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Two Ene–Yne Metathesis Approaches to the Total Synthesis of Amphidinolide P

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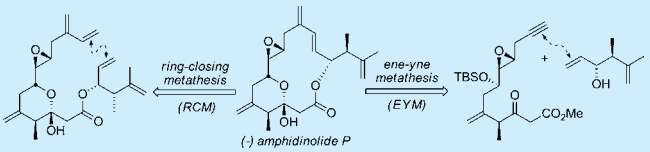
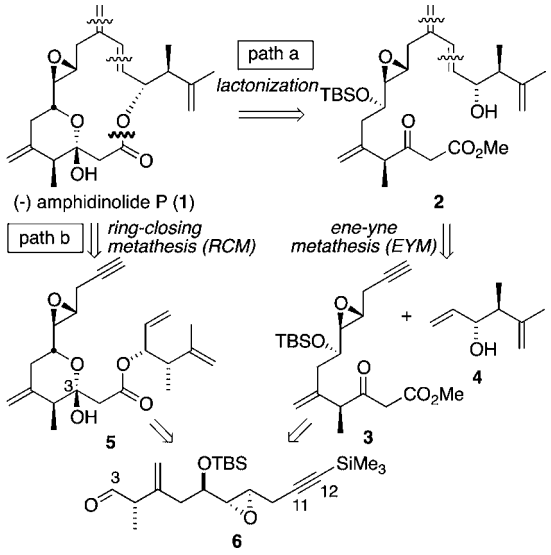
Supporting Information

ABSTRACT: The total synthesis of amphidinolide P was achieved through two different ene–yne metathesis approaches. In each approach, the metathesis step was performed at late stages in the synthesis with all other functionality present. By forging two successful pathways to the synthesis of **1**, some of the strengths and weaknesses of metathesis-intensive synthetic strategies were identified.



Amphidinolide P (**1**) is a cytotoxic macrolide natural product found in the marine dinoflagellate *Amphidinium* sp.[1] It shows mild cytotoxicity against the murine leukemia L1210 cancer cell line and epidermoid carcinoma KB cells with IC_{50}'s of 1.6 and 5.8 μg/mL, respectively. The density of π bonds, oxygen functionality, and seven stereogenic centers make **1** a challenging synthetic target. To date, three total syntheses[2] and one formal synthesis[2g] have been reported but none use an ene–yne metathesis approach. Due to the presence of the 1,3-diene, we envisioned that **1** could be accessed by ruthenium carbene-catalyzed ene–yne metathesis at the last or penultimate step, by either an intramolecular, ring-closing (RCM) enyne metathesis or an intermolecular (cross) ene–yne metathesis (EYM)[3] (Scheme 1). In this letter, we describe the total synthesis of **1** by two different approaches featuring late stage metathesis reactions: an unprecedented low temperature cross ene–yne metathesis[4] and a ring-closing metathesis pathway.

Scheme 1. Retrosynthetic Disconnections of Amphidinolide P Using Ene–Yne Metathesis



Late stage ene–yne metathesis is rare in complex molecule synthesis. Catalytic bond coupling can be problematic in advanced stages of total synthesis due to a high density of multiple functional groups. Specifically, in ene–yne metathesis of terminal alkynes, alkyne oligomerization is a problem that makes ene–yne metathesis more challenging than widely used ene–ene RCM reactions. Though rare, ene–yne metathesis approaches have been used in the early stages of the synthesis of two related amphidinolides, E and K.[5,6] Additionally, functional groups such as alcohols may trigger catalyst decomposition. We were inspired by two syntheses that feature successful late stage ene–yne metathesis. Fürstner et al. used an ethylene–alkyne cross metathesis as the last step to make amphidinolide V.[7] Second, Krische et al. employed a ring-closing diene–alkene metathesis en route to 6-deoxyerythronolide B.[8] These syntheses were successful; however, if a metathesis approach fails at a late stage, the entire synthetic plan may need to be abandoned.[9] A better understanding of metathesis approaches that work (or those that are less successful) at late stages would help inform future synthesis planning using ene–yne metathesis. For a successful ene–yne metathesis, the alkene must be reactive enough to form the metal carbene needed in catalysis[10,11] and alkyne polymerization must be effectively suppressed.

The two metathesis-oriented approaches are outlined in Scheme 1. Path a disconnects the macrocycle into seco ester **2**, which in turn could be garnered by a stereoselective cross (intermolecular) ene–yne metathesis between alkyne **3** and dienol **4**. Alkyne **3** features a terminal alkyne lacking propargylic substitution, a less reactive substrate for EYM. The alkene cross partner **4** bears two different alkenes, which demands chemoselectivity in the metathesis step. In path b, a ring-

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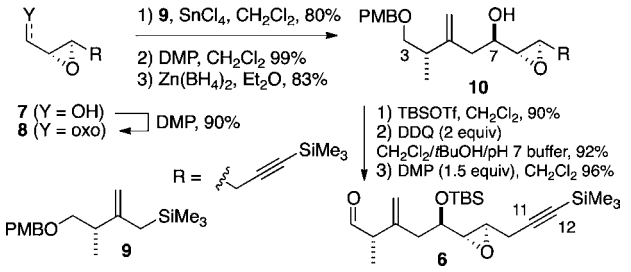
closing enyne metathesis (RCM) of **5** would access **1**. The syntheses of **5** and **3** are each derived from common aldehyde intermediate **6** which possesses the C_3-C_{12} segment of the amphidinolide P backbone.

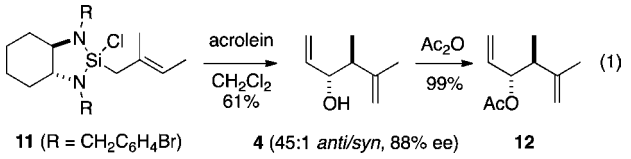
The synthesis commenced with the preparation of the common aldehyde intermediate (Scheme 2). Epoxyalcohol **7**

Scheme 2. Synthesis of Common Aldehyde Intermediate 6



was reported previously in our model studies and is available from commercial starting materials in six steps.[4,12] Oxidation of **7** with the Dess-Martin periodinane gave the aldehyde **8** needed for the Hosomi–Sakurai reaction. In the event, allyl silane **9** underwent transmetalation with $SnCl_4$ giving an intermediate allyl stannane which coupled with **8** in good yield, albeit with low diastereoselectivity. High stereoselectivity was conveniently obtained through a sequential oxidation and chelation-controlled reduction with $Zn(BH_4)_2$. In this way, intermediate **10** was obtained in a >99:1 *anti/syn* ratio. Next, a series of steps were needed to protect the secondary alcohol at C7 and to oxidize the C3 carbon, providing common aldehyde intermediate **6** in 87% overall yield.

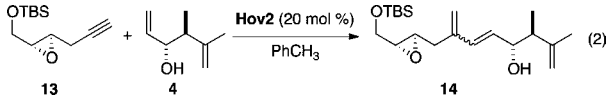
The dienol coupling partner was prepared using Leighton's diastereoselective allyl silane addition to acrolein eq 1.[13] To the



best of our knowledge, acrolein has not been previously used in this allylation. The diastereomer ratio of **4** was assigned based on integration of the diastereomers in the ^{1}H NMR spectrum of the crude mixture: *anti*-**4** had a vicinal J value of 8.5 Hz, similar to the reported J values for *anti*-stereodyads.[13b] Assignment of configuration of the secondary alcohol was made by comparison of the *R*- and *S*-Mosher esters, establishing the *R*-configuration. Dienol **4** is required for the intermolecular pathway. Esterification of **4** gave acetate **12**, a starting material needed for the second, ring-closing metathesis pathway.

At this stage, the chemo- and stereoselective EYM was investigated with a model alkyne. Model alkyne **13** bears an epoxide in close proximity to the alkyne and lacks propargylic substitution (eq 2, Table 1). Terminal, unhindered alkynes are difficult substrates for EYM because they may undergo competitive alkyne polymerization and can trigger catalyst decomposition particularly with the Hoveyda catalyst, **Hov2**.[14] The alkene partner requires a free allylic alcohol for favorable reactivity with **Hov2**,[15] but at the same time can potentially decompose the ruthenium carbenes into Ru hydrides.[16] Using 1.5 equiv of **4**, an excellent yield of diene **14** was obtained (entry 1). Low temperatures produced the highest mass

Table 1. Optimization Studies for the Ene–Yne Metathesis Cross-Coupling



entry[a]	equiv of 4	temp/°C	time/h	yield/%[a]
1	1.5	0	8	80(*E*) + 10(*Z*)[b]
2	1.5	−20	5	53(*E*) + 13(*Z*)[c]
3	3[d]	−20	18	78(*E*) + 22(*Z*)

[a]All reactions were quenched by addition of KO_2CCH_2NC in MeOH. Yield was determined by ^{1}H NMR integration vs internal standard (mesitylene). [b]60% isolated yield; 3% alkyne was recovered. [c]33% alkyne was recovered. [d]Excess **4** was present in the crude reaction mixture; no attempts were made to isolate unreacted **4**.

balances and gave dienol products that were colorless.[17] Significantly, the good mass balance indicated that alkyne polymerization was successfully controlled at the low reaction temperature. Low temperatures are not used in metathesis possibly due to perceptions of low reactivity. However, the Hoveyda catalyst reacts by an associative mechanism,[18] unique among most metathesis catalysts, and concentration is more important. In entries 2–3, alkyne concentration was doubled to 0.12 M allowing lower temperatures to be used. With a longer reaction time, complete conversion was obtained (entry 3). At these catalyst loadings,[19] a ruthenium removal method was critical. We found that treatment with KO_2CCH_2NC was highly effective for the quench and removal of Ru emanating from the metathesis catalyst.[20]

The key intermolecular ene–yne metathesis cross-coupling was successful and led to completion of the total synthesis (Scheme 3). First, common aldehyde **6** was converted to the required β-ketoester **3** by a three-step sequence. Next, the cross EYM was conducted. Low reaction temperature was found to limit decomposition of **3** and led to a good yield of 1,3-diene **2** obtained as a 4.5:1 E/Z mixture. Addition of **Hov2** in installments or by slow infusion did not improve the product yield or increase the stereoselectivity. Completion of the synthesis followed Williams' endgame to give (−)-**1**. Synthetic amphidinolide P was identical in all respects to that reported, except specific rotation. Our synthetic **1** was found to be pure enantiomer as analyzed by chiral HPLC vs Williams' original material, (+)-**1**. In addition, intermediates **2** and **15** were identical to Williams' intermediates, and each matched all spectroscopic properties, including the magnitude of their specific rotation. These data together show that synthesis of (−)-**1** was achieved and support the earlier contention[2b,c] that Williams originally synthesized (+) amphidinolide P. From the common aldehyde **6**, the yield is 21% (10% overall starting from **7**).

In the second approach, attempted ring-closing EYM demonstrated how sensitive EYM is to the enyne substrate (Scheme 4). The key enynes were formed by an aldol reaction between the ester enolate of **12** and common aldehyde **6**, followed by oxidation. Using a different ending sequence, **16A** and **16B** were each prepared. The direct EYM of **16B** (20 mol % **Hov2** at 110 °C for 5 h) failed to give any ring-closing product, **15**. Decomposition was observed, and none of **16B** could be recovered. To control and suppress alkyne polymerization, a TMS group was retained on the alkyne, to give **16A**. Attempted RCM under similar conditions gave only 30% recovered **16A** and additional byproducts, but no ring closure.

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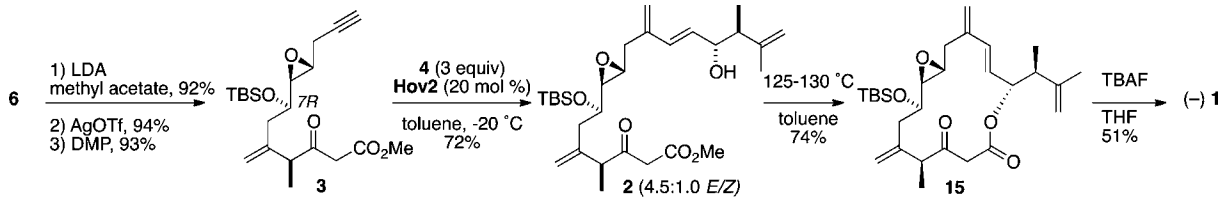
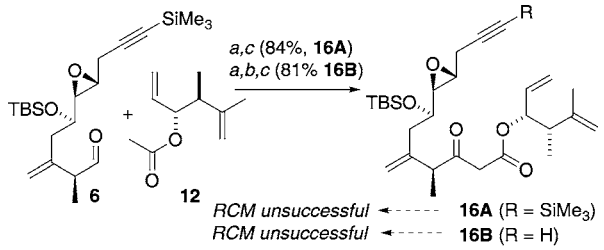
Scheme 3. Key Ene−Yne Metathesis and Completion of the Synthesis (Intermolecular Route)



Scheme 4. Preparation of Enyne and Unsuccessful Ring-Closing Enyne Metathesis

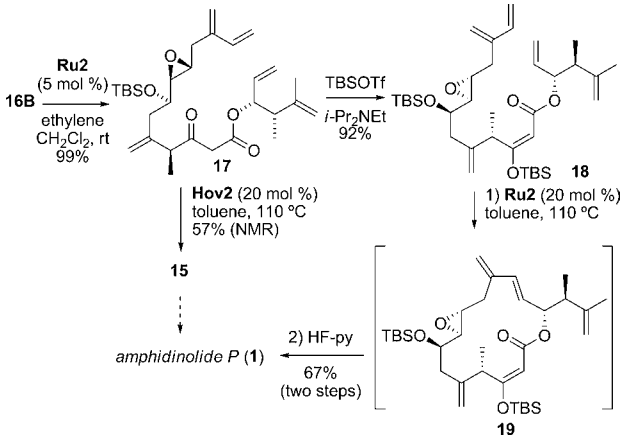


a) LDA, THF, -78 C; addition of aldehyde **6**, 92%; b) AgOTf (50 mol %), CH_2Cl_2/acetone, rt, 93%; c) DMP (2 equiv), $NaHCO_3$ (10 equiv), CH_2Cl_2, rt, 91-95%.

It was concluded that the terminal alkene in **16** is not sufficiently reactive to initiate ring-closing enyne metathesis. These findings agree with previous observations that showed that ester- or silyl-protecting groups of secondary allylic alcohols abrogated intermolecular metathesis reactivity.[21] Without a sufficiently reactive alkene,[3,10,11] the required metal carbene fails to form, giving no reaction or resulting in competitive alkyne oligomerization. If the alkyne reacts first, an oligomerization pathway results.

A successful ring-closing sequence was realized by first converting the terminal alkyne into a 1,3-diene prior to the RCM step. Butadiene **17** was synthesized in quantitative yield by ethylene−alkyne metathesis of **16B** (Scheme 5). Ring-closing metathesis of the TBS ether **17** gave a good yield of the *E*-isomer (57% yield **15**, *E*-only). Comparison of these data with the unsuccessful direct RCM of enynes **16** suggested that the 1,3-butadiene serves as the initiating alkene. This approach alters the ring-closing reaction from an enyne metathesis to that of a 1,3-diene-alkene metathesis.[3c] We considered that ring constraint in the flexible backbone might further improve the metathesis cyclization step.

Scheme 5. Ring-Closing Metathesis Approach to Amphidinolide P (Intramolecular Approach)



An improved RCM route to **1** was achieved by converting the β-keto ester into a silyl enol ether prior to the RCM step (Scheme 5). Locking the enol form would introduce an element of rigidity in the backbone joining the alkenes. Pentaene **17** was enolized to afford silyl enol ether **18**, assigned as the *E*-isomer on the basis of ^{1}H NMR studies. Ring-closing metathesis of **18** gave complete conversion to RCM products, isolated as a mixture of 42% intermediate **19** along with 37% **15**. The latter product provides evidence of some silyl enol ether deprotection occurring under the thermal conditions. The RCM products were separated for characterization, but for completion of the synthesis, the mixture was convergently deprotected with HF−pyridine to give **1** in 67% yield (two steps). The material obtained in this way also matched the spectroscopic properties with those of known amphidinolide. From the common aldehyde **6**, the yield was 50% (24% overall starting from **7**).

In conclusion, two different metathesis routes were used to complete the total synthesis of amphidinolide P. In the intermolecular ene−yne metathesis, low temperature conditions were critical for a successful intermolecular EYM. In the second pathway, direct ring-closing enyne metathesis was not successful. To suppress the suspected alkyne polymerization pathway and improve the initiation profile, the alkyne was converted to a 2-substituted-1,3-butadiene. Ring-closing alkene metathesis of this substrate produced the macrolide ring. The RCM also benefitted from rigidifying the backbone. By way of comparison, the intramolecular (RCM) pathway was one step longer than the cross EYM approach, but the RCM proceeded with the highest chemical yield and highest *E*-selectivity. These studies highlight the relative strengths of inter- and intramolecular ene−yne metathesis at advanced stages of total synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01601.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Isolation: (a) Ishibashi, M.; Takahashi, M.; Kobayashi, J. i. *J. Org. Chem.* **1995**, *60*, 6062–6066. Reviews: (b) Kobayashi, J. i.; Tsuda, M. *Natural Product Reports* **2004**, *21*, 77–93. (c) Kobayashi, J. i.; Kubota, T. *J. Nat. Prod.* **2007**, *70*, 451–460. (d) Kobayashi, J. i. *J. Antibiot.* **2008**, *61*, 271–284. (e) Fürstner, A. *Isr. J. Chem.* **2011**, *51*, 329–345.

(2) (a) Williams, D. R.; Myers, B. J.; Mi, L. *Org. Lett.* **2000**, *2*, 945–948. (b) Williams, D. R.; Myers, B. J.; Mi, L. *Org. Lett.* **2013**, *15*, 2070. (c) Trost, B. M.; Papillon, J. P. N. *J. Am. Chem. Soc.* **2004**, *126*, 13618–13619. (d) Trost, B. M.; Papillon, J. P. N.; Nussbaumer, T. *J. Am. Chem. Soc.* **2005**, *127*, 17921–17937. (e) Hwang, M.-h.; Han, S.-J.; Lee, D.-H. *Org. Lett.* **2013**, *15*, 3318–3321. (f) Williams, D. R.; Myers, B. J.; Mi, L.; Binder, R. J. *J. Org. Chem.* **2013**, *78*, 4762–4778. (g) Chakraborty, T. K.; Das, S. *Tetrahedron Lett.* **2001**, *42*, 3387–3390.

(3) Recent reviews: (a) Li, J.; Lee, D. In *Handbook of Metathesis*, 2nd ed.; Grubbs, R. H., O'Leary, D. J., Eds.; Wiley-VCH: Weinheim, 2015; Vol. *2*, pp 381–444. (b) Diver, S. T., Clark, J. R. In *Comprehensive Organic Synthesis*, 2nd ed.; Fürstner, A., Ed.; Pergamon: London, 2014; Vol. *5*, pp 1302–1356. (c) Diver, S. T. *Science of Synthesis* **2009**, *46.3*, 97–146.

(4) Jecs, E.; Diver, S. T. *Tetrahedron Lett.* **2014**, *55*, 4933–4937.

(5) (a) Kim, C. H.; An, H. J.; Shin, W. K.; Yu, W.; Woo, S. K.; Jung, S. K.; Lee, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 8019–8021. (b) Ko, H. M.; Lee, C. W.; Kwon, H. K.; Chung, H. S.; Choi, S. Y.; Chung, Y. K.; Lee, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 2364–2366.

(6) Select examples of ring-closing EYM used in total synthesis (small rings): (a) Kinoshita, A.; Mori, M. *J. Org. Chem.* **1996**, *61*, 8356–8357. (b) Aggarwal, V. K.; Astle, C. J.; Rogers-Evans, M. *Org. Lett.* **2004**, *6*, 1469–1471. (c) Brenneman, J. B.; Martin, S. F. *Org. Lett.* **2004**, *6*, 1329–1331. (d) Evans, M. A.; Morken, J. P. *Org. Lett.* **2005**, *7*, 3371–3373. (e) Kummer, D. A.; Brenneman, J. B.; Martin, S. F. *Org. Lett.* **2005**, *7*, 4621–4623. (f) Movassaghi, M.; Piizzi, G.; Siegel, D. S.; Piersanti, G. *Angew. Chem., Int. Ed.* **2006**, *45*, 5859–5863. (g) Paquette, L. A.; Lai, K. W. *Org. Lett.* **2008**, *10*, 2111–2113. Study on ring closure mode: (h) Hansen, E. C.; Lee, D. *J. Am. Chem. Soc.* **2004**, *126*, 15074–15080. Macrocyclization ring-closing EYM in total synthesis: (i) Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 773–775.

(7) (a) Fürstner, A.; Larionov, O.; Flügge, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 5545–5548. (b) Fürstner, A.; Flügge, S.; Larionov, O.; Takahashi, Y.; Kubota, T.; Kobayashi, J. i. *Chem.—Eur. J.* **2009**, *15*, 4011–4029.

(8) Gao, X.; Woo, S. K.; Krische, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 4223–4226.

(9) For instance, despite attempts to get an enyne metathesis to work successfully in their amphidinolide N synthesis, ultimately the authors had to redesign their route; see: Nicolaou, K. C.; Brenzovich, W. E.; Bulger, P. G.; Francis, T. M. *Org. Biomol. Chem.* **2006**, *4*, 2119.

(10) Grubbs classifies these as types I–IV, with types I and II alkenes reactive enough to initiate and give alkene metathesis. See: (a) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370. (b) O'Leary, D. J.; O'Neil, G. W. In *Handbook of Metathesis*, 2nd ed., Vol. *2*; Grubbs, R. H., O'Leary, D. J., Eds.; Wiley-VCH: Weinheim, 2015.

(11) (a) Galan, B. R.; Giessert, A. J.; Keister, J. B.; Diver, S. T. *J. Am. Chem. Soc.* **2005**, *127*, 5762–5763. DFT studies: (b) Lippstreu, J. J.; Straub, B. F. *J. Am. Chem. Soc.* **2005**, *127*, 7444–7457. (c) Nunez-Zarur, F.; Solans-Monfort, X.; Rodriguez-Santiago, L.; Pleixats, R.; Sodupe, M. *Chem.—Eur. J.* **2011**, *17*, 7506–7520.

(12) Prepared in six steps from methyl crotonate and TMS acetylene in 21% overall yield.

(13) (a) Kubota, K.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 946–948. (b) Coleman, R. S.; Gurrala, S. R.; Mitra, S.; Raao, A. *J. Org. Chem.* **2005**, *70*, 8932–8941.

(14) Diver, S. T.; Kulkarni, A. A.; Clark, D. A.; Peppers, B. P. *J. Am. Chem. Soc.* **2007**, *129*, 5832–5833.

(15) Clark, J. R.; Diver, S. T. *Org. Lett.* **2011**, *13*, 2896–2899.

(16) Dinger, M. B.; Mol, J. C. *Organometallics* **2003**, *22*, 1089–1095.

(17) For instance, heating at 60 °C gave dienol products that were dark colored, presumably due to greater catalyst decomposition at higher temperatures.

(18) (a) Kuhn, K. M.; Bourg, J.-B.; Chung, C. K.; Virgil, S. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **2009**, *131*, 5313–5320. (b) Vorfalt, T.; Wannowius, K.-J.; Plenio, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 5533–5536.

(19) Decreased loading of **Hov2** resulted in lower product yields.

(20) Galan, B. R.; Kalbarczyk, K. P.; Szczepankiewicz, S.; Keister, J. B.; Diver, S. T. *Org. Lett.* **2007**, *9*, 1203–1206.

(21) (a) Michaelis, S.; Blechert, S. *Org. Lett.* **2005**, *7*, 5513. Accelerating effect of allylic alcohols: (b) Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 1123. (c) Imahori, T.; Ojima, H.; Yoshimura, Y.; Takahata, H. *Chem.—Eur. J.* **2008**, *14*, 10762–10771.

NOTE ADDED AFTER ASAP PUBLICATION

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