Organic LETTERS

Letter

pubs.acs.org/OrgLett

Total Synthesis of Anticancer Agent EBC-23

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Supporting Information

ABSTRACT: Total synthesis of spiroketal EBC-23 has been described by two divergent approaches from three simple building blocks. Gold-catalyzed cycloisomerization of alkynol and acid-mediated spirocyclization of diketalketone were successfully utilized to effect spiroketal formation. A Cu(I)−P(Cy)$_3$-catalyzed protocol for the highly regio- and stereocontrolled hydroboration of internal propargylic alcohol was effectively applied toward the β-hydroxy ketone via vinylboronates.

In 2007, Reddell and Gordon[1] reported the isolation of a group of novel spiroketals EBC-23, -24, -25, -72, -73, -75, and -76 (Figure 1) from the fruit of *Cinnamomum laubatii* (family

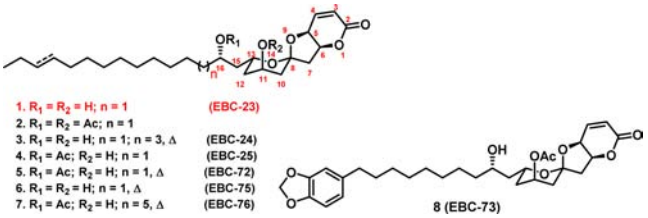
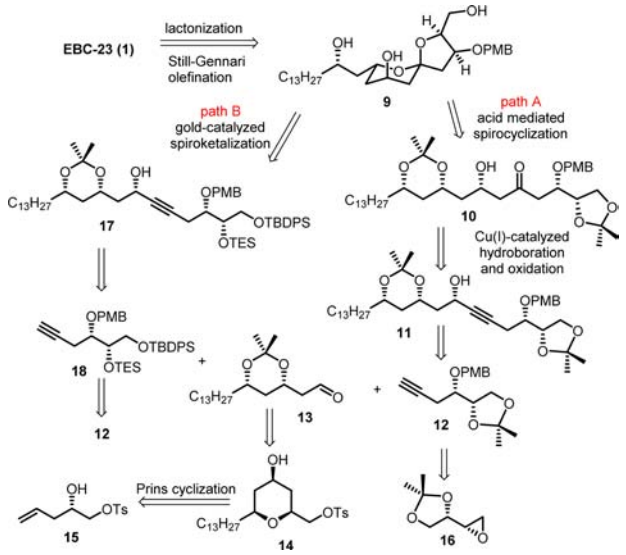


Figure 1. Spiroketals EBC-23, -24, -25, -72, -73, -75, and -76.

Lauraceae) found in the Australian tropical rainforests. Among them, EBC-23 (**1**) exhibited in vitro anticancer activity against several human cancer cell lines [i.e., melanoma (MM96L), breast carcinoma (MCF7), prostate cancer (DU145)] and, more importantly, inhibited the growth of a human prostate cancer xenograft in mice with no observable side effects.[2] This clearly indicated its potential for the treatment of refractory solid tumors in adults.[1] The structural features of EBC-23 comprise six stereocenters partly embedded in a unique fused α,β-unsaturated lactone consisting of an acid-labile spiroketal unit. The structure and absolute stereochemistry of EBC-23 was determined by the Williams research group by 2D NMR studies[2] and total synthesis using Linchpin technology.[3] The second synthesis was achieved by Yamamoto et al.[4] using super silyl chemistry.

Given the scarcity of **1** coupled with its anticancer activity and our long-standing interest in the synthesis of 1,6-dioxaspiro[4.5]-decane and 1,7-dioxaspiro[5.5]undecane moiety containing molecules,[5] we embarked on the total synthesis of **1** to enable additional biological evaluation. Herein, we report the total synthesis of EBC-23 (**1**) by two divergent approaches from three simple building blocks. Retrosynthetically (Scheme 1), EBC-23

Scheme 1. Retrosynthetic Analysis of EBC-23



(**1**) can be obtained from **9** by *Z*-selective olefination followed by lactonization. The spiro compound **9** could be prepared via two divergent approaches, that is, paths A and B. In path A, **9** can be derived via a one-pot acid-mediated deprotection/spirocyclization sequence of diketalketone **10**, which in turn could be prepared from propargylic alcohol **11** via a regioselective Cu(I)-catalyzed hydroboration followed by oxidation of vinylboronates. Compound **11** could be easily obtained by the coupling of intermediates aldehyde **13** and terminal alkyne **12**.

Received: June 25, 2016
Published: August 11, 2016

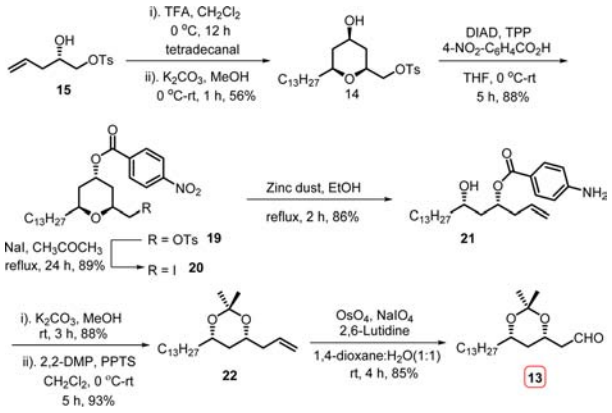
DOI: 10.1021/acs.orglett.6b01849
Org. Lett. 2016, 18, 4202−4205

Alkyne **12** could be obtained from known epoxide **16**, whereas aldehyde **13** could be derived from a monotosylated pyran **14**. Pyran **14** could be obtained from known **15** by employing Prins cyclization.

In path B, the spiro compound **9** could be generated via gold(I)chloride-catalyzed spiroketalization of alkynol **17**, which in turn could be easily generated by the coupling of aldehyde **13** and alkyne **18**. Alkyne **18** could be readily obtained from **12** by simple deprotection/protection strategies.

Synthesis of EBC-23 commenced with a Prins reaction[6] of known monotosylated homoallyl alcohol **15**,[6b] and tetradecanal in the presence of TFA furnished trisubstituted tetrahydropyran **14** with high diastereoselectivity (Scheme 2). Compound **14** was

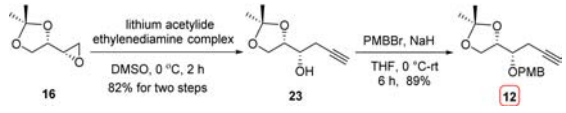
Scheme 2. Synthesis of Aldehyde 13



subjected to Mitsunobu reaction[7] using DIAD, TPP, and 4-nitrobenzoic acid to obtain **19**. Now, the tosyl group in **19** was converted to the corresponding iodide **20** utilizing NaI. Reductive ring opening of iodide **20** with Zn dust furnished[8] compound **21**, which upon ester hydrolysis followed by isopropylidene protection afforded **22**. The relative stereochemistry of hydroxy groups in **22** was assigned by the Rychnovsky acetonide method.[9] Finally, oxidative cleavage of the terminal double bond of **22** using Jin's protocol (Lemieux–Johnson oxidation)[10] furnished aldehyde **13** in 26% yield over seven steps from **15**.

Synthesis of alkyne **12** (Scheme 3) started with the opening of known epoxide **16**[11] with the lithium acetylide–ethylene

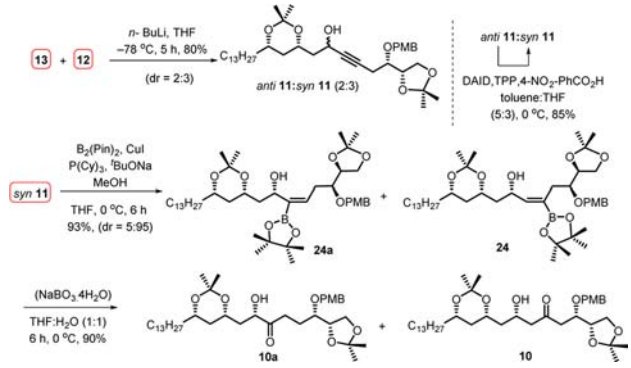
Scheme 3. Synthesis of Alkyne 12



diamine complex to afford alkynol **23**,[12] which was converted to its PMB ether **12** using PMBBr in 73% yield over two steps from **16**.

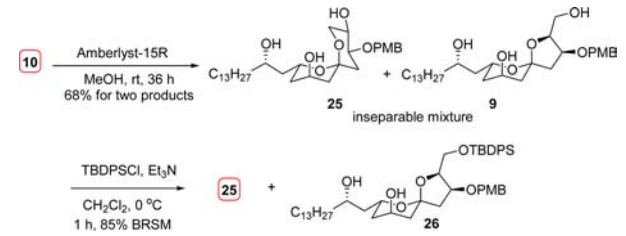
The coupling of lithium acetylide of alkyne **12** and the aldehyde **13** was achieved to afford the isomers *anti*-**11** and *syn*-**11** in a 2:3 ratio.[13] The stereochemistry of a newly generated stereogenic center at C11 in *syn*-**11** was confirmed by modified Mosher's analysis[14] of the ^{1}H chemical shifts that revealed the *S* absolute configuration at C11. The undesired isomer *anti*-**11** was converted to the required *syn*-**11** by Mitsunobu inversion.[7] To prepare *β*-hydroxy ketone **10**, *syn*-**11** was subjected to high levels of regio- and stereoselective hydroboration[15] using a Cu(I)–PCy_3–$B_2(pin)_2$ system in MeOH to give a diastereomeric mixture of vinylboronates **24a** and **24** in a 5:95 ratio (^{1}H NMR). The mixture was as such subjected to oxidation ($NaBO_3 \cdot 4H_2O$)[16] to afford separable ketones **10a** and **10** in good yield (Scheme 4).

Scheme 4. Synthesis of *β*-Hydroxy Keto Compound 10



The *β*-hydroxy ketone **10** upon treatment with acid (Amberlyst-15) in MeOH (Scheme 5) delivered as a chromato-

Scheme 5. Synthesis Spiro Compounds 25 and 26



graphically (using silica gel) inseparable mixture of spiroketals, 1,7-dioxaspiro[5.5]undecane **25** and 1,6-dioxaspiro[4.5]decane **9** in a combined yield of 68%.[17]

The silylation allowed us to separate the mixture by a simple chromatography to get **25** and **26** in a 3:2 ratio. The stereochemistry of a newly formed spiro carbon in **25** and **9** was controlled by anomeric effects,[13a,18] and the configuration of other stereocenters resulted from the configuration of precursor **10**. The complete structures of **25** and **26** were assigned by 1D (^{1}H, ^{13}C, and DEPT135) and 2D (COSY, NOESY, HSQC, HMBC, and TOCSY) NMR studies (see Supporting Information).

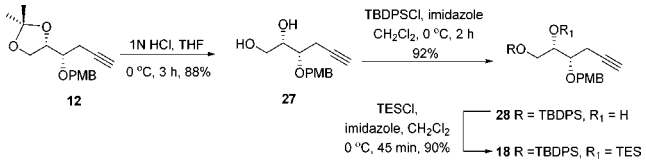
Since undesired isomer was obtained in the spiroketalization due to the presence of two competitive acetal groups, to enhance access to the desired spiroketal, another pathway was explored. Accordingly, in path B, to differentiate hydroxy groups in alkyne **12**, an isopropylidene group was cleaved to give diol **27**, in which the primary hydroxy group was selectively silylated as its TBDPS ether to give **28** (Scheme 6). Subsequently, protection of the secondary hydroxy group to its TES ether furnished alkyne **18** in good yield.

Union of the two fragments by nucleophilic addition of lithiated alkyne **18** to the aldehyde **13** (Scheme 7) afforded *syn*-**17** and *anti*-**17** in a 2:3 ratio.[13] The stereochemistry of the newly generated stereogenic center at C11 in *syn*-**17** was confirmed by modified Mosher's analysis.[14]

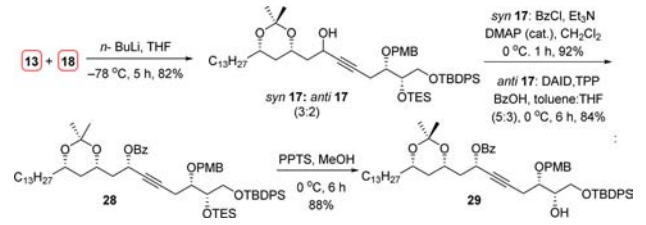
The *syn*-**17** upon esterification with BzCl afforded benzoate **28**. On the other hand, *anti*-**17** was also converged to **28** under

DOI: 10.1021/acs.orglett.6b01849
Org. Lett. 2016, 18, 4202–4205

Scheme 6. Synthesis of Alkyne 18



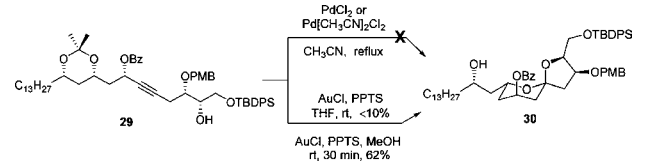
Scheme 7. Synthesis of Spiroketalization Precursor 29



Mitsunobu conditions. Selective deprotection of TES ether[19] provided spiroketalization precursor **29**.

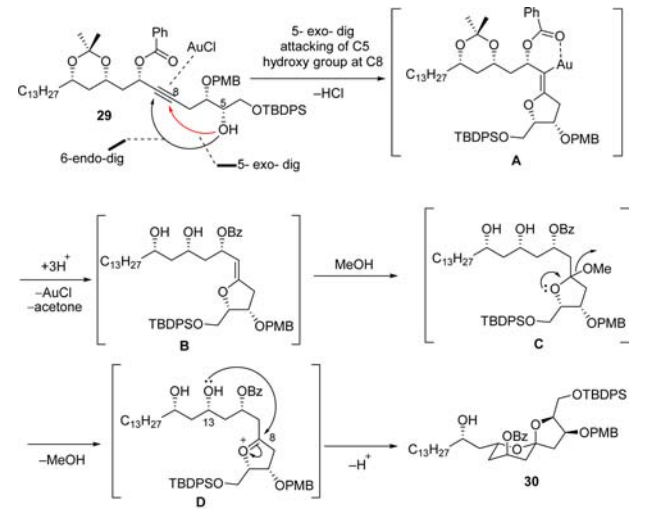
Treatment of **29** under Utimoto's conditions ($PdCl_2$, aqueous CH_3CN, reflux and $Pd[CH_3CN]_2Cl_2$, CH_3CN, reflux)[20] failed to give **30**. Next, Trost's precedent (AuCl, PPTS in THF) was examined to effect spiroketalization.[13a] This method gave the desired isomer with modest yield. Gratifyingly, changing the solvent to methanol furnished the desired spiro compound **30** in 62% yield (Scheme 8).

Scheme 8. Synthesis of Spiroketal 30



A plausible mechanism for the Au(I)-catalyzed cycloisomerization of 4-alkynol **29** is shown in Scheme 9. This reaction is initiated by the activation of the triple bond through the Au(I) catalyst[21] followed by addition of C5 alcohol to alkyne at C8 via a 5-*exo*-dig pathway to form an enol vinylgold[22] intermediate **A**.

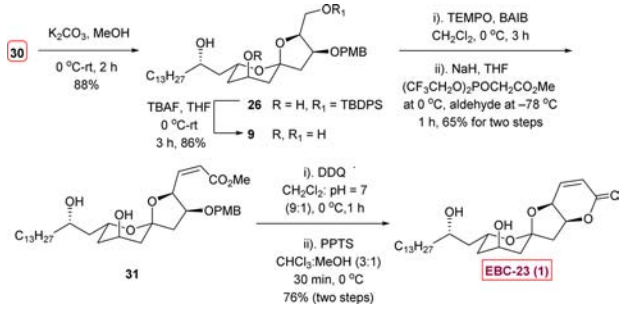
Scheme 9. Plausible Mechanism of the Cycloisomerization Reaction



The gold-catalyzed spiroketalization in methanol happens first to give rise to 5-*exo*-dig cyclization over a possible 6-*endo*-dig pathway. Solvolysis of the acetonide and protiodeauration of **A** gives vinyl ether **B**, which upon addition of methanol gives rise to ketal **C**, which on subsequent elimination of methanol forms oxocarbenium ion **D**. Intramolecular participation of C13 alcohol on C8 carbon of oxocarbenium ion forms the spiroketal **30**.[23]

The complete structure of **30** was assigned by 1D (^1H, ^{13}C, and DEPT135) and 2D (COSY, NOESY, HSQC, HMBC, and TOCSY) NMR studies (see Supporting Information). Saponification of the ester in **30** furnished **26** in 88% yield. The spectroscopic data of spiro compound **26** obtained by path B were found to match that synthesized by path A. Removal of the silyl group in **26** using TBAF provided triol **9** in 86% yield. Now, the stage was set for lactonization (Scheme 10).

Scheme 10. Synthesis of EBC-23



Selective oxidation of the primary hydroxy group in triol **9** using a TEMPO–BAIB reagent system[24] afforded aldehyde, which was immediately treated with Still–Gennari reagent[25] to form the *Z*-olefinic ester **31**. Finally, oxidative cleavage of PMB ether with DDQ followed by lactonization in the presence of PPTS furnished the target molecule, EBC-23 (**1**). The spectroscopic properties (^1H, ^{13}C NMR, IR, and HRMS-ESI) as well as specific rotation ($[\alpha]_D$) were in full accordance with the natural product and synthetic products.[1,3,4]

In conclusion, the total synthesis of anticancer agent EBC-23 was accomplished by employing gold-catalyzed spiroketalization of alkynol, wherein regioselectivity was achieved by selective activation of alkyne based on electronic bias. This synthetic route has 21 total and 16 linear steps and provides the natural product in 4% yield over the longest linear sequence. For the synthesis of β-hydroxy ketone, a Cu(I)–$P(Cy)_3$-catalyzed protocol for the highly regio- and stereoselective $B_2(pin)_2$ hydroboration of the internal propargylic alcohol system in the presence of MeOH was effectively utilized via vinylboronates. We believe that these methods will be applicable for the preparation of a wide range of natural products having spiroketals (such as 1,6-dioxaspiro[4.5]-decane and 1,7-dioxaspiro[5.5]undecane systems) and their analogues.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01849.

Experimental procedures, characterization details, ^1H and ^{13}C NMR spectra of all compounds (PDF)

DOI: 10.1021/acs.orglett.6b01849
Org. Lett. 2016, 18, 4202–4205

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

D.V.R. thanks the Council of Scientific and Industrial Research (CSIR), India, for financial assistance in the form of a fellowship, and D.V.R. and G.S. thank CSIR, India, for financial support as part of XII five-year programme under project ORIGIN (CSC-0108). J.S.Y. thanks CSIR and DST, India, for Bhatnagar and J.C. Bose Fellowships, respectively.

REFERENCES

(1) Reddell, P. W.; Gordon, V. A. PCT Int. Appl. WO 2007070984A1, 2007.

(2) (a) Dong, L.; Schill, H.; Grange, R. L.; Porzelle, A.; Johns, J. P.; Parsons, P. G.; Gordon, V. A.; Reddell, P. W.; Williams, C. M. *Chem. - Eur. J.* **2009**, *15*, 11307. (b) Williams, C. M. Sleepless Nights: The Total Synthesis of the Anticancer Australian Rainforest Polyketide EBC-23. In *Strategies and Tactics in Organic Synthesis*; Harmata, M., Ed.; Academic Press: Oxford, UK, 2014; Vol. *10*, pp 249−270.

(3) Dong, L.; Gordon, V. A.; Grange, R. L.; Johns, J.; Parsons, P. G.; Porzelle, A.; Reddell, P.; Schill, H.; Williams, C. M. *J. Am. Chem. Soc.* **2008**, *130*, 15262.

(4) Albert, B. J.; Yamaoka, Y.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 2610.

(5) (a) Yadav, J. S.; Chetia, L. *Org. Lett.* **2007**, *9*, 4587. (b) Yadav, J. S.; Rajender, V.; Rao, Y. G. *Org. Lett.* **2010**, *12*, 348. (c) Sabitha, G.; Rao, A. S.; Yadav, J. S. *Org. Biomol. Chem.* **2013**, *11*, 7218. (d) Yadav, J. S.; Reddy, P. A. N.; Reddy, Y. J.; Meraj, S.; Prasad, A. R. *Eur. J. Org. Chem.* **2013**, *2013*, 6317.

(6) (a) Arundale, E.; Mikeska, L. A. *Chem. Rev.* **1952**, *51*, 505. (b) Klunder, J. M.; Onami, T.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 1295. (c) Yadav, J. S.; Reddy, Y. J.; Reddy, P. A. N.; Reddy, B. V. S. *Org. Lett.* **2013**, *15*, 546. (d) Brun, E.; Bellosta, V.; Cossy, J. *Chem. Commun.* **2014**, *50*, 6718. (e) Brun, E.; Bellosta, V.; Cossy, J. *J. Org. Chem.* **2015**, *80*, 8668.

(7) (a) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 935. (b) Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679. (c) Yadav, J. S.; Kumar, N. N.; Reddy, M. S.; Prasad, A. R. *Tetrahedron* **2007**, *63*, 2689.

(8) Yadav, J. S.; Reddy, P. A. N.; Kumar, A. S.; Prasad, A. R.; Reddy, B. V. S.; Al Ghamdi, A. A. *Tetrahedron Lett.* **2014**, *55*, 1395.

(9) Rychnovsky, S. D.; Richardson, T. I.; Rogers, B. N. *J. Org. Chem.* **1997**, *62*, 2925.

(10) (a) Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478. (b) Yu, W.; Mei, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217. (c) Chakraborty, T. K.; Chattopadhyay, A. K. *J. Org. Chem.* **2008**, *73*, 3578.

(11) (a) Abushanab, E.; Bessodes, M.; Antonakis, K. *Tetrahedron Lett.* **1984**, *25*, 3841. (b) Abushanab, E.; Vemishetti, P.; Leiby, R. W.; Singh, H. K.; Mikkilineni, A. B.; Wu, D. C.; Saibaba, R.; Panzica, R. P. *J. Org. Chem.* **1988**, *53*, 2598. (c) Krishna, P. R.; Lavanya, B.; Sharma, G. V. M *Tetrahedron: Asymmetry* **2003**, *14*, 419. (d) Jung, M. E.; Yoo, D. *Org. Lett.* **2007**, *9*, 3543.

(12) (a) Inanaga, J.; Kawanami, Y.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1521. (b) Lee, J.; Parker, K. A. *Org. Lett.* **2012**, *14*, 2682.

(13) (a) Trost, B. M.; O'Boyle, B. M.; Hund, D. *J. Am. Chem. Soc.* **2009**, *131*, 15061. (b) Sabitha, G.; Rao, A. S.; Sandeep, A.; Yadav, J. S. *Eur. J. Org. Chem.* **2014**, *2014*, 455.

(14) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092. (c) Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17. (d) Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nat. Protoc.* **2007**, *2*, 2451.

(15) (a) Kim, H. R.; Yun, J. *Chem. Commun.* **2011**, *47*, 2943. (b) Park, J. K.; Ondrusek, B. A.; Mcquade, D. T. *Org. Lett.* **2012**, *14*, 4790. (c) Moure, A. L.; Gomez Arrayás, R.; Cárdenas, D. J.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc.* **2012**, *134*, 7219. (d) Semba, K.; Fujihara, T.; Terao, J.; Tsuji, Y. *Chem. - Eur. J.* **2012**, *18*, 4179. (e) Moure, A. L.; Mauleón, P.; Arrayás, R. G.; Carretero, J. C. *Org. Lett.* **2013**, *15*, 2054. (f) Barbeyron, R.; Benedetti, E.; Cossy, J.; Vasseur, J. J.; Arseniyadis, S.; Smietana, M. *Tetrahedron* **2014**, *70*, 8431.

(16) (a) Jung, M. E.; Yoo, D. *Org. Lett.* **2011**, *13*, 2698. (b) Liu, P.; Fukui, Y.; Tian, P.; He, Z.; Sun, C.; Wu, N.; Lin, G. *J. Am. Chem. Soc.* **2013**, *135*, 11700.

(17) Tursun, A.; Canet, I.; Aboab, B.; Sinibaldi, M. E. *Tetrahedron Lett.* **2005**, *46*, 2291.

(18) (a) Deslongchamps, P.; Rowan, D. D.; Pothier, N.; Sauve, G.; Saunders, J. K. *Can. J. Chem.* **1981**, *59*, 1105. (b) Deslongchamps, P. Stereoelectronic Effects in Organic Synthesis. In *Organic Chemistry Series*; Baldwin, J., Ed.; Pergamon Press: Oxford, UK, 1983; Vol. *1*, pp 5−53. (c) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617. (d) Juaristi, E.; Cuevas, G. *Tetrahedron* **1992**, *48*, 5019. (e) Takaoka, L. R.; Buckmelter, A. J.; LaCruz, T. E.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2005**, *127*, 528. (f) Aho, J. E.; Pihko, P. M.; Rissa, T. K. *Chem. Rev.* **2005**, *105*, 4406. (g) Trost, B. M.; O'Boyle, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 16190.

(19) (a) Denmark, S. E.; Kobayashi, T.; Regens, C. S. *Tetrahedron* **2010**, *66*, 4745. (b) Brandt, D.; Dittoo, A.; Bellosta, V.; Cossy, J. *Org. Lett.* **2015**, *17*, 816.

(20) (a) Utimoto, K. *Pure Appl. Chem.* **1983**, *55*, 1845. (b) Trost, B. M.; Horne, D. B.; Woltering, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5987.

(21) Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem.* **1998**, *110*, 1475; *Angew. Chem., Int. Ed.* **1998**, *37*, 1415.

(22) Dubé, P.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 12062 and refs therein.

(23) (a) Antoniotti, S.; Genin, E.; Michelet, V.; Genêt, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 9976. (b) Liu, B.; De Brabander, J. K. *Org. Lett.* **2006**, *8*, 4907. (c) Li, Y.; Zhou, F.; Forsyth, C. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 279. (d) Fang, C.; Pang, Y.; Forsyth, C. J. *Org. Lett.* **2010**, *12*, 4528. (e) Tlais, S. F.; Dudley, G. B. *Beilstein J. Org. Chem.* **2011**, *7*, 570. (f) Benson, S.; Collin, M. P.; Arlt, A.; Gabor, B.; Goddard, R.; Fürstner, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 8739. (g) Wang, X.; Paxton, T. J.; Li, N.; Smith, A. B., III. *Org. Lett.* **2012**, *14*, 3998.

(24) (a) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974. (b) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. *J. Am. Chem. Soc.* **2001**, *123*, 9535.

(25) (a) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405. (b) Ando, K. *Tetrahedron Lett.* **1995**, *36*, 4105. (c) Pihko, P. M.; Salo, T. M. *Tetrahedron Lett.* **2003**, *44*, 4361. (d) Reddy, D. V.; Sabitha, G.; Yadav, J. S. *Tetrahedron Lett.* **2015**, *56*, 4112.

DOI: 10.1021/acs.orglett.6b01849
Org. Lett. 2016, 18, 4202−4205