Organic LETTERS

Letter

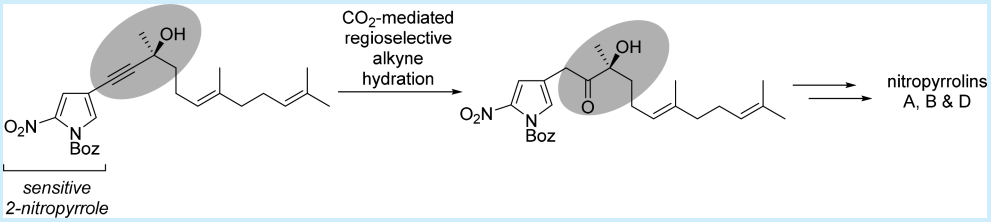
pubs.acs.org/OrgLett

# General Synthesis of the Nitropyrrolin Family of Natural Products via Regioselective $CO_2$-Mediated Alkyne Hydration

Xiao-Bo Ding, Daniel P. Furkert,* and Margaret A. Brimble*

School of Chemical Sciences and Maurice Wilkins Centre for Molecular Biodiscovery, University of Auckland, 23 Symonds Street, Auckland 1142, New Zealand

Supporting Information




**ABSTRACT:** The total synthesis of the 2-nitropyrrole natural products nitropyrrolins A and B and the formal synthesis of nitropyrrolin D are reported. The key 2-nitro-4-alkylpyrrole core was efficiently assembled by Sonogashira cross-coupling, with complete control of regioselectivity. An unusual carboxylative cyclization, sulfonylcarbamate formation, and base-promoted cleavage sequence enabled access to the key hydroxy ketone without affecting the protected 2-nitropyrrole unit. The total synthesis provides a general approach for preparation of the bioactive nitropyrrolin family of natural products.

Nitropyrrolins A–E (**1**–**5**, Figure 1) were isolated from the culture broth of the MAR4 strain CNQ-509 from a marine sediment sample collected off La Jolla, California in 2010.[1] Together with the heronapyrroles (e.g., **6**–**7**, Figure 1)[2] produced by *Streptomyces sp.* (CMB-M0423), these compounds are the only natural products reported to date bearing the rare 2-nitro-4-alkyl pyrrole core.[2a] Nitropyrrolins A (**1**), B (**2**), and D (**4**) exhibit cytotoxic activity toward the human colon carcinoma cell line HCT-116 (**1** $IC_{50}$ 31.1 $\mu$M, **2** $IC_{50}$ 31.0 $\mu$M, and **4** $IC_{50}$ 5.7 $\mu$M).[1] Inspired by the unique structures, promising biological activity and low abundance in nature, several groups have shown interest in the syntheses of these natural products.[3] Stark et al.[2b,4] and our group[5] have reported successful syntheses of heronapyrroles C and D in 2012 and 2014, respectively. We later reported a more efficient strategy for regioselective preparation of the 2-nitro-4-alkyl pyrrole framework, which enabled improved syntheses of heronapyrroles C and D.[6] Recently, Morimoto and co-workers accomplished syntheses of heronapyrroles A (**6**), B (**7**) and nitropyrrolins A (**1**), B (**2**), D (**4**).[7] In their syntheses of the nitropyrrolins, nonselective nitration of an alkylated pyrrole was employed as the key step to assemble the 2-nitro-4-farnesyl pyrrole core which only afforded the desired product as the minor regioisomer. At the outset of our studies, no synthesis of members of the nitropyrrolin family had been reported. Given our ongoing interest in 2-nitropyrrole containing natural products, we were interested in investigating the syntheses of nitropyrrolins A (**1**), B (**2**), and D (**4**), with the goal of establishing efficient and general access to this biologically active pharmacophore, to enable more thorough evaluation of their potential as leads for drug discovery.

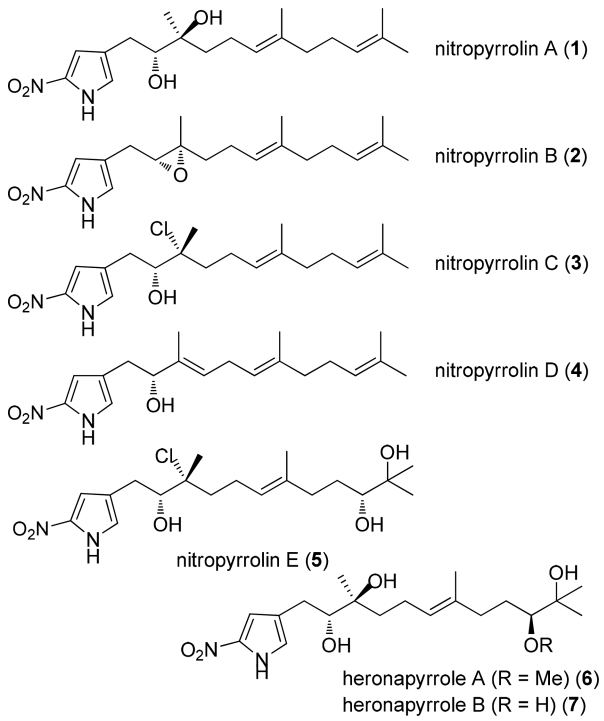



**Figure 1.** 2-Nitro-4-alkyl pyrrole natural products.

**Received:** August 28, 2017

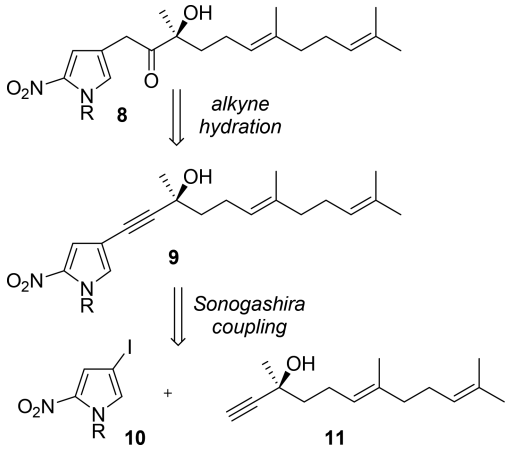




DOI: 10.1021/acs.orglett.7b02687
*Org. Lett.* XXXX, XXX, XXX–XXX

Based on our previous studies toward the closely related heronapyrroles,[5,6] we envisaged that a palladium catalyzed cross-coupling would enable efficient construction of the 2-nitro-4-farnesyl pyrrole core with complete regiochemical control. With this in mind, it was envisaged that nitropyrrolin A (**1**) could be accessed by stereoselective reduction of a suitably protected hydroxy ketone such as **8** (Scheme 1). We expected that ketone **8** could in turn be obtained from the propargylic alcohol **9** via regioselective hydration of the alkyne functionality. Carbon dioxide mediated hydration of propargylic alcohols has been reported for related transformations,[8] although its application in natural product synthesis has not been well established. The requisite propargylic alcohol **9** would be assembled by Sonogashira coupling of iodide **10**[5] with alkyne **11**.[9]

**Scheme 1. Retrosynthesis of the Nitropyrrolin Framework**



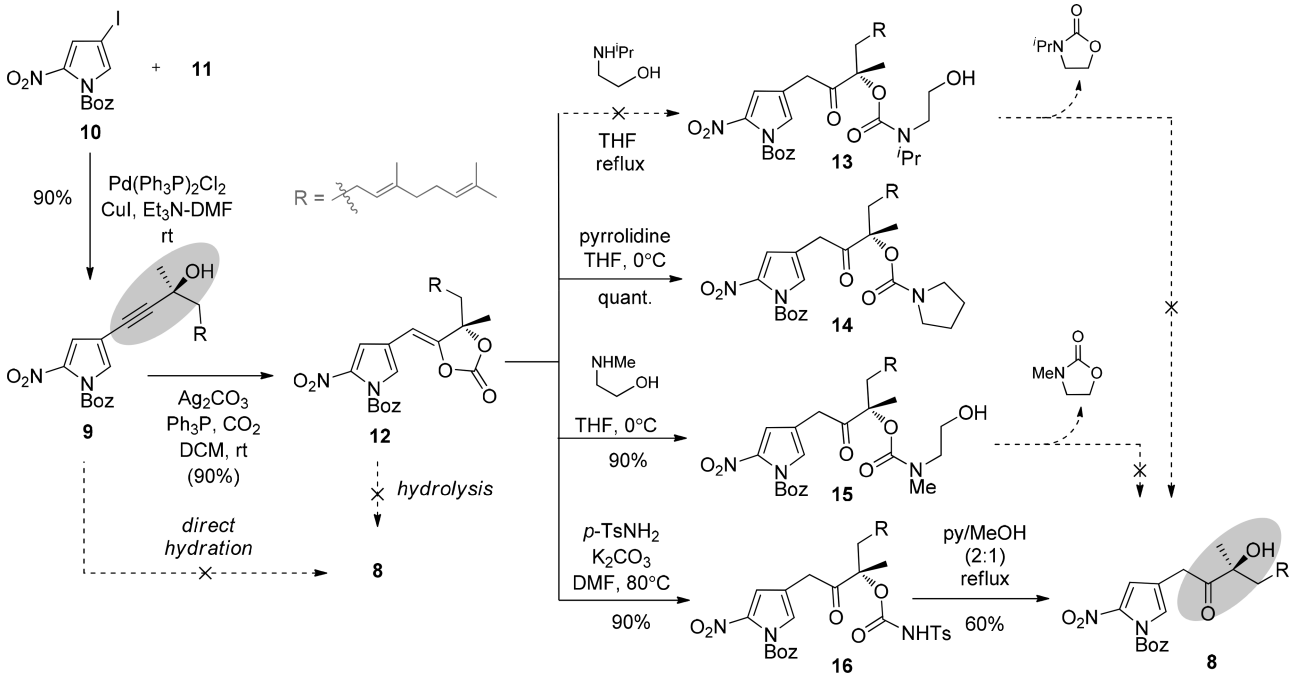

Our synthesis began with the preparation of the substrates for the key Sonogashira coupling reaction (Scheme 2). *N*-Benzyloxymethyl (*N*-Boz) protected iodide **10** was readily prepared from 2-nitropyrrole following our previously optimized procedures.[5] Enantiomerically pure alkyne **11** was prepared from commercially available farnesol in three steps using literature methods.[9] Sonogashira coupling of iodide **10** and terminal alkyne **11** then successfully assembled the 2-nitro-4-farnesylpyrrole framework, affording alkyne **9** in 90% yield.

Initial attempts to effect direct $CO_2$-promoted hydration of alkyne **9** using reported conditions including AgOAc/DBU[8b] and ionic liquid ($[Bu_4P][Im]$)[8b] in the presence of $CO_2$ failed to deliver the desired ketone **8** (Scheme 2), with only decomposition and/or recovery of the starting material observed. Extensive attempts to optimize the reaction conditions did not improve the outcome.

With this setback, we revised our approach to initially prepare the cyclic carbonate intermediate **12**, which was expected to then undergo hydrolysis to afford the desired hydroxy ketone **8** in a separate step (Scheme 2). After screening of reaction conditions, we were pleased to find that mild conditions involving exposure to silver(I) carbonate and carbon dioxide (generated from dry ice), with triphenyl phosphine as cocatalyst, in dichloromethane, successfully effected the carboxylative cyclization at room temperature,[8e] affording the desired carbonate **12** in high yield. Unfortunately, the subsequent hydrolysis step proved unexpectedly challenging. Examination of a wide range of acids and bases in various solvents (see the Supporting Information for details) did not reveal conditions for conversion of cyclic carbonate **12** to the target ketone **8**. Decomposition of the starting material was observed in most cases, indicating that the limited stability of the 2-nitropyrrole subunit under the reaction conditions examined was potentially problematic.

Inspired by the cleavage mechanism of the tetramethyl-1,3-oxazolidine-3-carbonyl (*Cby*) auxiliary (Scheme 3A),[10] we envisaged that conversion of the cyclic carbonate **12** to the corresponding $\beta$-hydroxyethylcarbamate (e.g., **13**) would facilitate an intramolecular cyclization upon subsequent treat-

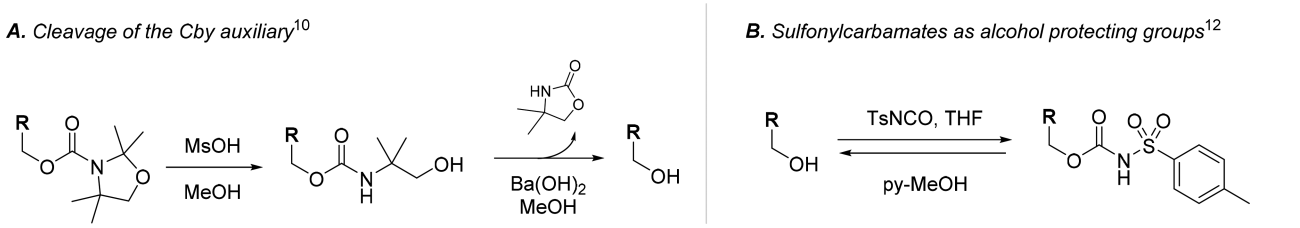
**Scheme 2. $CO_2$-Mediated Regioselective Hydration of Alkyne 9**






DOI: 10.1021/acs.orglett.7b02687
*Org. Lett.* XXXX, XXX, XXX−XXX

**Scheme 3. Literature Precedent for Investigations into the Two-Step Cleavage of Cyclic Carbonate 17**




ment with a suitable base, releasing the desired hydroxy ketone **8**. Accordingly, cyclic carbonate **12** was initially treated with *N*-isopropyl ethanolamine; however, none of the desired carbamate was isolated. The electrophilicity of carbonate **12** toward secondary amines was then examined by reaction with pyrrolidine, resulting in quantitative formation of carbamate **14**. Encouraged by this result, use of the less hindered *N*-methyl-ethanolamine as a nucleophile was also pursued affording carbamate **15** in 90% yield. With the required carbamate **15** in hand, investigations of the carbamate cleavage to yield the required hydroxy ketone **8** were next undertaken. Disappointingly, however, examination of a wide range of previously reported conditions including $Ba(OH)_2$/MeOH,[10a] $K_3CO_3$/MeOH,[10c] and NaH/THF[11] failed to effect formation of ketone **8**, with decomposition observed in most cases. Although use of the carbamate formation and cleavage strategy failed to afford the desired hydroxy ketone **8**, these experiments revealed the electrophilicity of carbonate **12** and laid a foundation for further investigation using other nucleophiles.

Sulfonyl carbamates have recently been reported as effective protecting groups for alcohols that are readily removed under mildly basic conditions (Scheme 3B).[12] It therefore seemed plausible that nucleophilic opening of cyclic carbonate **12** with *p*-toluenesulfonamide would afford the corresponding sulfonyl carbamate **16**, which would then release the desired hydroxy ketone **8** upon cleavage of the sulfonylcarbamate using the reported mild conditions. Accordingly, **12** was treated with the anion of *p*-toluenesulfonamide, generated by treatment of *p*-toluenesulfonamide with NaH in DMF. Pleasingly, the desired sulfonylcarbamate **16** was obtained in 40% yield. After optimization of the reaction conditions, sulfonylcarbamate **16** was finally obtained in a greatly improved yield of 92% by stirring **12** with excess *p*-toluenesulfonamide in the presence of potassium carbonate in DMF at elevated temperature. We next set out to cleave the sulfonylcarbamate motif and were pleased to discover that heating **16** under reflux in pyridine−MeOH (2:1) finally afforded the desired hydroxy ketone **8**, in 60% yield.

With access to the target hydroxy ketone **8** secured, investigations into the necessary diastereoselective reduction of the ketone were next undertaken (Scheme 4). Borohydride reduction of **8** in the presence of zinc chloride[13] or cerium chloride heptahydrate as chelating reagents afforded the separable epimeric diols **17a** and **17b** in a 2:1 to 3:1 ratio, in high yields (Table 1, entries 1−3). Zinc borohydride[14] was found to give an improved ratio of diastereomers (4.5:1) in 80% yield (Table 1, entry 4). Finally, Corey−Bakshi−Shibata (CBS) reduction using (*R*)-2-methyl-CBS-oxazaborolidine and a borane−dimethyl sulfide complex afforded diols **17a** and **17b** in 75% yield, with a further improved *d.r.* of 6:1 (Table 1, entry 5).

**Scheme 4. Final Synthesis of Nitropyrrolin A(1)**

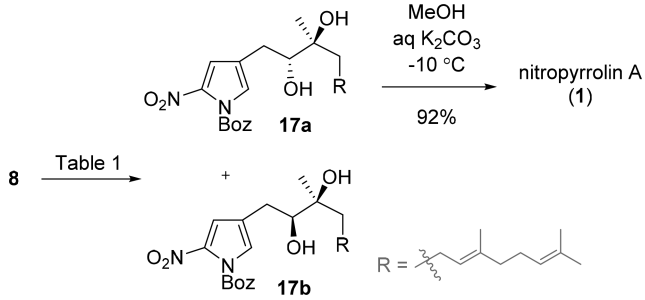



**Table 1. Diastereoselective Reduction of Hydroxy Ketone 8**

| entry | conditions | temp (°C) | yield (%)[a] | 17a:17b |
|---|---|---|---|---|
| 1 | $ZnCl_2$, $NaBH_4$, THF | 0 | 70 | 3:1 |
| 2 | $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH | −10 | 84 | 2:1 |
| 3 | $NaBH_4$, $CeCl_3{\cdot}7H_2O$, EtOH/THF (1:1) | −10 | 85 | 3:1 |
| 4 | $Zn(BH_4)_2$, THF | −20 | 80 | 4.5:1 |
| 5 | (*R*)-Me-CBS, $BH_3{\cdot}$DMS, THF | −40 | 75 | 6:1 |

[a]Isolated yield. [b]Determined by NMR analysis.

The total synthesis of nitropyrrolin A (**1**) was finally achieved in 92% yield by *N*-Boz deprotection of diol **17a**, using aqueous $K_2CO_3$ in methanol at 0 °C (Scheme 4). The spectroscopic data and specific rotation of our synthetic sample were in good agreement with the literature report and that reported by Morimoto [*this work* $[\alpha]_D$ +20.7; *natural* $[\alpha]_D$ +8; *Morimoto* $[\alpha]_D$ +26.6].[7b]

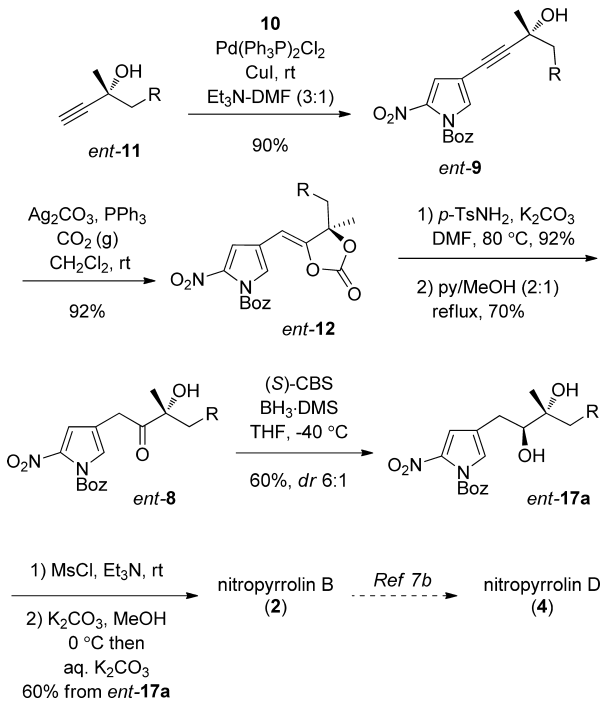
With the synthesis of initial target nitropyrrolin A (**1**) completed, the focus next turned to nitropyrrolin B (**2**). This required the enantiomer of *N*-Boz hydroxy ketone **8** used for nitropyrrolin A (**1**), which was prepared using the optimized method (Scheme 5). Diastereoselective CBS reduction of *ent*-**8** afforded *ent*-**17a**, which underwent successive mesylation and one-pot epoxide formation, followed by *N*-Boz deprotection under very mild conditions to afford nitropyrrolin B (**2**) in 60% overall yield from *ent*-**17a**. The spectroscopic data and specific rotation of our synthetic nitropyrrolin B (**2**) were in good agreement with the literature report [*this work* $[\alpha]_D$ +10.6; *natural* $[\alpha]_D$ +3; *Morimoto* $[\alpha]_D$ +12.3].[7b] In addition, synthesis of nitropyrrolin B (**2**) provides a formal synthesis of nitropyrrolin D (**4**) which is available by regioselective epoxide ring opening, as previously demonstrated by Morimoto and co-workers.[7b]

In conclusion, we have achieved the total synthesis of the 2-nitropyrrole natural products, nitropyrrolins A (**1**) and B (**2**), and a formal synthesis of nitropyrrolin D. The synthetic route is underpinned by a highly efficient Sonogashira coupling that enables direct regioselective construction of the 2-nitro-4-



DOI: 10.1021/acs.orglett.7b02687
*Org. Lett.* XXXX, XXX, XXX−XXX

**Scheme 5. Completion of Nitropyrrolin B (2) and Formal Synthesis of Nitropyrrolin D (4)**




alkylpyrrole framework shared by the nitropyrrolin and heronapyrrole natural product families. An unusual $CO_2$-mediated carboxylative cyclization, sulfonyl carbamate formation, and cleavage sequence was devised in this case to effect transformation of the alkyne coupling products into key hydroxy ketone intermediates, without affecting the sensitive 2-nitropyrrole subunit. Importantly, the synthetic strategy provides efficient general preparative access to 2-nitropyrrole natural products and will facilitate material supply for ongoing biological evaluation of the natural products and derivative libraries in medicinal chemistry contexts.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02687.

Experimental procedures and full spectroscopic data for all new compounds (PDF)

## ■ AUTHOR INFORMATION


### Corresponding Authors

*E-mail: m.brimble@auckland.ac.nz.
*E-mail: d.furkert@auckland.ac.nz.

### ORCID

Daniel P. Furkert: 0000-0001-6286-9105
Margaret A. Brimble: 0000-0002-7086-4096


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

The authors thank the NZ Ministry for Science and Innovation (IIOF) for financial support.

## ■ REFERENCES


(1) Kwon, H. C.; Espindola, A. P. D.; Park, J.-S.; Prieto-Davó, A.; Rose, M.; Jensen, P. R.; Fenical, W. *J. Nat. Prod.* **2010**, *73*, 2047−2052.
(2) (a) Raju, R.; Piggott, A. M.; Barrientos Diaz, L. X.; Khalil, Z.; Capon, R. J. *Org. Lett.* **2010**, *12*, 5158−5161. (b) Schmidt, J.; Khalil, Z.; Capon, R. J.; Stark, C. B. *Beilstein J. Org. Chem.* **2014**, *10*, 1228−1232.
(3) Ding, X.-B.; Brimble, M. A.; Furkert, D. P. *Org. Biomol. Chem.* **2016**, *14*, 5390−5401.
(4) Schmidt, J.; Stark, C. B. *Org. Lett.* **2012**, *14*, 4042−4045.
(5) Ding, X.-B.; Furkert, D. P.; Capon, R. J.; Brimble, M. A. *Org. Lett.* **2014**, *16*, 378−381.
(6) Ding, X.-B.; Furkert, D. P.; Brimble, M. A. *Chem. Commun.* **2016**, *52*, 12638−12641.
(7) (a) Matsuo, T.; Hashimoto, S.; Nishikawa, K.; Kodama, T.; Kikuchi, S.; Tachi, Y.; Morimoto, Y. *Tetrahedron Lett.* **2015**, *56*, 5345−5348. (b) Mitani, H.; Matsuo, T.; Kodama, T.; Nishikawa, K.; Tachi, Y.; Morimoto, Y. *Tetrahedron* **2016**, *72*, 7179−7184.
(8) (a) He, H.; Qi, C.; Hu, X.; Guan, Y.; Jiang, H. *Green Chem.* **2014**, *16*, 3729−3733. (b) Zhao, Y.; Yang, Z.; Yu, B.; Zhang, H.; Xu, H.; Hao, L.; Han, B.; Liu, Z. *Chem. Sci.* **2015**, *6*, 2297−2301. (c) Ouyang, L.; Tang, X.; He, H.; Qi, C.; Xiong, W.; Ren, Y.; Jiang, H. *Adv. Synth. Catal.* **2015**, *357*, 2556−2565. (d) Qi, C.; Jiang, H.; Huang, L.; Yuan, G.; Ren, Y. *Org. Lett.* **2011**, *13*, 5520−5523. (e) Song, Q. W.; Chen, W. Q.; Ma, R.; Yu, A.; Li, Q. Y.; Chang, Y.; He, L. N. *ChemSusChem* **2015**, *8*, 821−827. (f) Song, Q. W.; He, L. N. *Adv. Synth. Catal.* **2016**, *358*, 1251−1258. (g) Zhou, Z. H.; Song, Q. W.; Xie, J. N.; Ma, R.; He, L. N. *Chem. - Asian J.* **2016**, *11*, 2065−2071.
(9) Carreras, J.; Livendahl, M.; McGonigal, P. R.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2014**, *53*, 4896−4899.
(10) (a) Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1422−1424. (b) Guarnieri, W.; Grehl, M.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1734−1737. (c) van Bebber, J.; Ahrens, H.; Fröhlich, R.; Hoppe, D. *Chem. - Eur. J.* **1999**, *5*, 1905−1916. (d) Christoph, G.; Hoppe, D. *Org. Lett.* **2002**, *4*, 2189−2192. (e) Hoppe, D.; Padeken, L.; Gottschalk, K.; Guarnieri, W.; Fröhlich, R. *Synthesis* **2007**, *2007*, 1984−1994.
(11) (a) Derwing, C.; Hoppe, D. *Synthesis* **1996**, *1996*, 149−154. (b) Leroy, B.; Markó, I. E. *J. Org. Chem.* **2002**, *67*, 8744−8752.
(12) Manabe, S.; Yamaguchi, M.; Ito, Y. *Chem. Commun.* **2013**, *49*, 8332−8334.
(13) Robertson, J.; North, C.; Sadig, J. E. *Tetrahedron* **2011**, *67*, 5011−5023.
(14) (a) Nakata, T.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1983**, *24*, 2653−2656. (b) Narasimhan, S.; Madhavan, S.; Prasad, K. G. *J. Org. Chem.* **1995**, *60*, 5314−5314.




DOI: 10.1021/acs.orglett.7b02687
*Org. Lett.* XXXX, XXX, XXX−XXX