JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Synthesis of Chiral Tertiary Boronic Esters: Phosphonate-Directed Catalytic Asymmetric Hydroboration of Trisubstituted Alkenes

Suman Chakrabarty and James M. Takacs*

Department of Chemistry, University of Nebraska—Lincoln, Lincoln, Nebraska 68588-0304, United States

Supporting Information

ABSTRACT: Highly enantioselective rhodium-catalyzed hydroboration of allylic phosphonates by pinacolborane affords chiral tertiary boronic esters. The β-borylated phosphonates are readily converted to chiral β- and γ-hydroxyphosphonates and aminophosphonates and to phosphonates bearing a quaternary carbon stereocenter. The utility of the latter is illustrated by the synthesis of (*S*)-(+)-bakuchiol methyl ether.

Chiral organoboronates are valuable reagents in asymmetric synthesis due to the versatility with which the C−B bond can be utilized via a myriad of diverse stereospecific transformations.[1] The direct introduction of boron via the catalytic asymmetric hydroboration (CAHB) of alkenes,[2] particularly of vinylarenes,[3] has received much recent interest.[4,5] We focus on accessing functionalized, chiral boronic esters via rhodium-catalyzed, directed CAHB of β,γ-unsaturated substrates.[6] For example, the oxime-directed CAHB of trisubstituted alkene (*E*)-**1** affords the novel chiral, tertiary boronic ester (*R*)-**2** (84%, 95:5 er; Figure 1).[6a] The TADDOL-derived chiral cyclic monophosphite ligand (*R,R*)-**T1** is used to control the π-facial selectivity.

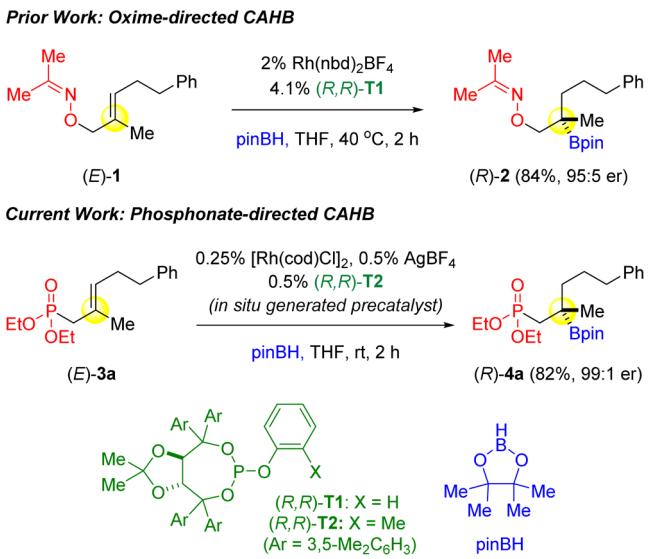

Figure 1. Chiral tertiary boronic esters via phosphonate-directed CAHB (nbd = norbornadiene; cod = cyclooctadiene).

Encouraged by the success of oxime-directed CAHB, we turned our attention to exploring the potential effectiveness of phosphonate functionality as a directing group. Recently, phosphonates have been elegantly used to enable novel modes of C−H activation.[7] However, the overall effectiveness of phosphonates as directing groups in asymmetric catalysis remains largely unexplored. We now report that phosphonate (*E*)-**3a** undergoes efficient borylation to yield the chiral tertiary boronic ester **4a** in excellent yield (82%) and with high levels of enantioinduction (99:1 er). While commercial $Rh(nbd)_2BF_4$ is a suitable catalyst precursor, a catalyst generated *in situ* from $[Rh(cod)Cl]_2$ and $AgBF_4$, in combination with the TADDOL-derived chiral monophosphite **T2**,[8] is more economical and efficiently catalyzes hydroboration with pinacolborane (pinBH). We often find that the nature of the directing group strikingly influences the regio- and stereoselectivity of the CAHB.[6] In the present case, however, the observed β-regiochemistry and π-facial selectivity for CAHB of (*E*)-**3a** match those of oxime-directed borylation (Figure 1).

Chiral phosphonates, particularly hydroxy- and aminophosphonates are bioisosteres of the corresponding amino acids and key structural elements of antibiotics, antiviral, and anticancer drugs.[9] However, the toolbox for introducing chirality via the functionalization of phosphonates is largely limited to catalytic asymmetric hydrogenation.[10,11] Chiral, borylated phosphonates can enable new possibilities as chiral synthons. Figure 2 illustrates stereospecific transformations we have investigated for tertiary boronic ester **4a**, including its conversion to chiral β- and γ-hydroxyphosphonates and aminophosphonates and to phosphonates bearing a quaternary all-carbon stereocenter. All-carbon quaternary stereocenters are a common structural motif in bioactive natural products and pharmaceutical drugs.[12]

The reaction of (*E*)-**3a** has been carried out on gram scale using a 0.5 mol % catalyst loading and only a slight excess of pinBH (1.1 equiv). Oxidation of **4a** by $NaBO_3$ yields the chiral, tertiary β-hydroxyphosphonate **5a** (95%, 99:1 er). Cross-couplings of **4a** under conditions reported by Aggarwal et al. are facile and afford the furan derivative **7a** (71%)[1e] and the vinylated derivative **8a** (93%).[13] Attempts to convert **4a** directly to latent aldehyde or carboxylic acid moieties using the typical conditions employed for boronic esters[13] were not successful, perhaps due to the all-alkyl substitution pattern of the tertiary boronic ester in **4a**. However, ozonolysis of **8a** followed by a mild reductive workup[14] yields the chiral

Received: March 11, 2017
Published: April 17, 2017

DOI: 10.1021/jacs.7b02324
J. Am. Chem. Soc. 2017, 139, 6066−6069

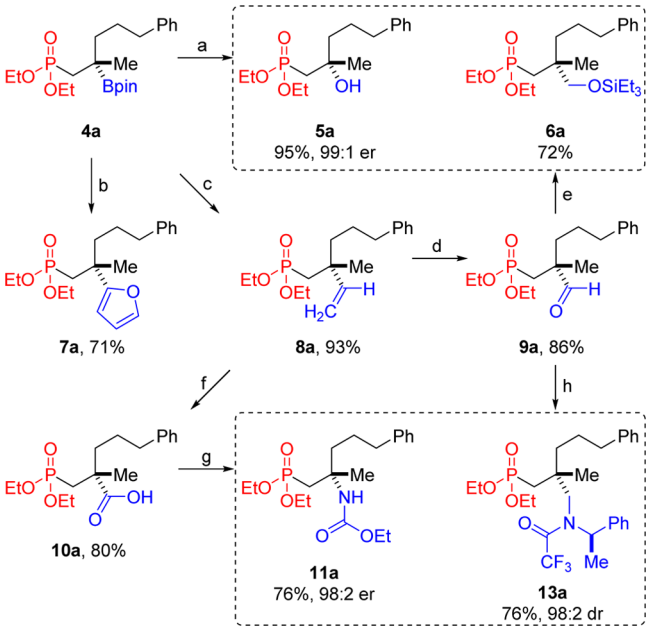

Figure 2. Utility of phosphonate functionalized tertiary boronic esters is illustrated by selected transformations of **4a**. Reagents and conditions: (a) $NaBO_3{\cdot}4H_2O$; (b) (i) *n*BuLi, furan, −78 °C, THF; (ii) NBS; (iii) aq. $Na_2S_2O_3$; (c) (i) $CH_2{=}CHMgBr$, THF; (ii) I_2, MeOH (iii) MeONa, MeOH; (d) (i) O_3, CH_2Cl_2, 0 °C; (ii) Et_3N, rt (e) Et_3SiH, $[Ru(p\text{-cymene})Cl_2]_2$, toluene, 50 °C; (f) (i) O_3, CH_2Cl_2, 0 °C; (ii) Et_3N; (iii) NaH_2PO_4, $NaClO_2$, 2-methyl-2-butene, *t*-BuOH, rt; (g) (i) DPPA, toluene reflux; (ii) EtOH; (h) (i) (*R*)-(+)-α-methylbenzylamine, AcOH, $NaCNBH_3$; (ii) $(CF_3CO)_2O$, Et_3N, THF, rt.

phosphonoaldehyde **9a** (86%). Ruthenium-catalyzed reductive silylation[15] affords the silyl protected chiral γ-hydroxyphosphonate **6a** (72%). Reductive amination[16] of **9a** with (*R*)-(+)-α-methylbenzylamine yields **12a** (see the Supporting Information (SI)) which followed by acylation affords the chiral γ-aminophosphonate **13a** (76% overall, 98:2 dr). Our attempts to convert **4a** directly to the chiral, tertiary β-aminophosphonate[10] using several commonly employed methods[17] were unsuccessful. However, ozonolysis of **8a** followed by Pinnick oxidation[3b] affords the chiral carboxylic acid **10a** (80%). Its conversion to the chiral β-aminophosphonate **11a** (76%, 98:2 er) via Curtius rearrangement proceeded smoothly under standard conditions.[18]

Figure 3 summarizes results obtained for a series of trisubstituted alkenes differing in the nature of alkyl chain at the position labeled R^E. Substrates similar to **3a** bearing substituted aromatics and heteroaromatics (i.e., **3b**–**e**) undergo efficient β-borylation. For example, the trifluoromethylphenyl derivative **3b** affords **4b** (78%, >99:1 er). The 4-chlorophenyl derivative **4c** (76%, 99:1 er) could in principle be used in subsequent cross-coupling chemistry, further highlighting the goal to prepare multifunctional synthons via CAHB. Substrates **3d** and **3e** demonstrate that simple heteroaromatic ring systems can be carried through the CAHB sequence; **4d** (77%, 98.5:1.5 er) and **4e** (71%, 97:3 er) are obtained in good yields and high enantioselectivities.

Substrates with saturated alkyl substituents (i.e., **3f** and **3g**) give **4f** (83%, 97:3 er) and **4g** (80%, 98:2 er), respectively. The structurally related chiral substrate **3h** undergoes highly diastereoselective CAHB (>20:1 dr) with catalyst control; (*R*,*R*)-**T2** affords (*R*,*S*)-**4h** (83%), and (*S*,*S*)-**T2** affords (*S*,*S*)-**4h** (82%). β-Borylated products bearing a Boc-protected nitrogen substituent (**4i**) or hydroxy substituents, protected as the benzoate, benzyl ether, or benzyloxymethyl ether (i.e., **4j**–**l**), are obtained with high levels of asymmetric induction. The chiral acetal substrate **3m** undergoes efficient CAHB, again

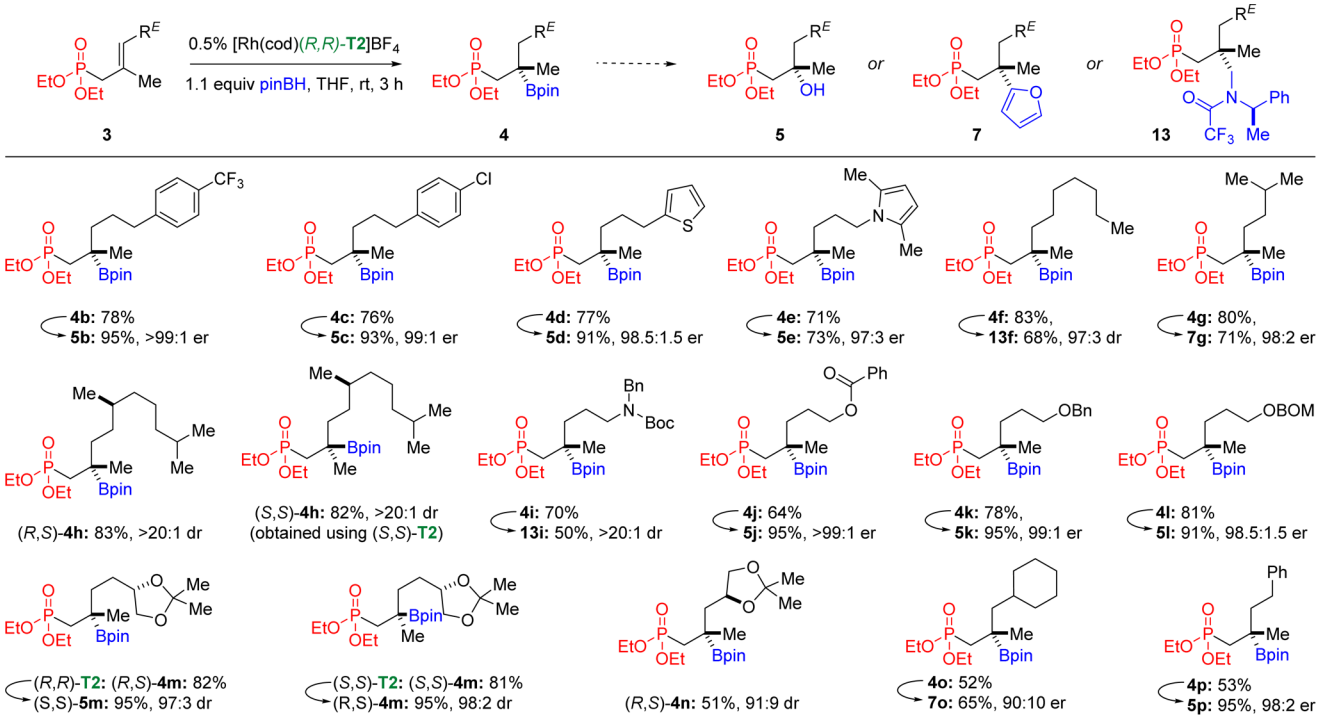

Figure 3. Substrate scope. Note: er is determined either by chiral HPLC analysis of tertiary alcohol derivative **5** or cross-coupled derivative **7** or by NMR analysis of the amino derivative **13**.

DOI: 10.1021/jacs.7b02324
J. Am. Chem. Soc. 2017, 139, 6066–6069

with good catalyst control over diastereoselectivity. Depending on the configuration of **T2**, either (*R*,*S*)-**4m** or (*S*,*S*)-**4m** is obtained in high yield (81−82%) and high diastereoselectivity, 97:3 dr and 98:2 dr, respectively. The one carbon shorter analogue **3n** affords (*R*,*S*)-**4n** (51%, 91:9 dr) using (*R*,*R*)-**T2** but forms a complex mixture using (*S*,*S*)-**T2**. Substrates related to **3n**, bearing a bulkier vinyl substituent such as in **3o** and **3p**, and substrates related to **3a**, in which the vinyl methyl substituent is replaced by bulkier substituents, tend to react more sluggishly and give more side products; for example, lower yields are obtained for **4o** (52%, 90:10 er) and **4p** (53%, 98:2 er). The alkene geometry plays an important role in the reaction. (*Z*)-**3a** yields (*R*)-**4a** (40%, 99:1 er) with high enantioselectivity but in much lower yield compared to (*E*)-**3a**.[19]

In addition to their potential as pharmacophores for medicinal chemistry, phosphonates enable useful synthetic transformations. A formal total synthesis of the natural product (*S*)-(+)-bakuchiol[20,21] further illustrates the synthetic utility of these chiral phosphonate-functionalized, tertiary boronic esters (Figure 4). (*S*)-(+)-Bakuchiol possesses a remote alkene as well as a challenging skipped diene subunit in which the two alkene moieties are separated by a quaternary all-carbon stereocenter. We envisioned utilizing the chemistry of the boronic ester and the phosphonate in **4q** sequentially to form the skipped diene subunit.

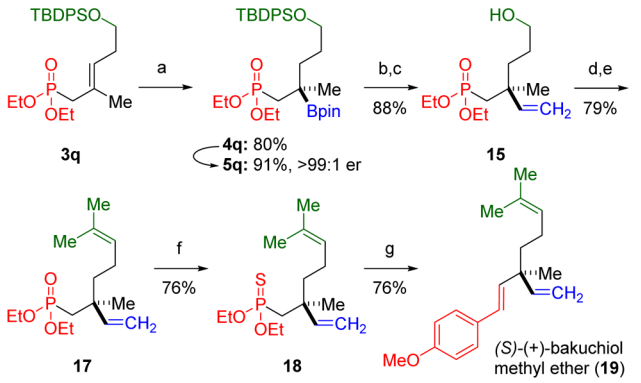

Figure 4. Formal total synthesis of (*S*)-(+)-bakuchiol. Reagents and conditions: (a) 0.25% $[Rh(cod)Cl]_2$, 0.50% $AgBF_4$, 0.50% (*S*,*S*)-**T2**, 1.1 equiv of pinBH, THF (c = 1M), rt, 12 h; (b) (i) CH_2═$CHMgBr$, THF, −78 °C; (ii) I_2, MeOH, − 78 °C; (iii) NaOMe, MeOH; (iv) $Na_2S_2O_3$ (*aq.*); (c) TBAF, H_2O; (d) DMSO, Py·SO_3, Hünig's base; (e) $(CH_3)_2CH$═PPh_3; (f) Lawesson's reagent, toluene reflux; (g) *n*BuLi, 4-methoxy-benzaldehyde.

CAHB of **3q** with (*S*,*S*)-**T2** affords **4q** (80% on gram scale); the enantioselectivity (>99:1 er) is determined after oxidation to tertiary alcohol **5q**. Cross-coupling of **4q** with vinyl magnesium bromide[13] to **14** (see the SI) followed by deprotection of the silyl ether yields **15**. Oxidation to the aldehyde **16** (see the SI) followed by Wittig olefination to **17** sets the stage for exploiting the phosphonate functionality to complete the synthesis. Direct phosphonate olefination is limited in scope since β-hydroxy phosphonates lacking electron withdrawing substituents on the α-carbon are not prone to eliminate without activation.[22] However, Corey[23] found that β-hydroxy thionophosphonates readily undergo elimination to form alkenes. Treating phosphonate **17** with Lawesson's reagent[24] affords thionophosphonate **18**. Deprotonation by *n*BuLi followed by the addition of 4-methoxy benzaldehyde smoothly yields (*S*)-(+)-bakuchiol methyl ether (**19**).[25] Conversion of **19** to the natural product was previously reported.[21a] Since either enantiomer of the chiral monophosphite **T2** is equally accessible, a sequence beginning with (*R*,*R*)-**T2** was carried out to give the enantiomeric (*R*)-(−)-bakuchiol methyl ether.[21c]

Figure 5 summarizes data obtained probing three mechanistic aspects of phosphonate-directed CAHB. (i) The distance separating the phosphonate directing group and the alkene undergoing reaction is a key factor for efficient reaction. While (*E*)-**3a** reacts efficiently to yield the boronic ester **4a**, the one carbon homologue **20** is unreactive under the same conditions. We speculate that efficient chelation by the substrate is necessary for efficient catalysis. (ii) The ligand-to-metal ratio (i.e., **T2**:Rh) strongly influences the activity of the catalyst. Graph A (Figure 5) compares the yield of **4a** over time for catalysts prepared with a 1:1 **T2**:Rh ratio (blue line) and 2:1 **T2**:Rh ratio (red line). The catalyst formed using a 1:1 **T2**:Rh yields **4a** in about 80% yield after roughly an hour. The catalyst formed using a 2:1 **T2**:Rh ratio produces **4a** but in only 60% yield after roughly 4 h. While the reaction is much slower, the enantiomer ratio of **4a** (99:1 er) is unchanged by the change in **T2**:Rh ratio. (iii) Graph B (Figure 5) shows the linear dependence of percent ee of product **4a** on the enantiomeric purity of **T2**. The lack of a nonlinear effect[26] in this case is consistent with a 1:1 **T2**:Rh complex in the active catalyst.

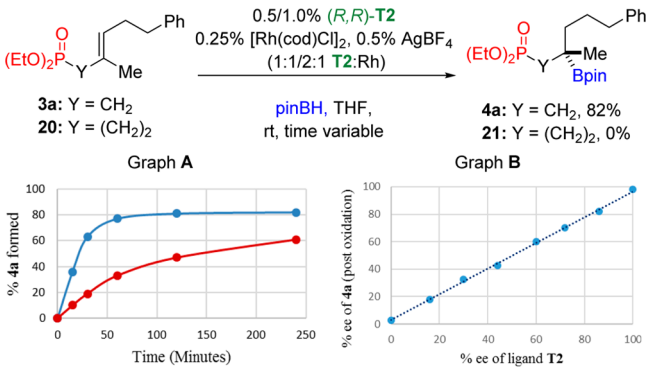

Figure 5. Key mechanistic considerations: Graph **A** compares the yield of **4a** over time for catalysts prepared using 1:1 (blue line) versus 2:1 (red line) **T2**:Rh ratios; Graph **B** plots percent ee of the product versus percent ee of the chiral catalyst.

In conclusion, the successful use of phosphonate functionality as a directing group in Rh-catalyzed CAHB of trisubstituted alkenes leads to the formation of functionalized chiral, tertiary boronic esters, in high yield (up to 83%) and with high levels of enantioselectivity (up to 99:1 er, or greater). A simple TADDOL-derived ligand system efficiently controls the π-facial selectivity, and the reaction exhibits tolerance toward a range of functional groups. Stereospecific routes to generate quaternary all-carbon stereocenters are demonstrated, and the multifunctional utility of these novel molecules as chiral synthons is demonstrated in the synthesis of bakuchiol. Mechanistic experiments indicate that a 1:1 Rh-to-monophosphite complex is relevant to catalysis. Further studies are in progress.

DOI: 10.1021/jacs.7b02324
J. Am. Chem. Soc. 2017, 139, 6066−6069

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b02324.

Experimental procedures and characterization data (PDF)

NMR data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*jtakacs1@unl.edu

ORCID

Suman Chakrabarty: 0000-0002-6611-3839

James M. Takacs: 0000-0002-1903-6535

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Funding from the NIH National Institutes of General Medical Sciences (R01-GM100101) is gratefully acknowledged. We sincerely thank P. H. Dussault (UNL) for use of equipment and V. M. Shoba (UNL) for helpful discussions.

■ REFERENCES

(1) Recent reviews: (a) Leonori, D.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2015**, *54*, 1082. (b) Scott, H. K.; Aggarwal, V. K. *Chem. - Eur. J.* **2011**, *17*, 13124. Recent methodology developments: (c) Zhang, L.; Lovinger, G. J.; Edelstein, E. K.; Szymaniak, A. A.; Chierchia, M. P.; Morken, J. P. *Science* **2016**, *351*, 70. (d) Matthew, S. C.; Glasspoole, B. W.; Eisenberger, P.; Crudden, C. M. *J. Am. Chem. Soc.* **2014**, *136*, 5828. (e) Bonet, A.; Odachowski, M.; Leonori, D.; Essafi, S.; Aggarwal, V. K. *Nat. Chem.* **2014**, *6*, 584.

(2) (a) Xi, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2016**, *138*, 6703. (b) Ceinos, M. G.; Parra, A.; Heras, V. M.; Tortosa, M. *Angew. Chem., Int. Ed.* **2016**, *55*, 6969. (c) Sasaki, Y.; Zhong, C.; Sawamura, M.; Ito, H. *J. Am. Chem. Soc.* **2010**, *132*, 1226.

(3) (a) Zhang, H.; Lu, Z. *ACS Catal.* **2016**, *6*, 6596. (b) Zhang, L.; Zuo, Z.; Wan, Z.; Huang, Z. *J. Am. Chem. Soc.* **2014**, *136*, 15501. (c) He, Z.-T.; Zhao, Y.-S.; Tian, P.; Wang, C.-C.; Dong, H.-Q.; Lin, G.-Q. *Org. Lett.* **2014**, *16*, 1426. (d) Feng, X.; Jeon, H.; Yun, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 3989. (e) Mazet, C.; Gérard, D. *Chem. Commun.* **2011**, *47*, 298. (f) Corberán, R.; Mszar, N. W.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2011**, *50*, 7079.

(4) For recent partial summary of other ways, including stereoconvergent cross-coupling methods to prepare chiral organoboron derivatives, see: Schmidt, J.; Choi, J.; Liu, A. T.; Slusarczyk, M.; Fu, G. C. *Science* **2016**, *354*, 1265.

(5) For other approaches to chiral tertiary boronic esters, see: (a) Hu, N.; Zhao, G.; Zhang, Y.; Liu, X.; Li, G.; Tang, W. *J. Am. Chem. Soc.* **2015**, *137*, 6746. (b) Hong, K.; Liu, X.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 10581. (c) Pulis, A. P.; Blair, D. J.; Torres, E.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2013**, *135*, 16054. (d) O'Brien, J. M.; Lee, K. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10630. (e) Chen, I. H.; Yin, L.; Itano, W.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 11664.

(6) (a) Shoba, V. M.; Thacker, N. C.; Bochat, A. J.; Takacs, J. M. *Angew. Chem., Int. Ed.* **2016**, *55*, 1465. (b) Hoang, G. L.; Yang, Z. D.; Smith, S. M.; Pal, R.; Miska, J. L.; Perez, D. E.; Pelter, L. S. W.; Zeng, X. C.; Takacs, J. M. *Org. Lett.* **2015**, *17*, 940. (c) Smith, S. M.; Takacs, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 1740. (d) Smith, S. M.; Thacker, N. C.; Takacs, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 3734.

(7) (a) Chary, B. C.; Kim, S. *Org. Biomol. Chem.* **2013**, *11*, 6879. (b) Zhao, D.; Nimphius, C.; Lindale, M.; Glorius, F. *Org. Lett.* **2013**, *15*, 4504. (c) Bera, M.; Sahoo, S. K.; Maiti, D. *ACS Catal.* **2016**, *6*, 3575.

(8) Yields for phosphonate-directed CAHB are typically slightly higher (*ca.* 4−5%) using **T2** than those obtained using **T1**; the er of **4a** obtained using **T1** is 98.5:1.5.

(9) (a) Kaplan, A. P.; Bartlett, P. A. *Biochemistry* **1991**, *30*, 8165. (b) Tebby, J. C. Aminophosphonic and aminophosphinic acids: chemistry and biological activity; Kukhar, V. P., Hudson, H. R., Eds.; John Wiley & Sons Ltd: Chichester, 2000. (c) Horsman, G. P.; Zechel, D. L. *Chem. Rev.* Article ASAP, DOI: 10.1021/acs.chemrev.6b00536.

(10) For a review of synthetic methods to construct α- and β-aminophosphonates, see: Ma, J. A. *Chem. Soc. Rev.* **2006**, *35*, 630.

(11) (a) Yan, Z.; Wu, B.; Gao, X.; Chen, M.-W.; Zhou, Y.-G. *Org. Lett.* **2016**, *18*, 692. (b) Corbett, M. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2013**, *135*, 594. (c) Zhang, J.; Li, Y.; Wang, Z.; Ding, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 11743.

(12) Bueschleb, M.; Dorich, S.; Hanessian, S.; Tao, D.; Schenthal, K. B.; Overman, L. E. *Angew. Chem., Int. Ed.* **2016**, *55*, 4156 and references cited therein.

(13) Sonawane, R. P.; Jheengut, V.; Rabalakos, C.; Larouche-Gauthier, R.; Scott, H. K.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2011**, *50*, 3760.

(14) Hon, Y.-S.; Lin, S. W.; Lu, L.; Chen, Y.-J. *Tetrahedron* **1995**, *51*, 5019.

(15) Chatterjee, B.; Gunanathan, C. *Chem. Commun.* **2014**, *50*, 888.

(16) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.

(17) (a) Mlynarski, S. N.; Karns, A. S.; Morken, J. P. *J. Am. Chem. Soc.* **2012**, *134*, 16449. (b) Bagutski, V.; Elford, T. G.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2011**, *50*, 1080.

(18) (a) Patel, H. H.; Sigman, M. S. *J. Am. Chem. Soc.* **2016**, *138*, 14226. For synthesis of α-amino phosphonates via Curtis rearrangement, see: (b) Moore, J. D.; Sprott, K. T.; Hanson, P. R. *J. Org. Chem.* **2002**, *67*, 8123.

(19) Alkene reduction is a significant side reaction for (*Z*)-**3a**.

(20) Majeed, R.; Reddy, M. V.; Chinthakindi, P. K.; Sangwan, P. L.; Hamid, A.; Chashoo, G.; Saxena, A. K.; Koul, S. *Eur. J. Med. Chem.* **2012**, *49*, 55.

(21) For recent syntheses of bakuchiol, see: (a) Xiong, Y.; Zhang, G. *Org. Lett.* **2016**, *18*, 5094. (b) Esumi, T.; Yamamoto, C.; Fukuyama, Y. *Synlett* **2013**, *24*, 1845. (c) Gao, F.; McGrath, K. P.; Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 14315.

(22) Reichwein, J. F.; Pagenkopf, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 1821.

(23) Corey, E. J.; Kwiatkowski, G. T. *J. Am. Chem. Soc.* **1966**, *88*, 5654.

(24) Yamagishi, T.; Muronoi, S.; Hikishima, S.; Shimeno, H.; Soeda, S.; Yokomatsu, T. *J. Org. Chem.* **2009**, *74*, 6350 and references cited therein.

(25) The stereochemistry of CAHB is assigned based on correlation via this synthesis.

(26) Guillaneux, D.; Zhao, S.-H.; Samuel, O.; Rainford, D.; Kagan, K. H. *J. Am. Chem. Soc.* **1994**, *116*, 9430.

DOI: 10.1021/jacs.7b02324
J. Am. Chem. Soc. 2017, 139, 6066−6069