Organic LETTERS

Letter

pubs.acs.org/OrgLett

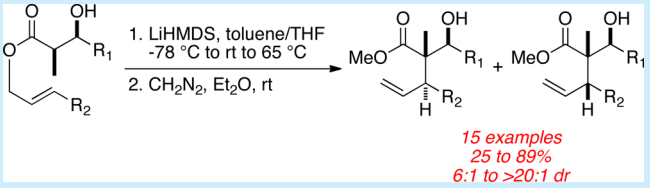
# Stereoselective Synthesis of Quaternary Carbons via the Dianionic Ireland–Claisen Rearrangement

Michael T. Crimmins,* John D. Knight, Philip S. Williams, and Yan Zhang

Kenan, Caudill, Murray and Venable Laboratories of Chemistry University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599, United States

Supporting Information

**ABSTRACT:** A dianionic Ireland–Claisen rearrangement of chiral, nonracemic $\alpha$-methyl-$\beta$-hydroxy allylic esters has been developed that proceeds with high diastereoselectivity and provides products containing three contiguous stereogenic carbons, including a quaternary center. The potential utility of the rearrangement for complex molecule synthesis is also demonstrated.

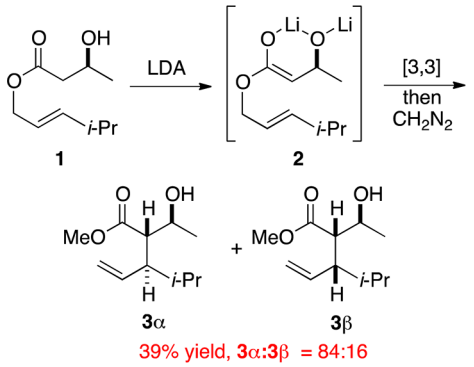



The Claisen rearrangement was first reported in 1912 and has become one of the most powerful methods for carbon–carbon bond formation in organic synthesis[1] as illustrated by the successful application of its numerous variants to natural product synthesis.[2] The Ireland–Claisen rearrangement, which proceeds through the enolate or the corresponding silyl ketene acetal of an allylic ester, affords pentenoic acid derivatives at moderate temperatures with a high degree of stereoselectivity.[1d]

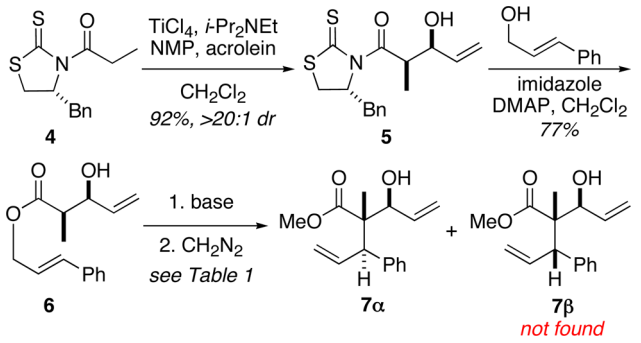
The dianionic Ireland–Claisen rearrangement that employs $\beta$-hydroxy allyl esters was independently reported by Fujisawa and Kurth in the early 1980s.[3,4] In the original report, Kurth showed that when allyl $\beta$-hydroxy ester **1** was exposed to an excess of strong base, the resulting $\beta$-alkoxy enolate **2** underwent a chelate-controlled [3,3]-sigmatropic rearrangement to give two diastereomeric pentenoic acid products (**3**) demonstrating that the $\beta$-hydroxy group could serve as a stereochemical directing element.[3] While the yields and diastereoselectivity obtained were moderate, higher selectivity was observed with more sterically demanding substrates (Scheme 1). All the examples reported by Fujisawa and Kurth involved the use of racemic substrates and lack $\alpha$-substitution in the starting ester substrate. No examples that produced single enantiomers or quaternary carbon centers have been reported. Since these initial reports, further investigation of this transformation has been limited to an attempt by Gilbert to use the reaction in a synthesis of (−)-trichodiene.[5]

We were interested in extending the dianionic Ireland–Claisen rearrangement to include chiral, nonracemic substrates bearing an $\alpha$-substituent to the ester that could lead to pentenoic acid derivatives bearing three contiguous stereogenic centers, including an all-carbon quaternary center, in a highly enantioselective fashion. Establishment of quaternary carbon centers has been previously achieved through Claisen rearrangements but not through the dianionic Ireland–Claisen reaction.[6] The requisite enantioenriched substrate for the initial investigation was obtained through the use of a thiazolidinethione-mediated propionate aldol reaction of *N*-propionylthiazolidinethione **4** with acrolein to give aldol adduct **5** (Scheme 2).[7] Nucleophilic displacement of the chiral auxiliary by direct transesterification under mild conditions with cinnamyl alcohol

**Scheme 1. Example of Dianionic Ireland–Claisen Rearrangement Reported by Kurth**




**Scheme 2. Synthesis of Dianionic Ireland–Claisen Substrate**




**Received:** March 20, 2014
**Published:** April 15, 2014





dx.doi.org/10.1021/ol5008422 | Org. Lett. 2014, 16, 2458–2461

in the presence of imidazole and DMAP produced allyl ester **6**, which became the initial focus for our study on the dianionic Ireland–Claisen rearrangement.

Initially, allylic ester **6** was treated with excess LDA in THF in a manner similar to the conditions reported by Kurth.[3] The rearrangement occurred at room temperature (Table 1, entry 1) to give a single diastereomeric product (**7α**) whose absolute configuration was confirmed by X-ray crystallography. The yield was further enhanced by substituting LiHMDS as the base (entry 2). Changing the solvent to diethyl ether resulted in reduced yield without a reduction in diastereoselectivity, however conducting the reaction in toluene improved the yield with an accompanying small decrease in diastereoselectivity (entries 3 and 4). In all cases, the only byproduct obtained was cinnamyl alcohol, which likely results from deacylation of the intermediate alkoxy enolate.[8] Because the production of cinnamyl alcohol was minimized in toluene solvent and the diastereoselectivity was maximized in THF, the rearrangement was conducted in toluene with the addition of a small amount of THF (4 equiv). Under these conditions, the yield was similar to that using toluene alone without compromising the diastereoselectivity (entry 5). Variation of the alkali metal counterion in toluene/THF gave no improvement. While selectivity was maintained when NaHMDS was used as a base, the overall yield was significantly lower (entry 6) and the potassium alkoxy enolate prepared with KHMDS decomposed upon warming above −78 °C (entry 7). The addition of Mg- and Zn-based salts, which have been shown to improve both the yield and diastereoselectivity of other Ireland–Claisen-type rearragements,[9] did not improve the overall yield.

**Table 1. Initial Investigation of Dianionic Ireland–Claisen Reaction with Ester 6**

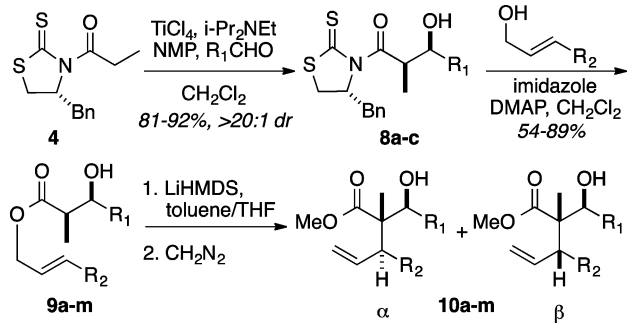
| | solvent | base | temp (°C) | yield (%) | $\alpha$:$\beta^a$ |
|---|---|---|---|---|---|
| 1 | THF | LDA | −78 to 25 | 45 | 20:1 |
| 2 | THF | LiHMDS | −78 to 25 | 60 | 20:1 |
| 3 | $Et_2O$ | LiHMDS | −78 to 25 | 41 | 20:1 |
| 4 | toluene | LiHMDS | −78 to 25 | 75 | 9:1 |
| 5 | toluene/THF[b] | LiHMDS | −78 to 25 | 72[c,d] | 20:1 |
| 6 | toluene/THF[b] | NaHMDS | −78 to 25 | 26 | 20:1 |
| 7 | toluene/THF[b] | KHMDS | −78 to 25 | dec | |

[a]Diastereoselectivity determined by $^1$H NMR by observing the $OCH_3$ signal and/or the $CH_3$ signal of the quaternary carbon. [b]Reactions were conducted in toluene with 4.0 equiv of THF added prior to addition of ester. [c]With 1.0 equiv of anhydrous $MgBr_2$, the yield was 73%. [d]With 1.0 equiv of anhydrous $ZnCl_2$, the yield was 65%.

With an acceptable set of conditions in hand, we next sought to investigate the substrate scope of the dianionic Ireland–Claisen rearrangement. Various allylic esters were prepared in a manner similar to ester **6** where both the initial aldehyde used in the aldol addition step and the allylic alcohol used in the esterification step were varied (see Table 2).

Although all allyl esters from propenal aldol adducts underwent the rearrangement step at room temperature (Table 2, entries 1–3), using esters of aldol adducts derived from 3-butenal (entries 4–7), 4-pentenal (entries 8–11), benzaldehyde (entry 12), or methacrolein (entry 13) required a higher reaction temperature of 65 °C for the rearrangement to proceed. Not surprisingly, the diastereoselectivity of the rearrangement was lower for esters derived from allylic alcohols with sterically smaller substituents (entries 1 and 2) when compared to ester **6**. Interestingly, however, increasing the steric bulk of the $R_1$ position led to a noticeable increase in diastereoselectivity to the point that a single diastereomer was obtained in many cases even when the substituent at $R_2$ was relatively small (see entries 5, 10, 12, and 13). In general, the yields were moderate to good with the only byproduct obtained being the corresponding allylic alcohol, presumably as a result of deacylation of the enolate dianion. Attempts to prepare the silyl ketene acetal of the alkoxy enolate to compare the rates and diastereoselectivity to the dianionic process were unsuccessful.[10]

**Table 2. Dianionic Ireland–Claisen of Other Substrates**




| | $R_1$ | $R_2$ | temp (°C) | pdt | yield(%) | $\alpha$:$\beta^a$ |
|---|---|---|---|---|---|---|
| 1 | | Et | -78 to 25 | **10a** | 38 | 6:1 |
| 2 | | *n*-Pr | -78 to 25 | **10b** | 44 | 9:1 |
| 3 | | *i*-Pr | -78 to 25 | **10c** | 25 | >20:1 |
| 4 | | Ph | -78 to 65 | **10d** | 73 | >20:1 |
| 5 | | Et | -78 to 65 | **10e** | 53 | >20:1 |
| 6 | | *n*-Pr | -78 to 65 | **10f** | 48 | >20:1 |
| 7 | | *i*-Pr | -78 to 65 | **10g** | 50 | >20:1 |
| 8 | | Ph | -78 to 65 | **10h** | 89 | >20:1 |
| 9 | | Et | -78 to 65 | **10i** | 62 | >20:1 |
| 10 | | *n*-Pr | -78 to 65 | **10j** | 57 | >20:1 |
| 11 | | *i*-Pr | -78 to 65 | **10k** | 43 | >20:1 |
| 12 | | Et | -78 to 65 | **10l** | 44 | 9:1 |
| 13 | | Et | -78 to 65 | **10m** | 43 | 9:1 |

[a]Diastereoselectivity determined by $^1$H NMR.

The high diastereoselectivity of the process is consistent with a chelated chairlike transistion state **11** shown in Figure 1. The alkene of the allylic alcohol approaches the enolate from the opposite side of the $\beta$-substituent of the enolate ($R_1$), thus minimizing unfavorable steric interactions.[6c]

The ability to construct an all-carbon quaternary center while simultaneously setting the configuration of three contiguous asymmetric centers is potentially useful in the preparation of complex synthetic intermediates. As part of a broader program directed toward the synthesis of marine natural products,[11,12] we were attracted to the class of briarane diterpenes because of their unique structural features and interesting biological properties. The briaranes are highly oxygenated marine metabolites that possess a modified cembranoid skeleton.[13]

Examination of the core structure of briarane diterpenes reveals a *trans*-fused 6,10 carbon-ring system with an angular methyl group completing the substitution of a quaternary


dx.doi.org/10.1021/ol5008422 | Org. Lett. 2014, 16, 2458–2461

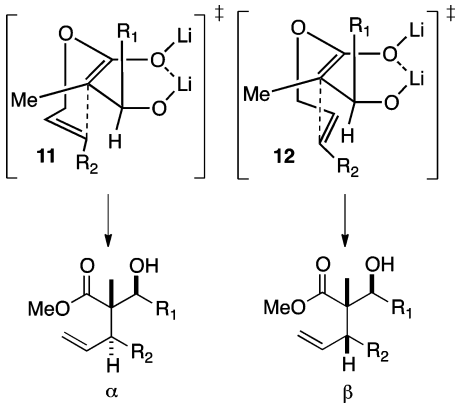
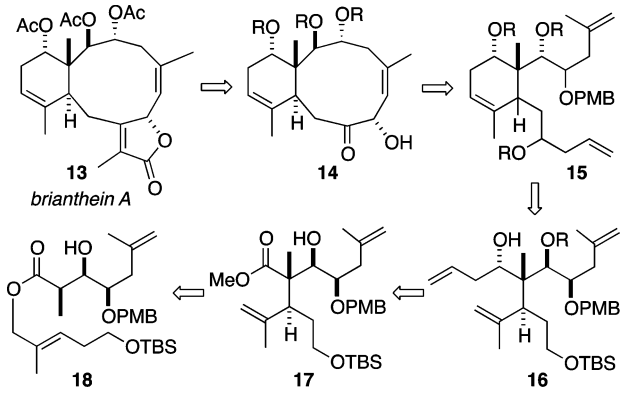



**Figure 1.** Proposed transition states leading to the observed products.

carbon at the ring fusion.[18,19] Prior synthetic approaches to the briaranes have led to progress toward the 6,10 ring fusion, but no total synthesis has been reported to date.[14−17] Of the many briaranes that have been isolated and identified, we focused our initial efforts on the core of brianthein A (Scheme 3, **13**) due to

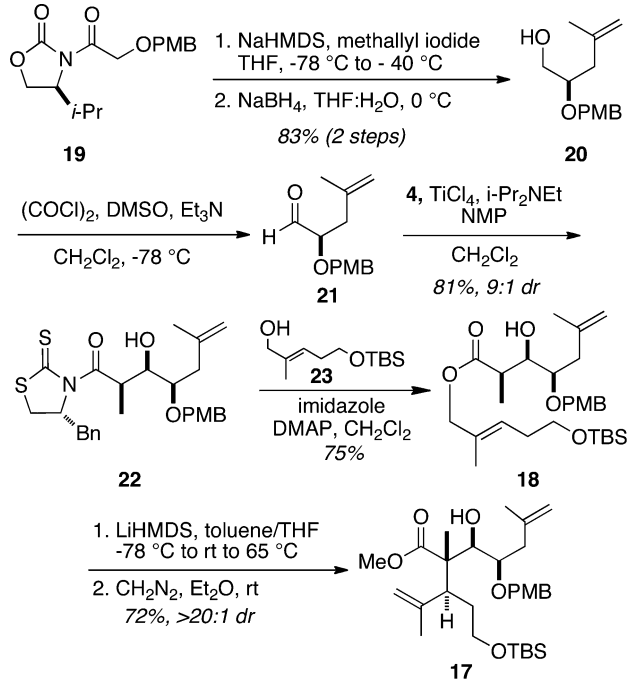
**Scheme 3. Proposed Retrosynthesis of Brianthein A**




its relatively low level of oxygenation and interesting biological activity profile, including its ability to reverse multidrug resistance in human carcinoma cell lines.[20] Retrosynthetically, the required ring fusion stereochemistry could be established early in the synthesis via a dianionic Ireland−Claisen rearrangement of ester **18** to give the substituted pentenoic acid **17** followed by the construction of the 6,10 bicyclic system to give the core structure (**14**).

The preparation of hydroxy ester **18** for the key rearrangement step is illustrated in Scheme 4. Aldehyde **21**, required for the initial auxiliary-mediated aldol addition, was prepared in three steps from glycolyloxazolidinone **19**. Alkylation[21] of the sodium enolate of **19** with methallyl iodide followed by reductive cleavage of the auxiliary afforded alcohol **20**, which was oxidized to aldehyde **21** under Swern conditions.[22] Subsequent auxiliary-mediated aldol addition of thiazolidinethione **4** with aldehyde **21** gave aldol adduct **22** in good yield and 9:1 diastereoselectivity. Exposure of aldol adduct **22** to alcohol **23**, imidazole, and catalytic DMAP over 72 h afforded the dianionic Ireland−Claisen substrate **18**. Upon treatment of allylic ester **18** with LiHMDS, under optimized conditions for the dianionic Ireland−Claisen rearrangement, the rearranged product **17** was obtained as a single diastereomer in 72% yield. This rearrangement successfully established the necessary two contiguous stereocenters that would constitutute the ring

**Scheme 4. Prepration of Substrate for the Synthesis of Brianthein A**




juncture for the briarane core structure as well as the two additional resident carbinol stereocenters of the 10-membered carbocycle. Further work toward the synthesis of brianthein A, including the synthesis of the 6,10-fused ring system, is currently ongoing.

In summary, we have extended previous work on the dianionic Ireland−Claisen rearrangement to include chiral, nonracemic allylic esters with $\alpha$-substitution. The rearrangement proceeds with good facial selectivity to give products containing three contiguous asymmetric carbons, including an all-carbon quaternary center. The prepararation of an intermediate which may prove valuable for further studies toward the synthesis of the marine natural product brianthein A was also accomplished.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, full spectroscopic data for all new compounds, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

### Corresponding Author

*E-mail: crimmins@email.unc.edu.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

Financial support from the National Institute of General Medical Sciences (GM60567) is acknowledged.

## ■ REFERENCES

(1) (a) Enders, D.; Knopp, M.; Schiffers, R. *Tetrahedron: Asymmetry* **1996**, *7*, 1847. (b) Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939. (c) Ito, H.; Taguchi, T. *Chem. Soc. Rev.* **1999**, *28*, 43. (d) For a leading

reference, see: Ireland, R. E.; Wipf, P.; Armstrong, J. D. *J. Org. Chem.* **1991**, *56*, 650. (e) Williams, D. R.; Nag, P. P. In *Name Reactions for Homologations Part II*; Lie, J. J., Ed.; Wiley: New York, 2009; pp 33−87.

(2) (a) Chai, Y.; Hong, S.-p.; Lindsay, H. A.; McFarland, C.; McIntosh, M. C. *Tetrahedron* **2002**, *58*, 2905. (b) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Org. Chem.* **1976**, *41*, 986. (c) Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wicox, C. S. *J. Org. Chem.* **1980**, *45*, 48. (d) Irealand, R. E.; Daub, J. P. *J. Org. Chem.* **1991**, *46*, 479. (e) Corey, E. J.; Roberts, B. E.; Dixon, B. R. *J. Am. Chem. Soc.* **1995**, *117*, 193. (f) Corey, E. J.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 1229. (g) Hong, S.-p.; McIntosh, M. C. *J. Org. Chem.* **2004**, *69*, 4185. (h) Ariza, X.; Fernandez, N.; Garcia, J.; Lopez, M.; Montserrat, L.; Ortiz, J. *Synthesis* **2004**, 128. (i) Picoul, W.; Urchegui, R.; Haudrechy, A.; Langlois, Y. *Tetrahedron Lett.* **1999**, *40*, 4797. (j) Majumdar, K. C.; Nandi, R. K. *Tetrahedron* **2013**, *69*, 6921.

(3) Kurth, M. J.; Yu, C. M. *Tetrahedron Lett.* **1984**, *25*, 5003. (b) Kurth, M. J.; Yu, C. M. *J. Org. Chem.* **1985**, *50*, 1840. (c) Kurth, M. J.; Beard, R. L. *J. Org. Chem.* **1988**, *53*, 4085.

(4) Fujisawa, T.; Tajima, K.; Ito, M.; Sato, T. *Chem. Lett.* **1984**, 1169.

(5) Gilbert, J. C.; Selliah, R. D. *J. Org. Chem.* **1993**, *58*, 6255−6265.

(6) (a) Williams, D. R.; Klein, J. C.; Chow, N. S. C. *Tetrahedron Lett.* **2011**, *52*, 2120. (b) Williams, D. R.; Mondal, P. K.; Bawel, S. A.; Nag, P. P. *Org. Lett.* **2014**, *16*, 1956. (c) Williams, D. R.; Walsh, M. J.; Miller, N. A. *J. Am. Chem. Soc.* **2009**, *131*, 9039.

(7) (a) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *65*, 894. (b) Crimmins, M. T.; Chaudhary, K. *Org. Lett.* **2000**, *2*, 775.

(8) (a) Evans, D. A.; Ennis, M. C.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1752 and references cited therein. (b) Struder, A.; Hinterman, T.; Seebach, D. *Helv. Chim. Acta* **1995**, *78*, 1185. (c) Casper, D. M.; Blackburn, J. R.; Maroules, C. D.; Brady, T.; Eksen, J. M.; Ferrence, G. M.; Standard, J. M.; Hithcock, S. M. *J. Org. Chem.* **2002**, *67*, 8871.

(9) Selected examples: (a) Kazmaier, U.; Maier, S. *Tetrahedron* **1996**, *52*, 941. (b) Krebs, A.; Kazmaier, U. *Terahedron Lett.* **1996**, *37*, 7945.

(10) Tsunoda, T.; Tatsuki, S.; Shiraishi, Y.; Akasaka, M.; Ito, S. *Tetrahedron Lett.* **1993**, *34*, 3297.

(11) Crimmins, M. T.; Brown, B. H. *J. Am. Chem. Soc.* **2004**, *126*, 10264.

(12) Crimmins, M. T.; Mans, M. C.; Rodríguez, A. D. *Org. Lett.* **2010**, *12*, 5028.

(13) (a) Faulker, D. J. *Nat. Prod. Rep.* **1995**, *12*, 223 and earlier reviews in this series and references cited therein. For reviews of briarane-type diterpenes, see: (b) Sung, P.-J.; Sheu, J.-H.; Xu, J.-P. *Heterocycles* **2002**, *57*, 535. (c) Sung, P.-J.; Chang, P.-C.; Fang, L.-S.; Sheu, J.-H.; Chen, W.-C.; Chen, Y.-P.; Lin, M.-L. *Heterocycles* **2005**, *55*, 195. (d) Sung, P.-J.; Sheu, J.-H.; Wang, W.-H.; Fang, L.-S.; Chung, H.-M.; Pai, C.-H.; Su, Y.-D.; Tsai, W.-T.; Chen, B. Y.; Lin, M.-R.; Li, G.-Y. *Heterocycles* **2008**, *75*, 2627.

(14) Ellis, J. M.; Crimmins, M. T. *Chem. Rev.* **2008**, *108*, 5278.

(15) (a) Roe, M. B.; Whittaker, M.; Procter, G. *Tetrahedron Lett.* **1995**, *36*, 8103. (b) Balasubramaniam, R. P.; Moss, D. K.; Wyatt, J. K.; Spence, J. D. *Tetrahedron* **1997**, *53*, 7429.

(16) Iwasaki, J.; Ito, H.; Nakamura, M.; Iguchi, K. *Tetrahedron Lett.* **2006**, *47*, 1483.

(17) Bates, R. W.; Pinsa, A.; Kan, X. *Tetrahedron* **2010**, *66*, 6340.

(18) Christoffers, J.; Baro, A. *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Wiley-VCH: New York, 2005.

(19) Petersen, E. A.; Overman, L. E. *Proced. Nat. Acad. Sci. U.S.A.* **2004**, *101*, 11493.

(20) Aoki, S.; Okano, M.; Matsui, K.; Itoh, T.; Satari, R.; Akiyama, S.-i.; Kobayashi, M. *Tetrahedron* **2001**, *57*, 8951.

(21) Crimmins, M. T.; Emmitte, K. A.; Katz, J. D. *Org. Lett.* **1999**, *1*, 953.

(22) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.



dx.doi.org/10.1021/ol5008422 | *Org. Lett.* 2014, 16, 2458−2461