C−H borylation, and inaugural uses of e-amination and Sigman−Heck reactions in complex molecule construction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b13697.

Experimental procedures, analytical data (^{1}H and ^{13}C NMR, MS) for all new compounds, and optimization tables (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*pbaran@scripps.edu

ORCID

Phil S. Baran: 0000-0001-9193-9053

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support for this work was provided by NIH (GM-118176), JSPS (postdoctoral fellowship to H. N. and predoctoral fellowship to K. Y.), and Honjo international scholarship (predoctoral fellowship to Y. K.). We also thank Dr. Shota Asai and Dr. Yu Kawamata. We are grateful to Dr. D.-H. Huang and Dr. L. Pasternack for NMR spectroscopic assistance, Prof. A. L. Rheingold and Dr. C. E. Moore for X-ray crystallographic analysis, and Dr. Jason Chen and Ms. Brittany Sanchez for analytical support.

■ REFERENCES

(1) (a) Takashima, M.; Sakai, H. *Bull. Agric. Chem. Soc. Jpn.* **1960**, *24*, 647. (b) Takashima, M.; Sakai, H. *Bull. Agric. Chem. Soc. Jpn.* **1960**, *24*, 652. (c) Takashima, M.; Sakai, H.; Arima, K. *Agric. Biol. Chem.* **1962**, *26*, 660. (d) Takashima, M.; Sakai, H.; Mori, R.; Arima, K. *Agric. Biol. Chem.* **1962**, *26*, 669.

(2) (a) Sakabe, N.; Harada, H.; Hirata, Y.; Tomiie, Y.; Nitta, I. *Tetrahedron Lett.* **1966**, *7*, 2523. (b) Sakai, S.; Aimi, N.; Yamaguchi, K.; Hitotsuyanagi, Y.; Watanabe, C.; Yokose, K.; Koyama, Y.; Shudo, K.; Itai, A. *Chem. Pharm. Bull.* **1984**, *32*, 354. (c) Sakai, S.; Hitotsuyanagi, Y.; Yamaguchi, K.; Aimi, N.; Ogata, K.; Kuramochi, T.; Seki, H.; Hara, R.; Fujiki, H.; Suganuma, M.; Sugimura, T.; Endo, Y.; Shudo, K.; Koyama, Y. *Chem. Pharm. Bull.* **1986**, *34*, 4883.

(3) (a) Umezawa, K.; Weinstein, I. B.; Horowitz, A.; Fujiki, H.; Matsushima, T.; Sugimura, T. *Nature* **1981**, *290*, 411. (b) Fujiki, H.; Mori, M.; Nakayasu, M.; Terada, M.; Sugimura, T.; Moore, R. E. *Proc. Natl. Acad. Sci. U. S. A.* **1981**, *78*, 3872.

(4) Irie, K.; Hirota, M.; Hagiwara, N.; Koshimizu, K.; Hayashi, H.; Murao, S.; Tokuda, H.; Ito, Y. *Agric. Biol. Chem.* **1984**, *48*, 1269.

(5) For completed total syntheses of indolactam V, see: (a) Endo, Y.; Shudo, K.; Furuhata, K.; Ogura, H.; Sakai, S.; Aimi, N.; Hitotsuyanagi, Y.; Koyama, Y. *Chem. Pharm. Bull.* **1984**, *32*, 358. (b) Endo, Y.; Shudo, K.; Itai, A.; Hasegawa, M.; Sakai, S. *Tetrahedron* **1986**, *42*, 5905. (c) de Laszlo, S. E.; Ley, S. V.; Porter, R. A. *J. Chem. Soc., Chem. Commun.* **1986**, 344. (d) Mascal, M.; Moody, C. J. *J. Chem. Soc., Chem. Commun.* **1988**, 589. (e) Masuda, T.; Nakatsuka, S.; Goto, T. *Agric. Biol. Chem.* **1989**, *53*, 2257. (f) Kogan, T. P.; Somers, T. C.; Venuti, M. C. *Tetrahedron* **1990**, *46*, 6623. (g) Mascal, M.; Moody, C. J.; Slawin, A. M. Z.; Williams, D. *J. Chem. Soc., Perkin Trans. 1* **1992**, 823. (h) Semmelhack, M. F.; Rhee, H. *Tetrahedron Lett.* **1993**, *34*, 1395. (i) Quick, J.; Saha, B.; Driedger, P. E. *Tetrahedron Lett.* **1994**, *35*, 8549. (j) Bronner, S. M.; Goetz, A. E.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 3832. (k) Xu, Z.; Zhang, F.; Zhang, L.; Jia, Y. *Org. Biomol. Chem.* **2011**, *9*, 2512. (l) Nathel, N. F. F.; Shah, T. K.; Bronner, S. M.; Garg, N. K. *Chem. Sci.* **2014**, *5*, 2184. (m) Noji, T.; Okano, K.; Tokuyama, H. *Tetrahedron* **2015**, *71*, 3833. (n) Haynes-Smith, J.; Diaz, I.; Billingsley, K. L. *Org. Lett.* **2016**, *18*,

DOI: 10.1021/jacs.8b13697
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

2008. For synthesis of (−)-epi-indolactam, see: (o) Mari, M.; Bartoccini, F.; Piersanti, G. *J. Org. Chem.* **2013**, *78*, 7727.
(6) (a) Irie, K.; Nakagawa, Y.; Tomimatsu, S.; Ohigashi, H. *Tetrahedron Lett.* **1998**, *39*, 7929. (b) Awakawa, T.; Zhang, L.; Wakimoto, T.; Hoshino, S.; Mori, T.; Ito, T.; Ishikawa, J.; Tanner, M. E.; Abe, I. *J. Am. Chem. Soc.* **2014**, *136*, 9910. (c) Awakawa, T.; Abe, I. *Org. Biomol. Chem.* **2018**, *16*, 4746.
(7) Corey, E. J.; Cheng, X. *The Logic of Chemical Synthesis*; John Wiley & Sons, Inc.: New York, 1995. 47−57.
(8) (a) Nakatsuka, S.; Masuda, T.; Goto, T. *Tetrahedron Lett.* **1986**, *27*, 6245. (b) Webb, R. B., II; Venuti, M. C.; Eigenbrot, C. *J. Org. Chem.* **1991**, *56*, 4706. (c) Dangel, B. D.; Godula, K.; Youn, S. W.; Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 11856. (d) Vital, P.; Norrby, P.; Tanner, D. *Synlett* **2006**, *2006*, 3140.
(9) (a) Nakatsuka, S.; Masuda, T.; Goto, T. *Tetrahedron Lett.* **1987**, *28*, 3671. (b) Muratake, H.; Natsume, M. *Tetrahedron* **1991**, *47*, 8535. (c) Muratake, H.; Okabe, K.; Natsume, M. *Tetrahedron* **1991**, *47*, 8545. (d) Okabe, K.; Muratake, H.; Natsume, M. *Tetrahedron* **1991**, *47*, 8559.
(10) Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010**, *75*, 4657.
(11) (a) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. (b) Leitch, J. A.; Bhonoah, Y.; Frost, C. G. *ACS Catal.* **2017**, *7*, 5618. (c) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976.
(12) (a) Werner, E. W.; Mei, T.-S.; Burckle, A. J.; Sigman, M. S. *Science* **2012**, *338*, 1455. (b) Mei, T.-S.; Werner, E. W.; Burckle, A. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2013**, *135*, 6830. (c) Xu, L.; Hilton, M. J.; Zhang, X.; Norrby, P.-O.; Wu, Y.-D.; Sigman, M. S.; Wiest, O. *J. Am. Chem. Soc.* **2014**, *136*, 1960. (d) Mei, T.-S.; Patel, H. H.; Sigman, M. S. *Nature* **2014**, *508*, 340. (e) Hilton, M. J.; Xu, L.-P.; Norrby, P.-O.; Wu, Y.-D.; Wiest, O.; Sigman, M. S. *J. Org. Chem.* **2014**, *79*, 11841. (f) Patel, H. H.; Sigman, M. S. *J. Am. Chem. Soc.* **2015**, *137*, 3462. (g) Zhang, C.; Santiago, C. B.; Kou, L.; Sigman, M. S. *J. Am. Chem. Soc.* **2015**, *137*, 7290. (h) Zhang, C.; Santiago, C. B.; Crawford, J. M.; Sigman, M. S. *J. Am. Chem. Soc.* **2015**, *137*, 15668. (i) Patel, H. H.; Sigman, M. S. *J. Am. Chem. Soc.* **2016**, *138*, 14226. (j) Patel, H. H.; Prater, M. B.; Squire, S. O.; Sigman, M. S. *J. Am. Chem. Soc.* **2018**, *140*, 5895. (k) Yuan, Q.; Sigman, M. S. *J. Am. Chem. Soc.* **2018**, *140*, 6527.
(13) Li, C.; Kawamata, Y.; Nakamura, H.; Vantourout, J. C.; Liu, Z.; Hou, Q.; Bao, D.; Starr, J. T.; Chen, J.; Yan, M.; Baran, P. S. *Angew. Chem., Int. Ed.* **2017**, *56*, 13088.
(14) Wolfard, J.; Xu, J.; Zhang, H.; Chung, C. K. *Org. Lett.* **2018**, *20*, 5431.
(15) (a) Feng, Y.; Holte, D.; Zoller, J.; Umemiya, S.; Simke, L. R.; Baran, P. S. *J. Am. Chem. Soc.* **2015**, *137*, 10160. (b) Takagi, J.; Sato, K.; Hartwig, J. F.; Ishiyama, T.; Miyaura, N. *Tetrahedron Lett.* **2002**, *43*, 5649. (c) Kallepalli, V. A.; Shi, F.; Paul, S.; Onyeozili, E. N.; Maleczka, R. E.; Smith, M. R. *J. Org. Chem.* **2009**, *74*, 9199. (d) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890.

DOI: 10.1021/jacs.8b13697
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX