

Efficient and Selective Syntheses of (all-*E*)- and (6*E*,10*Z*)-2'-*O*-Methylmyxalamides D via Pd-Catalyzed Alkenylation–Carbonyl Olefination Synergy

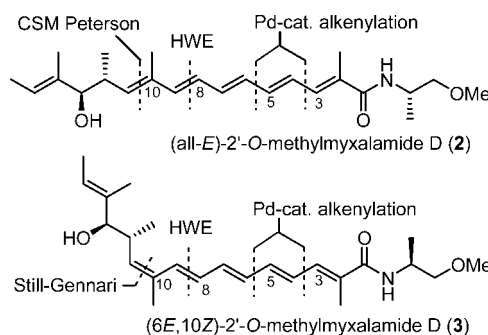
Guangwei Wang, Zhihong Huang, and Ei-ichi Negishi*

Herbert C. Brown Laboratories of Chemistry, Purdue University, 560 Oval Drive, West Lafayette, Indiana 47907-2084

negishi@purdue.edu

Received May 14, 2008

ABSTRACT



Highly efficient and selective syntheses of both (all-*E*) and (6*E*,10*Z*)-isomers of 2'-*O*-methylmyxalamide D (**2** and **3**), in which the crucial conjugated pentaene moieties were assembled in $\geq 98\%$ stereoselectivity through the use of two Pd-catalyzed alkenylation reactions, the Horner–Wadsworth–Emmons (HWE) olefination, and either the Corey–Schlessinger–Mills modified (CSM-modified) Peterson olefination for **2** or the Still–Gennari olefination for **3**, are reported. Either **2** or **3** was prepared in 16% yield in seven steps from propargyl alcohol.

Ojika and co-workers reported in 2004 the isolation and identification of three polyene antifungal agents **1**–**3** from the myxobacterium *Cystobacter fuscus*.¹ 2'-*O*-Methylmyxalamide D (**1a**) is an *O*-methylated derivative of the previously known myxalamide D (**1b**),² and the other two are its (6*E*)-isomer (**2**) and (6*E*,10*Z*)-isomer (**3**) (Figure 1). Myxalamide D (**1b**), 2'-*O*-methylmyxalamide D (**1a**) and its (6*E*)-isomer (**2**) have recently been synthesized by using the Pd-catalyzed cross-coupling with (all-*E*)-1-stanna-6-bora-1,3,5-hexatriene.³ To the best of our knowledge, however,

the (6*E*,10*Z*)-isomer (**3**) does not appear to have been synthesized.

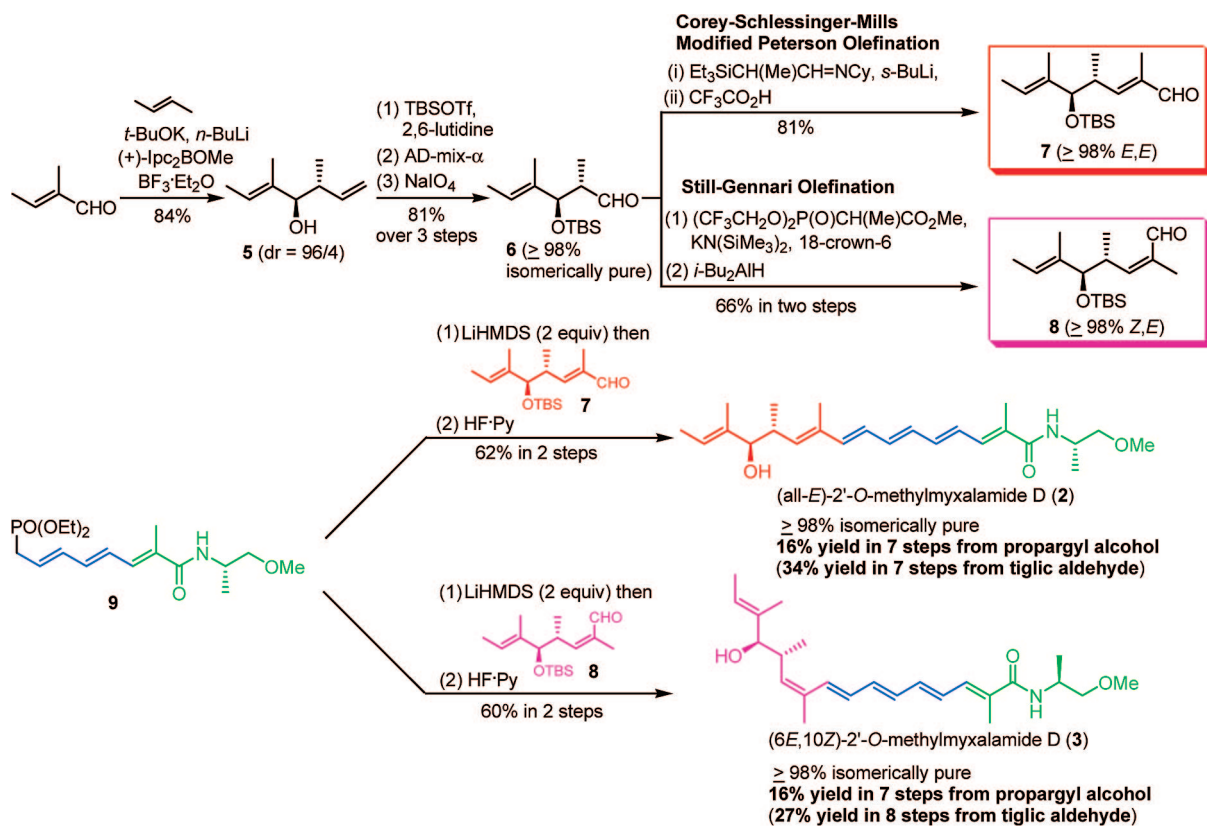
Over the past few decades, two methodologically discrete routes to regio- and stereodefined alkenes have been developed as widely applicable and selective methods. Carbonyl olefination,⁴ especially variants of the Wittig reaction^{4a} including the *E*-selective Horner–Wadsworth–Emmons (HWE hereafter) reaction^{4b,c} and its *Z*-selective Still–Gennari modification,^{4d} as well as the Corey–Schlessinger–Mills modified Peterson olefination (CSM-modified Peterson olefination hereafter),^{4e–g} can in some cases be highly stereoselective ($\geq 98\%$). Much more widely applicable and

(1) Kundim, B. A.; Itou, Y.; Sakagami, Y.; Fudou, R.; Yamanaka, S.; Ojika, M. *Tetrahedron* **2004**, *60*, 10217–10221.

(2) Jansen, R.; Reifensahl, G.; Gerth, K.; Reichenbach, H.; Höfle, G. *Liebigs Ann. Chem.* **1983**, 1081–1095.

(3) Coleman, R. S.; Lu, X.; Modolo, I. *J. Am. Chem. Soc.* **2007**, *129*, 3826–3827.

Scheme 1



strictly stereoselective (≥ 98 –99%) in most cases is the *Pd*-catalyzed alkenylation.⁵ Nevertheless, other synthetic require-

A case in point is the synthesis of allylically Me-branched trisubstituted alkenes (**4**) that can be most readily and selectively prepared by either the CSM-modified Peterson olefination (*E*-isomers)^{4c–g} or the Still–Gennari-modified HWE reaction (*Z*-isomer).^{4d}

Herein, we report highly efficient and selective syntheses of both (all-*E*) and (6*E*,10*Z*)-isomers of 2'-*O*-methylmyxalamide D (**2** and **3**), in which the crucial conjugated pentaene moieties are assembled in $\geq 98\%$ stereoselectivity through the use of two *Pd*-catalyzed alkenylation reactions for the formation of the C3–C4 and C5–C6 bonds, the HWE olefination for the C8–C9 double bond, and either the CSM-modified Peterson olefination (for **2**) or the Still–Gennari olefination (for **3**) for the formation of the C10–C11 double bond. As summarized in Schemes 1 and 2, either **2** or **3** was

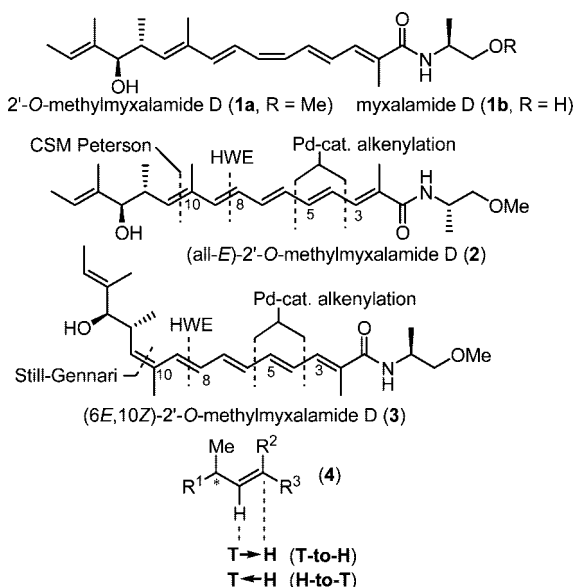


Figure 1. Myxalamide D and its derivatives.

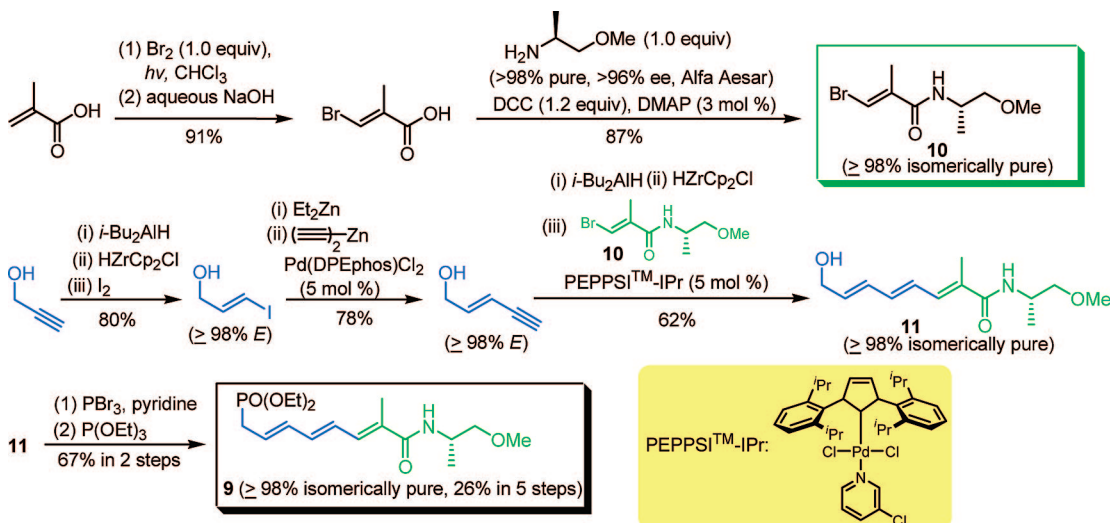
ments and restrictions have made it desirable to use both methods, i.e., *alkenylation*–*carbonyl olefination synergy*.⁶

(4) For a review of the Wittig and related olefinations, see: (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, 89, 863–927. (b) Horner, L.; Hoffmann, H.; Wippel, J. H. G.; Klahre, G. *Chem. Ber.* **1959**, 92, 2499–2505. (c) Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Soc. Chem.* **1961**, 83, 1733–1738. (d) For a seminal work on the Still–Gennari olefination, see: Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, 24, 4405–4408. (e) Corey, E. J.; Enders, D.; Bock, M. G. *Tetrahedron Lett.* **1976**, 7–10. (f) Schlessinger, R. H.; Poss, M. A.; Richardson, S.; Lin, P. *Tetrahedron Lett.* **1985**, 26, 2391–2394. (g) Desmond, R.; Mills, S. G.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1988**, 29, 3895–3898.

(5) For reviews on *Pd*-catalyzed alkenylation, see: (a) Negishi, E., Ed. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley-Interscience: New York, 2002; 2 Vols., pp 3279; Chap. III.2.6, pp 335–408; Chap. III.2.14.2, pp 721–766; Chap. III.2.15, pp 767–789; Chap. III.2.17, pp 807–823; Chap. III.2.18, pp 863–942. (b) Negishi, E.; Hu, Q.; Huang, Z.; Qian, M.; Wang, G. *Aldrichimica Acta* **2005**, 38, 71–88.

(6) Negishi, E.; Huang, Z.; Wang, G.; Mohan, S.; Wang, C.; Hattori, H. *Acc. Chem. Res.*, submitted.

Scheme 2



prepared in 16% overall yield in just seven steps from propargyl alcohol. In fact, the overall yield of **2** in the same seven steps from tiglic aldehyde ($\geq 96\%$, Aldrich) is significantly higher at 34%, while the overall yield of **3** in eight steps in the longest linear sequence is 27%. Except in the Brown crotylboration of tiglic aldehyde ($\geq 96\%$) producing a 96/4 diastereomeric mixture of **5** and requiring chromatographic isomer separation after the conversion of **5** into **6**, no isomer formation was detectable throughout either of the two syntheses. The ready availability of **5** in one step, its high yielding three-step conversion to **6**, and one- or two-step conversion of **6** into isomerically $\geq 98\%$ pure **7** or **8** dictated their HWE olefination with the trienoic amide containing phosphonate (**9**) prepared in 26% yield in five steps from propargyl alcohol (or in 33% yield in five steps from methacrylic acid) via a series of two Pd-catalyzed alkenylation reactions followed by phosphonation, as detailed in Scheme 2.

Of various selective and asymmetric routes^{3,7–11} to two key intermediates **7** and **8** tested and/or considered, the one via the Brown crotylboration⁷ of tiglic aldehyde proved to be the most efficient and selective, albeit noncatalytic (Scheme

1). Thus, the reaction of tiglic aldehyde with a crotylborane reagent generated from *trans*-2-butene and (+)-*B*-methoxydiisopinocampheylborane (Aldrich) according to the literature procedure⁷ afforded **5** in 84% yield. The observed diastereomeric ratio of 96/4 indicates the overall enantiomeric purity to be $>99.9\%$ by virtue of kinetic resolution operative in the crotylboration. After protection of the hydroxyl group with TBSOTf and 2,6-lutidine, the Sharpless dihydroxylation with AD-mix- α ¹² (Aldrich) followed by oxidation with NaIO₄ provided **6**, which was purified by chromatography (Silica gel, 5% EtOAc in hexanes). The yield of $\geq 98\%$ pure **6** was 81% over three steps. For the conversion of **6** to **7**, the CSM-modified Peterson olefination proved to be both efficient requiring just one step and highly stereoselective. The crudely isolated **7** was $\geq 98\%$ *E,E* by ¹³C NMR after simple chromatographic purification, and $\geq 98\%$ pure **7** was obtained in 81% yield (55% yield in five steps from tiglic aldehyde). The Still–Gennari olefination of **6** with (CF₃CH₂O)₂P(O)CH(Me)CO₂Me, KN(SiMe₃)₂, and 18-crown-6 (1.5 equiv)^{4d} proved to be $\geq 98\%$ *Z*-selective. After reduction with *i*-Bu₂AlH, **8** was obtained as a $\geq 98\%$ pure compound in 66% yield over two steps (Scheme 1).

In view of the current high cost of (CF₃CH₂O)₂P(O)CH(Me)CO₂Me and the variable *Z*-selectivity of the Still–Gennari olefination, we initially considered the conversion of **6** to **12** via Corey–Fuchs reaction,¹³ bromoalkyne hydroboration–migratory insertion, zincation–iodinolysis, and Pd-catalyzed alkenylation,^{11c} as depicted in Scheme 3. Even though a model transformation for converting TBDPSOCH₂CH=CH₂ to **14** via **13**¹⁴ was achieved in 30% yield in seven steps, its application to the conversion of **6** to

(7) For the Brown crotylboration, see: (a) Brown, H. C.; Bhatt, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919–5923. (b) Brown, H. C.; Jadhav, P. K.; Bhatt, K. S. *J. Am. Chem. Soc.* **1988**, *110*, 1535–1538.

(8) For the T-to-H (tail-to-head) construction of natural products containing (*E*)-**4** via the CSM-modified Peterson olefination, see: (a) Magnin-Lachaux, M.; Tan, Z.; Liang, B.; Negishi, E. *Org. Lett.* **2004**, *6*, 1425–1427. (b) Zeng, X.; Zeng, F.; Negishi, E. *Org. Lett.* **2004**, *6*, 3245–3248.

(9) For other T-to-H (tail-to-head) routes to (*E*)-**4**, see: (a) Tan, Z.; Negishi, E. *Angew. Chem., Int. Ed.* **2004**, *43*, 2911–2914. (b) Zhu, G.; Negishi, E. *Chem.–Eur. J.* **2008**, *14*, 311–318.

(10) For the H-to-T (head-to tail) construction of (*E*)-**4**, see: Hoyer, T. R.; Temakoon, M. A. *Org. Lett.* **2000**, *2*, 1481–1483.

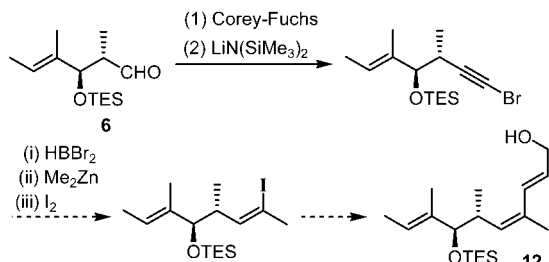
(11) For the T-to-H (tail-to-head) construction of (*Z*)-**4**, see: (a) Panek, J. S.; Hu, T. *J. Org. Chem.* **1997**, *62*, 4912–4913. (b) Panek, J. S.; Hu, T. *J. Org. Chem.* **1997**, *62*, 4914–4915. (c) Arefolov, A.; Panek, J. S. *Org. Lett.* **2002**, *4*, 2397–2400. (d) Roethle, P. A.; Chen, I. T.; Trauner, D. *J. Am. Chem. Soc.* **2007**, *129*, 8960–8961. (e) Tanino, K.; Arakawa, K.; Satoh, M.; Iwata, Y.; Miyashita, M. *Tetrahedron Lett.* **2006**, *47*, 861–864. (f) Tan, Z.; Negishi, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 762–765. (g) Huang, Z.; Negishi, E. *J. Am. Chem. Soc.* **2007**, *129*, 14788–14792.

(12) (a) AD-mix- α : Sharpless asymmetric dihydroxylation agent containing hydroquinone 1,4-phthalazinediyl diether [(DHQD)₂PHAL], K₃Fe(CN)₆, K₂CO₃, and K₂OsO₄·2H₂O. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768–2771. (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.

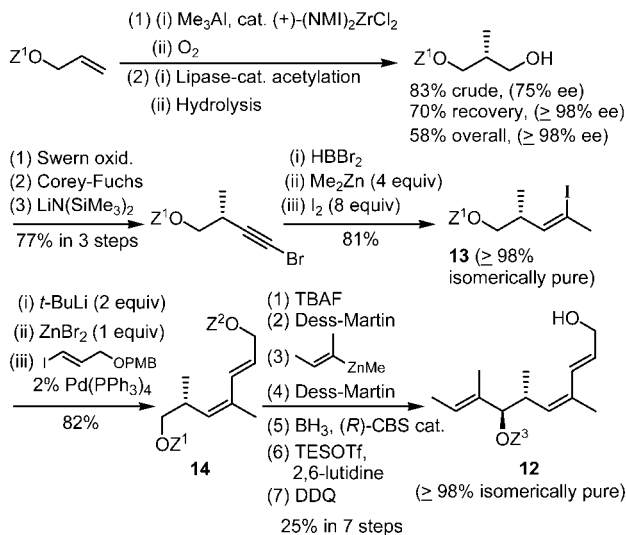
(13) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769–3772.

Scheme 3

Unsuccessful Route



Successful Route



$\text{Z}^1 = \text{TBDPS}$, $\text{Z}^2 = \text{PMB}$, $\text{Z}^3 = \text{TES}$

12 encountered an unexpected and as yet unsolved difficulty in the attempted conversion of the bromoalkyne intermediate to the corresponding iodoalkene. We therefore opted for the conversion of **14** to **12**, which was achieved in 25% yield in seven steps. In the absence of external chiral reagents, the reaction of α -methylaldehyde derived from **14** with (*E*)-2-butenylmethylzinc gave nearly 1:1 C7 epimers of **12** which was converted to **12** of $\geq 98\%$ purity via Dess–Martin oxidation¹⁵ and Corey–Bakshi–Shibata reduction.¹⁶ At this point, however, it became unmistakably clear that the route summarized in Scheme 1 would be superior to that shown in Scheme 3.

For the construction of the C1–C8 fragment **9**, propargyl alcohol was converted to 3-iodoallyl alcohol of $\geq 99\%$ *E* in 80% yield via (i) in situ OH protection with *i*-Bu $_2\text{AlH}$, (ii) hydrozirconation with $\text{HZrCp}_2\text{Cl}\text{-ClAl}(\text{i-Bu})_2$ generated in

situ from *i*-Bu $_2\text{AlH}\text{-ZrCp}_2\text{Cl}_2$,¹⁷ and (iii) iodinolysis all in one pot. Ethynylation¹⁸ of (*E*)-3-iodoallyl alcohol was performed in 78% yield by (i) OH protection with Et_2Zn and (ii) ethynylation with $(\text{HC}\equiv\text{C})_2\text{Zn}$ in the presence of 5 mol % of $\text{Pd}(\text{DPEphos})\text{Cl}_2$. Hydrozirconation of (*E*)-2-penten-4-yn-1-ol performed as in the first step followed by Pd-catalyzed cross-coupling with **10** and 5 mol % of PEPPSI-IPr (98%, Aldrich)¹⁹ provided **11** of $\geq 98\%$ isomeric purity in 62% yield. The required intermediate **10** was prepared in three steps in 79% yield by β -bromination of methacrylic acid²⁰ and amidation with (*S*)-H $_2\text{NCH}(\text{Me})\text{CH}_2\text{OMe}$ (98% pure, Alpha Aesar). As detailed in an upcoming publication, an *N*-heterocyclic carbene-containing PEPPSI-IPr proved to be distinctly superior to $\text{Pd}(\text{PPh}_3)_4$, $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, or $\text{Pd}(\text{DPEphos})\text{Cl}_2$. Thus, **11** was prepared as a $\geq 98\%$ isomerically pure compound in just three steps either from propargyl alcohol (39% overall yield) or from methacrylic acid (49% overall yield) via a series of two Pd-catalyzed alkenylation reactions. Conversion of **11** to **9** via bromination with PBr_3 and pyridine followed by phosphonation with $\text{P}(\text{OEt})_3$ according to the literature²¹ proceeded in 67% yield over two steps (26% from propargyl alcohol or 33% from methacrylic acid in five steps). All isolated compounds were $\geq 98\%$ isomerically pure by ^{13}C NMR either as crude products or as purified compounds. With **7**, **8**, and **9** in hand, the final assembly of **2** and **3** proceeded smoothly as shown in Scheme 1 and described earlier. The spectral data for **2** and **3** are in excellent agreement with those reported in the literature.^{1,3}

In summary, combined use of the Pd-catalyzed alkenylation and carbonyl olefination reactions, such as the HWE olefination, its Still–Gennari modification, and the CSM-modified Peterson olefination, permits efficient and selective synthesis of various oligoenes containing *E*- and/or *Z*-trisubstituted alkenes. This protocol has been applied to the synthesis of (all-*E*)- and (6*E*,10*Z*)-2'-*O*-methylmyxalamides **D** (**2** and **3**).

Acknowledgment. We thank the National Institutes of Health (GM 36792) and Purdue University for support of this research. We also thank Sigma-Aldrich for samples of PEPPSI-IPr and Albemarle for organoaluminum compounds.

Supporting Information Available: Detailed experimental procedures and ^1H and ^{13}C NMR spectra of isolated pure compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL801115S

(14) Liang, B.; Novak, T.; Tan, Z.; Negishi, E. *J. Am. Chem. Soc.* **2006**, 128, 2770–2771.

(15) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, 48, 4155–4156.

(16) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, 53, 2861–2863.

(17) Huang, Z.; Negishi, E. *Org. Lett.* **2006**, 8, 3675–3678.

(18) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, 103, 1979–2017.

(19) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Angew. Chem., Int. Ed.* **2007**, 46, 2768–2813.

(20) Dzierba, C. D.; Zandi, K. S.; Möllers, T.; Shea, K. J. *J. Am. Chem. Soc.* **1996**, 118, 4711–4712.

(21) Lira, R.; Roush, W. R. *Org. Lett.* **2007**, 9, 533–536.