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Enantioselective *syn*- and *anti*-Alkoxyallylation of Aldehydes via Brønsted Acid Catalysis

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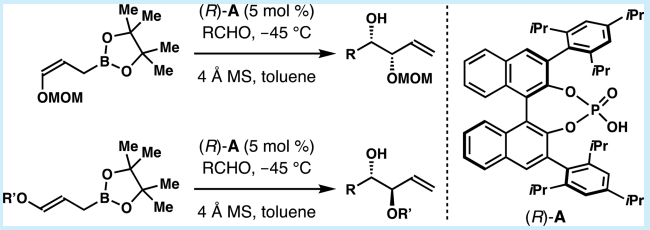
Supporting Information

ABSTRACT: A diastereo- and enantioselective alkoxyallylation via phosphoric acid catalysis was reported. Under the developed conditions, either 1,2-*syn*- or 1,2-*anti*-alkoxyallylation adducts were obtained in good yields with high enantioselectivities.



Enantioenriched 1,2-*syn*- and *anti*-3-ene-diols are important building blocks in organic synthesis. In particular, they are key structural motifs in numerous biologically active natural products (Figure 1).[1] Consequently, many efforts have been devoted to diastereo- and enantioselective syntheses of 3-ene-1,2-diols.[2] The addition of enantioselective γ-alkoxyallyl organometallic reagents to carbonyl compounds is one classic approach to synthesize these 1,2-diols, although a stoichiometric amount of chiral auxiliaries is often required for the asymmetric induction.[3,4] Similarly, reactions of carbonyl compounds with masked enantioselective γ-alkoxy allylmetal reagents, such as γ-boryl or γ-silyl reagents, also produce chiral 3-ene-1,2-diols upon oxidation of the resulting adducts.[5] Recently, several key advances have been achieved to access enantioenriched 1,2-*anti*-3-ene-diols without resorting to chiral auxiliaries. For example, Krische and co-workers developed an elegant Ir-catalyzed allylation strategy for the syntheses of bisbenzoyl-protected 1,2-*anti*-3-ene-diols (Scheme 1, eq 1).[6a] A chirality-transfer approach was reported by the Ito group using enantioenriched γ-alkoxyallylboron reagents,[6b] and monoprotected 1,2-*anti*-3-ene-diols were obtained with excellent conservation of enantioselectivities (Scheme 1, eq 2).

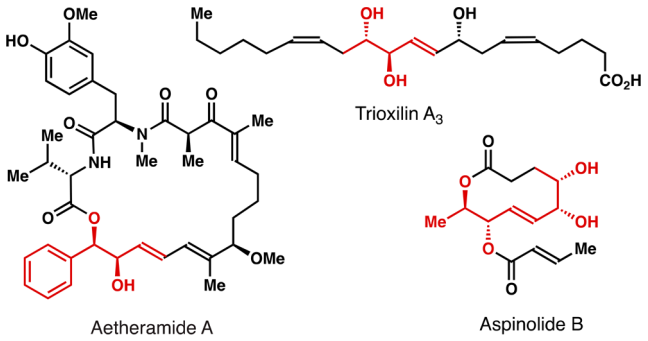


Figure 1. Selected natural products containing 1,2-*syn* and *anti*-3-ene-diols.

Enantioselective addition of γ-alkoxyallylboron reagents to imines was recently disclosed by the Hoveyda group.[6c] In comparison to the available methods to synthesize 1,2-*anti*-3-ene-diols, catalytic asymmetric approaches that allow access to analogous 1,2-*syn*-3-ene-diols are underdeveloped. One notable example is the addition of chiral, nonracemic γ-alkoxy-substituted allylstannanes to aldehydes developed by Marshall and co-workers (Scheme 1, eq 3).[7] The toxicity and sensitive nature associated with the organo-tin reagents, however, make them less desirable in a practical scale. Therefore, development of nontoxic reagents and practical methods to synthesize enantioenriched 1,2-*syn*-3-ene-diols is an important objective in organic synthesis.

In 2010, the Antilla group reported the first chiral phosphoric-acid-catalyzed enantioselective allylboration to obtain homoallylic alcohols with high enantiomeric excess.[8] It is well-established that the reaction of an aldehyde with either (*Z*)- or (*E*)-crotylboronate proceeds through a chair-like transition state to give either *syn*- or *anti*-homoallylic alcohol with high fidelity of stereochemistry.[9] Therefore, it was envisaged that 1,2-*syn*- and 1,2-*anti*-3-ene-diols should be accessible with high diastereo- and enantioselectivities through the reaction of aldehydes with either a (*Z*)- or (*E*)-(γ-alkoxyallyl)boron reagent by proper selection of a chiral phosphoric acid catalyst. To our surprise, there is only a single example of chiral phosphoric-acid-catalyzed addition of (*E*)-(γ-silyloxyallyl)boronate to benzaldehyde to give monosilyl-protected 1,2-*anti*-3-ene-diol with 17% ee.[10] To the best of our knowledge, there is no report for the phosphoric-acid-catalyzed enantioselective syntheses of 1,2-*syn*-3-ene-diols with achiral (γ-alkoxyallyl)boronates. Inspired by the previous work on chiral phosphoric-acid-catalyzed enantioselective carbonyl addition reactions,[11−13] we report herein asymmetric γ-alkoxyallylation of aldehydes with (*Z*)- or (*E*)-γ-alkoxyallyl-boronate, **1** or **3**, to provide 1,2-*syn*- or 1,2-*anti*-alkoxyallylation

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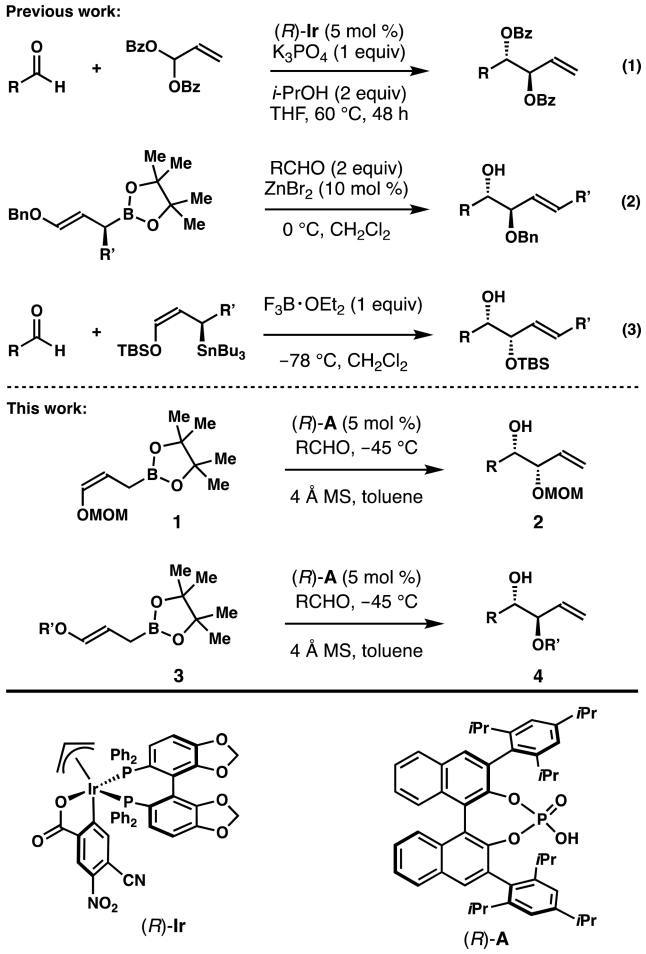
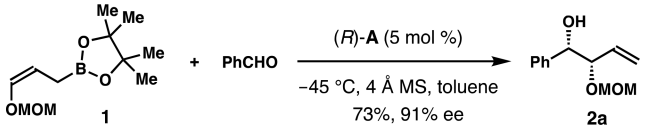
Scheme 1. Approaches for Catalytic, Asymmetric Synthesis of 1,2-*syn*- or *anti*-3-Ene-diols



products, **2** or **4**, in good yields with high enantiomeric excess (Scheme 1).

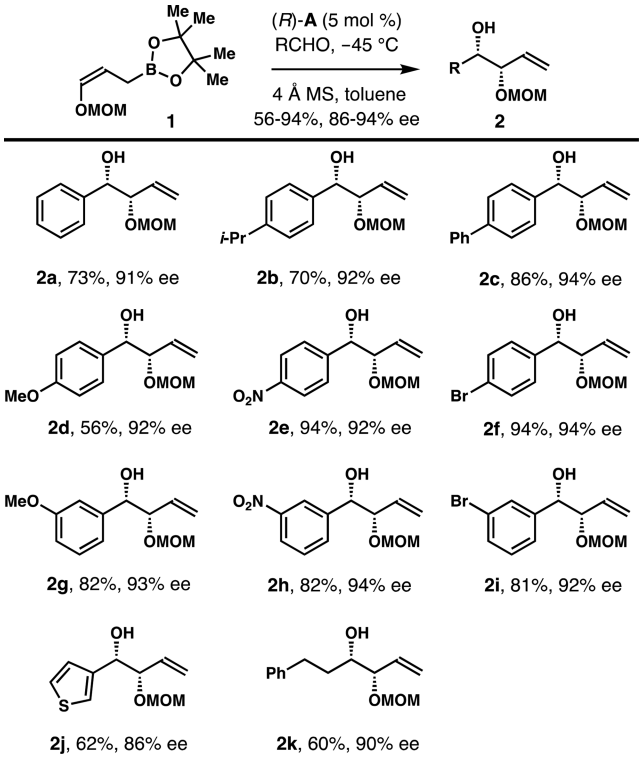
We began our studies on asymmetric *syn*-alkoxyallylation by examining the reaction between (*Z*)-(γ-methoxymethoxyallyl)-boronate **1** and benzaldehyde.[14] In the presence of 4 Å molecular sieves with 5 mol % of phosphoric acid (*R*)-**A** as the catalyst, the reaction of benzaldehyde with (*Z*)-allylboronate **1** at −45 °C in toluene provided the *syn*-adduct **2a** in 73% yield with 91% ee as a single diastereomer.



The reaction without the addition of 4 Å molecular sieves gave product **2a** with much lower enantioselectivity. In addition, it is crucial to conduct the reaction at temperatures below −40 °C to obtain homoallylic alcohol **2a** with high enantioselectivity. Product **2a** was formed with low enantiomeric excess when the reaction was performed at ambient temperature.

We next explored the scope of aldehydes that underwent the *syn*-alkoxyallylation reaction with allylboronate **1** (Scheme 2). Under the standard reaction conditions, a variety of aldehydes with diverse electronic properties participated in the reaction to give *syn*-products **2** in good yields with high enantioselectivities. Aromatic aldehydes with an alkyl or aryl group at the *para*-position reacted to give products **2b**,**c** in 70−86% yields with

Scheme 2. Scope of *syn*-Alkoxyallylation[a−c]



[a]Reaction conditions: allylboronate **1** (0.13 mmol, 1.3 equiv), aldehyde (0.1 mmol, 1.0 equiv), phosphoric acid (*R*)-**A** (5 mol %), 4 Å molecular sieves (50 mg), toluene (0.3 mL), −45 °C. [b]Enantioselectivities were determined by HPLC analysis using a chiral stationary phase. [c]Yields of isolated products are listed.

92−94% ee. Aldehydes with an electron-donating group, an electron-withdrawing group, or a halogen atom at either the *para*- or *meta*-position are also suitable substrates for the reaction. Alcohols **2d**−**i** were obtained in 56−94% yields with 92−94% ee. The reaction of allylboronate **1** with heteroaromatic aldehyde, for example, 3-thiophene carboxaldehyde, proceeded smoothly to give product **2j** in 62% yield with 86% ee. Significantly, aliphatic aldehyde, such as hydrocinnamic aldehyde, also reacted to give product **2k** in 60% yield with 90% ee. The absolute configuration of the secondary hydroxyl groups in the products was determined by modified Mosher ester analysis of **2e**.[15] In general, aldehydes bearing an electron-withdrawing group showed a reactivity much higher than that of aromatic aldehydes substituted with an electron-donating group in the arene.

To access 1,2-*anti*-alkoxyallylation products, we then examined reactions of various aldehydes with (*E*)-γ-ethoxyallylboronate **3**.[16] As summarized in Scheme 3, the standard reaction conditions tolerated a broad scope of aldehydes, and *anti*-ethoxyallylation products **4** were formed as a single diastereomer in 74−97% yield with high enantioselectivities. Benzaldehyde and aromatic aldehydes containing an aryl, an electron-donating group, or an electron-withdrawing group at the *para*-position reacted with (*E*)-allylboronate **3** to give products **4a**−**f** in excellent yields with 94−97% ee. Reactions with *para*-halogen-substituted aromatic aldehydes afforded alcohols **4g**−**i** in 93−97% yields with 96−97% ee. These halogen-containing adducts provide a platform for further elaborations (e.g., cross-coupling reactions). Similar results were

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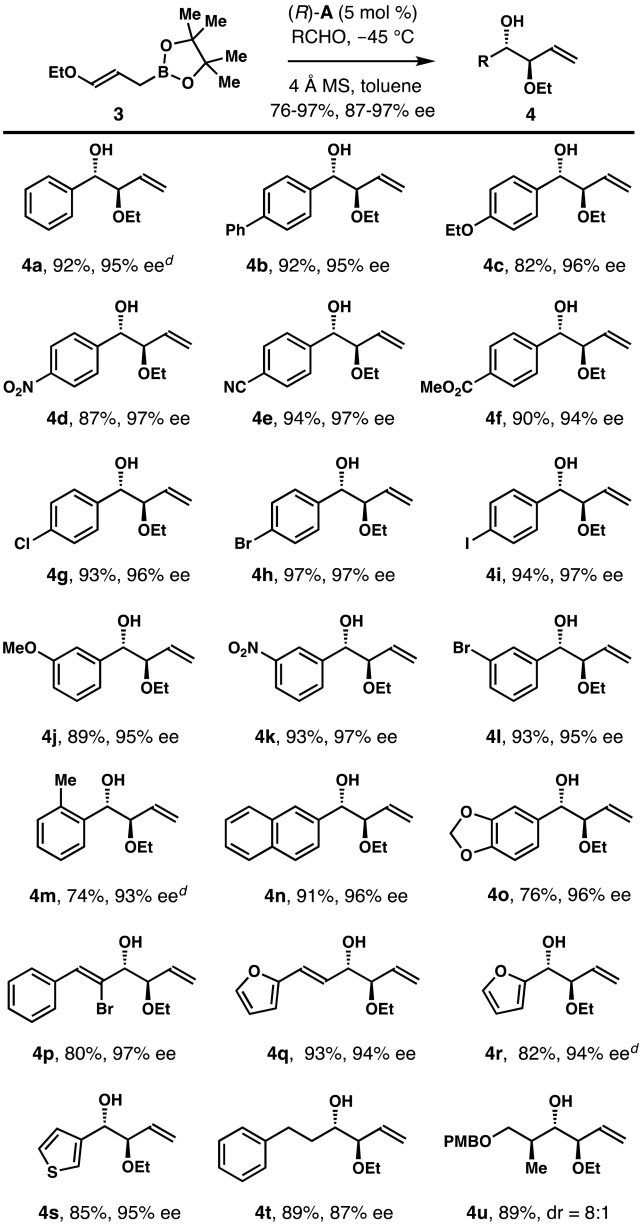
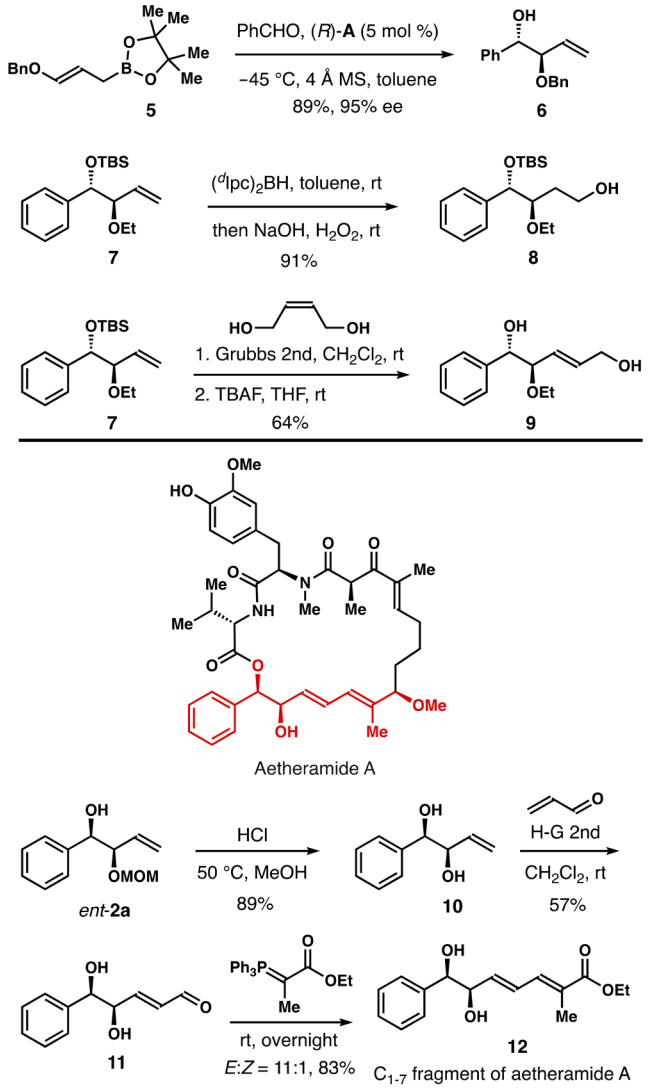
Scheme 3. Scope of *anti*-Alkoxyallylation[a−c]



[a]Reaction conditions: allylboronate **3** (0.13 mmol, 1.3 equiv), aldehyde (0.1 mmol, 1.0 equiv), phosphoric acid (*R*)-**A** (5 mol %), 4 Å molecular sieves (50 mg), toluene (0.3 mL), −45 °C. [b]Enantioselectivities were determined by HPLC analysis using a chiral stationary phase. [c]Yields of isolated products are listed. [d]The ee was determined by modified Mosher ester analysis.[15]

obtained with aromatic aldehydes with various substitutions at the *meta*- or *ortho*-position to furnish products **4j**−**m** in 74−93% yield with 93−97% ee. Reactions with 2-naphthaldehyde and piperonal occurred to provide alcohols **4n**,**o** in 76−91% yields with 96% ee. *α*,*β*-Unsaturated aldehydes and heteroaromatic aldehydes were also tolerated under the reaction conditions to generate alcohol products **4p**−**s** in 80−93% yields with 94−97% ee. The reaction of hydrocinnamic aldehyde with allylboronate **3** gave product **4t** in 89% yield with 87% ee. The absolute configuration of the secondary hydroxyl groups in the products was determined by modified Mosher ester analysis[15] of **4a**, **4m**, and **4r**. Additionally, double stereodifferentiation reaction[17] of allylic boronate **3** with an enantioenriched aldehyde was conducted. The *anti*,*anti*-stereoisomer **4u** was obtained in 89% yield with a synthetically useful diastereoselectivity (8:1). We also prepared (*E*)-*γ*-benzyloxyallylboronate **5**, and the reaction of **5** with benzaldehyde under the standard conditions gave product **6** in 89% yield with 95% ee (Scheme 4).

Scheme 4. Transformation of the Reaction Products



To demonstrate the synthetic utility of this method, further derivatization of the *syn*- or *anti*-alkoxyallylation products was conducted. As shown in Scheme 4, hydroboration of TBS ether **7** followed by oxidative workup gave alcohol **8** in 91% yield. Cross-metathesis[18] of **7** with (*Z*)-2-butene-1,4-diol in the presence of 10 mol % of Grubbs second generation catalyst and subsequent TBS deprotection with TBAF gave diol **9** in 64% yield in two steps.

The *syn*-alkoxyallylation adduct *ent*-**2a** was used as the starting material for the synthesis of the C_{1-7} fragment of natural product, aetheramide A (Scheme 4).[19] First, the methoxymethyl ether (MOM group) of *ent*-**2a** was deprotected under acidic conditions to give diol **10**. In the presence of 10 mol % of Hoveyda-Grubbs second generation catalyst, cross-metathesis[18] of **10** with acrolein generated aldehyde **11**. Horner−Wads-

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worth−Emmons olefination of aldehyde **11** provided ester **12**, which represents the C_{1-7} fragment of aetheramide A.

In summary, we developed a chiral phosphoric-acid-catalyzed *syn*- and *anti*-alkoxyallylation of aldehydes. The *syn*- and *anti*-3-ene-1,2-diol derivatives are useful building blocks in organic synthesis as illustrated in the synthesis of the C_{1-7} fragment of aetheramide A. Other synthetic applications of this method are currently ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02653.

^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Cragg, G. M.; Grothaus, P. G.; Newman, D. *Chem. Rev.* **2009**, *109*, 3012. (b) Plaza, A.; Garcia, R.; Bifulco, G.; Martinez, J. P.; Hüttel, S.; Sasse, F.; Meyerhans, A.; Stadler, M.; Müller, R. *Org. Lett.* **2012**, *14*, 2854. (c) Fuchser, J.; Zeeck, A. *Liebigs Ann. Recueil* **1997**, *1997*, 87. (d) Pace-Asciak, C. R.; Lee, W.-S. *J. Biol. Chem.* **1989**, *264*, 9310.

(2) For selected reviews, see: (a) Lombardo, M.; Trombini, C. *Chem. Rev.* **2007**, *107*, 3843. (b) Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2013**, *113*, 5595. (c) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(3) For selected examples, see: (a) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1988**, *110*, 1535. (b) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321. (c) Roush, W. R.; VanNieuwenhze, M. S. *J. Am. Chem. Soc.* **1994**, *116*, 8536. (d) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1995**, *60*, 1920. (e) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1996**, *61*, 105. (f) Ganesh, P.; Nicholas, K. M. *J. Org. Chem.* **1997**, *62*, 1737. (g) Chika, J.-i.; Takei, H. *Tetrahedron Lett.* **1998**, *39*, 605. (h) Yamamoto, Y.; Miyairi, T.; Ohmura, T.; Miyaura, N. *J. Org. Chem.* **1999**, *64*, 296. (i) Muñoz-Hernández, L.; Soderquist, J. A. *Org. Lett.* **2009**, *11*, 2571. (j) Muñoz-Hernández, L.; Seda, L. A.; Wang, B.; Soderquist, J. A. *Org. Lett.* **2014**, *16*, 4052.

(4) (a) Gao, X.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 9308. (b) Deligny, M.; Carreaux, F.; Toupet, L.; Carboni, B. *Adv. Synth. Catal.* **2003**, *345*, 1215. (c) Gao, X.; Hall, D. G. *J. Am. Chem. Soc.* **2005**, *127*, 1628. (d) Lessard, S.; Peng, F.; Hall, D. G. *J. Am. Chem. Soc.* **2009**, *131*, 9612. (e) Penner, M.; Rauniyar, V.; Kaspar, L. T.; Hall, D. G. *J. Am. Chem. Soc.* **2009**, *131*, 14216.

(5) (a) Roush, W. R.; Gover, P. T.; Lin, X. *Tetrahedron Lett.* **1990**, *31*, 7563. (b) Barrett, A. G. M.; Malecha, J. W. *J. Org. Chem.* **1991**, *56*, 5243. (c) Brown, H. C.; Narla, G. *J. Org. Chem.* **1995**, *60*, 4686. (d) Hunt, J. A.; Roush, W. R. *J. Org. Chem.* **1997**, *62*, 1112. (e) Kister, J.; DeBaillie, A. C.; Lira, R.; Roush, W. R. *J. Am. Chem. Soc.* **2009**, *131*, 14174. (f) Winbush, S. M.; Roush, W. R. *Org. Lett.* **2010**, *12*, 4344.

(6) (a) Han, S. B.; Han, H.; Krische, M. J. *J. Am. Chem. Soc.* **2010**, *132*, 1760. (b) Yamamoto, E.; Takenouchi, Y.; Ozaki, T.; Miya, T.; Ito, H. *J. Am. Chem. Soc.* **2014**, *136*, 16515. (c) Morrison, R. J.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2018**, *57*, 11654. (d) Kim, D.; Lee, J. S.; Kong, S. B.; Han, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 4203.

(7) (a) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31. (b) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163. (c) Marshall, J. A. *J. Org. Chem.* **2007**, *72*, 8153. (d) Marshall, J. A.; Welmaker, G. S.; Gung, B. W. *J. Am. Chem. Soc.* **1991**, *113*, 647.

(8) Jain, P.; Antilla, J. C. *J. Am. Chem. Soc.* **2010**, *132*, 11884.

(9) (a) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920. (b) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, Germany, 2000; p 403. (c) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (d) Lachance, H.; Hall, D. G. *Org. React.* **2008**, *73*, 1. (e) Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2011**, *111*, 7774.

(10) Miura, T.; Nishida, Y.; Morimoto, M.; Murakami, M. *J. Am. Chem. Soc.* **2013**, *135*, 11497.

(11) For selected examples, see: (a) Xing, C.-H.; Liao, Y.-X.; Zhang, Y.; Sabarova, D.; Bassous, M.; Hu, Q.-S. *Eur. J. Org. Chem.* **2012**, *2012*, 1115. (b) Incerti-Pradillos, C. A.; Kabeshov, M. A.; Malkov, A. V. *Angew. Chem., Int. Ed.* **2013**, *52*, 5338. (c) Huang, Y.; Yang, X.; Lv, Z.; Cai, C.; Kai, C.; Pei, Y.; Feng, Y. *Angew. Chem., Int. Ed.* **2015**, *54*, 7299. (d) Barrio, P.; Rodríguez, E.; Saito, K.; Fustero, S.; Akiyama, T. *Chem. Commun.* **2015**, *51*, 5246. (e) Clot-Almenara, L.; Rodríguez-Escrich, C.; Osorio-Planes, L.; Pericàs, M. A. *ACS Catal.* **2016**, *6*, 7647. (f) Miura, T.; Nakahashi, J.; Murakami, M. *Angew. Chem., Int. Ed.* **2017**, *56*, 6989. (g) Miura, T.; Nakahashi, J.; Zhou, W.; Shiratori, Y.; Stewart, S. G.; Murakami, M. *J. Am. Chem. Soc.* **2017**, *139*, 10903. (h) Park, J.; Choi, S.; Lee, Y.; Cho, S. H. *Org. Lett.* **2017**, *19*, 4054.

(12) For computational studies, see: (a) Grayson, M. N.; Pellegrinet, S. C.; Goodman, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 2716. (b) Wang, H.; Jain, P.; Antilla, J. C.; Houk, K. N. *J. Org. Chem.* **2013**, *78*, 1208. (c) Grayson, M. N.; Goodman, J. M. *J. Am. Chem. Soc.* **2013**, *135*, 6142. (d) Grayson, M. N.; Yang, Z.; Houk, K. N. *J. Am. Chem. Soc.* **2017**, *139*, 7717.

(13) (a) Jain, P.; Wang, H.; Houk, K. N.; Antilla, J. C. *Angew. Chem., Int. Ed.* **2012**, *51*, 1391. (b) Reddy, L. R. *Org. Lett.* **2012**, *14*, 1142. (c) Chen, M.; Roush, W. R. *J. Am. Chem. Soc.* **2012**, *134*, 10947. (d) Reddy, L. R. *Chem. Commun.* **2012**, *48*, 9189. (e) Wang, M.; Khan, S.; Miliordos, E.; Chen, M. *Org. Lett.* **2018**, *20*, 3810.

(14) (a) Hoffmann, R. W.; Kemper, B. *Tetrahedron Lett.* **1982**, *23*, 845. (b) Hoffmann, R. W.; Metternich, R.; Lanz, J. W. *Liebigs Ann. Chem.* **1987**, *1987*, 881.

(15) (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) Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nat. Protoc.* **2007**, *2*, 2451.

(16) Zhang, P.; Roundtree, I. A.; Morken, J. P. *Org. Lett.* **2012**, *14*, 1416.

(17) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

(18) (a) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360. (b) Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746.

(19) (a) Ghosh, A. K.; Rao, K. V.; Akasapu, S. *Tetrahedron Lett.* **2014**, *55*, 5191. (b) Gerstmann, L.; Kalesse, M. *Chem. - Eur. J.* **2016**, *22*, 11210. (c) Qi, N.; Allu, S. R.; Wang, Z.; Liu, Q.; Guo, J.; He, Y. *Org. Lett.* **2016**, *18*, 4718. (d) Qi, N.; Wang, Z.; Allu, S. R.; Liu, Q.; Guo, J.; He, Y. *J. Org. Chem.* **2016**, *81*, 12466.

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