Enantioselective Homocrotylboration of Aliphatic Aldehydes

Hongkun Lin,[†] Wenbo Pei,[†] Hao Wang,[‡] Kendall N. Houk,*,[‡] and Isaac J. Krauss*,[†]

[†]Department of Chemistry, Brandeis University, Waltham, Massachusetts 02454-9110, United States

[‡]Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569, United States

S *Supporting Information*

ABSTRACT: A practical route to optically pure *syn*-homocrotylation reagents is described, including highly diastereo- and enantioselective preparation of numerous *syn*-homocrotyl products, as well as several matched mismatched pairs. NMR experiments suggest that the active homocrotylating species is a cyclopropylcarbinyldichloroborane generated by chloride exchange from the $PhBCl_2$ activator. Computational studies support the intermediacy of chloroboranes and suggest that homoallyl/homocrotyl transfers occur through Zimmerman–Traxler transition states.

Highly enantio- and diastereoselective methods have been developed for allylation and crotylation of aldehydes.[1] The success of these methods is in part due to the fact that six-membered Zimmerman–Traxler transition states[2] are possible for allylation. Not only does this result in high selectivity, but the stereochemical outcome of these reactions is readily predictable from the chairlike transition state model. We recently showed that this logic can be extended to homoallylation reactions (Scheme 1), in which the alkene

Scheme 1. Homoallylation Using Allylation Logic
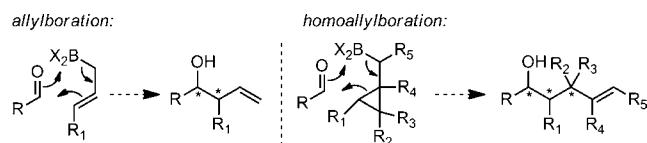
component of the allylation reagent is replaced with a cyclopropane.[3] Not only does this enable access to homocrotyl products which are difficult to obtain stereoselectively by other methods, but either *syn* or *anti* homocrotylation can be selected through the choice of *trans* or *cis* cyclopropane reagents, respectively. Herein we report further advances enabling enantioselective homocrotylation, as well as NMR spectroscopic and computational insight into the mechanism of the reaction.

A difference between crotylation and homocrotylation reagents is that the latter contain chiral centers in the B−C carbon fragment being transferred (Scheme 2); thus, no chiral diol auxiliary is necessary for an asymmetric reaction. According to the Zimmerman–Traxler model, homocrotylation of RCHO with optically pure **1** can lead to only one enantiomer of **3**. The pseudoenantiomeric transition state **4** would lead to disfavored

Scheme 2. Prediction of Highly Enantioselective Homocrotylation
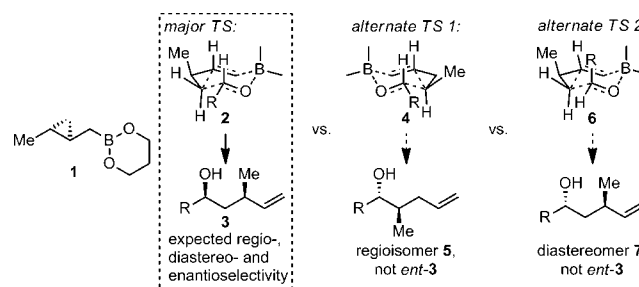
regioisomer **5** rather than *ent*-**3**, and axial placement of the aldehyde R in transition state **6** would lead to diastereomer **7**.

Thus, we predicted that optically pure **1** would be useful for enantioselective homocrotylations, and the primary challenge was to develop a nonracemic reagent synthesis (Scheme 3).

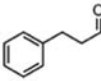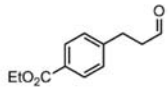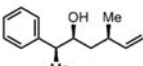### Scheme 3. Synthesis of Homocrotylation Reagent
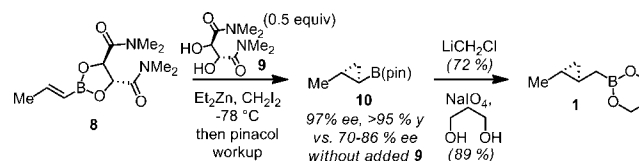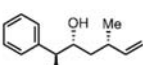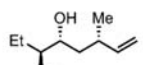
Whereas we previously obtained homocrotylation reagents by cyclopropanation of crotylboronates, we suspected that enantioselective cyclopropanation could more easily be achieved on vinylboronates. Known auxiliary-directed vinylboronate cyclopropanations required diazomethane and/or did not consistently afford the desired level of selectivity.[4] Due to its easy removal, we opted to reexamine the *N,N*-tartaramides utilized by Deng,[4f,g] substituting Et_2Zn/CH_2I_2 for his published conditions with diazomethane/Pd(OAc)2. At −78 °C, the cyclopropanation of **8** gave promising but variable results (70−86% ee after pinacol addition to displace the auxiliary). We suspected that impurities present 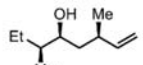in the boronate could account for the variation in ee, and we were pleased to see that addition of 0.5 equiv of excess tartaramide diol **9** to the reaction resulted in a consistently excellent ee of 97% for **10** on multigram scale. One-carbon homologation[5] and conversion of the pinacol boronate to the more reactive propanediol boronate[3] afforded the desired homocrotylation reagent **1** in multigram quantities.

As predicted by the Zimmerman−Traxler model, **1** homocrotylated a wide range of aliphatic aldehydes[6] **11x** with high diastereo- and enantioselectivity (Table 1). Enantiose-

Table 1. Enantioselective Homocrotylation Scope[a]

entry	aldehyde		time	% y	% ee[b] product/dr
1	(phenyl-CH2CH2CHO)	(**11a**)	14 h	83	97
2	*n*-hept-CHO	(**11b**)	14 h	89	97
3	(C₆H₁₁)CHO	(**11c**)	14 h	89	97
4	*i*-PrCHO	(**11d**)	50 h	72 (83)	98
5	*t*-BuCHO	(**11e**)	7 d	62 (84)	98
6	PhCH₂CHO	(**11f**)	14 h	82	97
7	(EtO₂C-aryl-CH2CH2CHO)	(**11g**)	14 h	89	97
8	(PhCH(Me)CHO)	(**11h**)	48 h	83	**12h** >20:1 dr[d]
9[c]	(PhCH(Me)CHO)	(**11h**)[c]	48 h	78	**12h'** >20:1 dr[d]
10	(EtCH(Me)CHO)	(**11i**)	90 h	76 (87)	**12i** >99:1[d]
11[c]	(EtCH(Me)CHO)	(**11i**)[c]	90 h	81 (96)	**12i'** >99:1[d]

[a] 3.0 equiv of **1** and 1.5 equiv of PhBCl₂. Yields are isolated except where parentheses indicate NMR yields. [b] Ee's measured by chiral HPLC of alcohol or its benzoate derivative and are probably equal within error of measurement. Entries 1−7: No *anti* diastereomer was detected. [c] *Ent*-**1** was used. [d] Dr's measured by RP HPLC or GC.

lectivities (entries 1−7) were uniformly high, and in these cases only the *syn* products were observed by NMR. *These results are significant in that no other type of aldehyde addition is capable of affording these syn adducts, either racemic or optically active.* Previous nonracemic syntheses of this motif have required sequences of 4−9 steps.[7]

We were also interested in the ability of **1** to overcome aldehyde facial bias (Table 1, entries 8−11). **11h** is known to undergo Grignard additions with significant Felkin control.[8]

Homocrotylation with **1** proceeded with virtually complete (>20:1) selectivity for the matched Felkin product. By contrast, *ent*-**1** homocrotylated **11h** with virtually complete *anti*-Felkin selectivity, demonstrating essentially complete reagent control of stereochemistry. Similar homocrotylations of optically pure aldehyde **11i** with **1** and *ent*-**1** each resulted in a single homocrotylated product.

To help delineate the nature of activation by PhBCl₂, we initiated spectroscopic studies. Unsubstituted cyclopropyl reagent **13** was treated with 0.5 equiv of PhBCl₂ in CDCl₃, and the reaction was monitored by ¹H NMR (Figure 1A). In
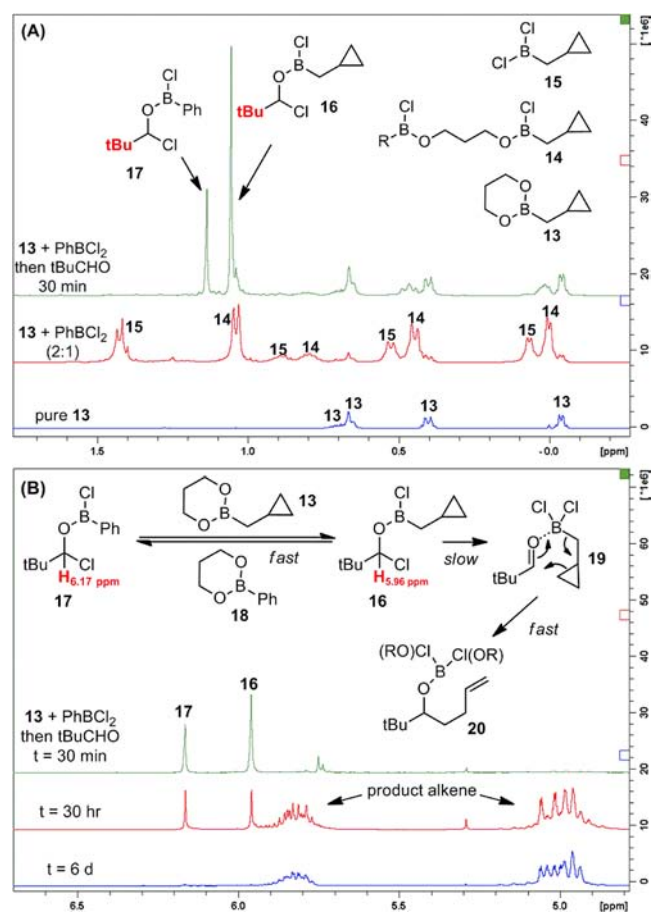
Figure 1. ¹H NMR of (A) addition of 0.5 equiv of PhBCl₂ to boronate **13** in CDCl₃, followed by addition of 0.5 of equiv of ᵗBuCHO and (B) the final mixture from 30 min until completion of the reaction.

addition to the original cyclopropylcarbinyl peaks, two additional sets of peaks were now observed downfield; due to the deshielding effect of chlorides, we interpret the most downfield peaks as cyclopropylcarbinylborondichloride **15** and the remaining peaks as a mixture of monochloride species **14**. After addition of pivaldehyde, no CHO resonance was observed. Instead, two singlets (Figure 1B) appeared at 6.17 and 5.96 ppm δ, concurrent with the disappearance of the resonances for dichloride **15**. We interpret the two singlets around 6 ppm, together with ᵗBu resonances at 1.14 and 1.06 ppm, as belonging to RBCl₂ adducts of the aldehyde, **16** and **17**. Similar adducts with BCl₃ have been proposed by Lappert,[9] and more recently SiCl₄ adducts were observed by Denmark.[10] As homoallylation progresses, adducts **16**/**17** gradually disappear as product alkene peaks grow in (Figure 1B).

Although only **16** can proceed to form product **20**, it is consumed more slowly than **16** and **17** interconvert: thus **16** and **17** disappear at roughly the same rates. Although **16/17** are the only aldehyde-derived species observed during the course of the reaction, the homoallylation likely proceeds through a short-lived intermediate **19**.

We then investigated the possible intermediacy of **19** and compared various transition state energies by DFT computational methods. The calculated enthalpy of complexation to form **19** from aldehyde and **13** is favorable, but the free energy of **19** is 5.9 kcal/mol above that of **16**, consistent with the fact that only **16** is observed (see Supporting Information). We next looked at possible homoallylation transition states (Figure 2),
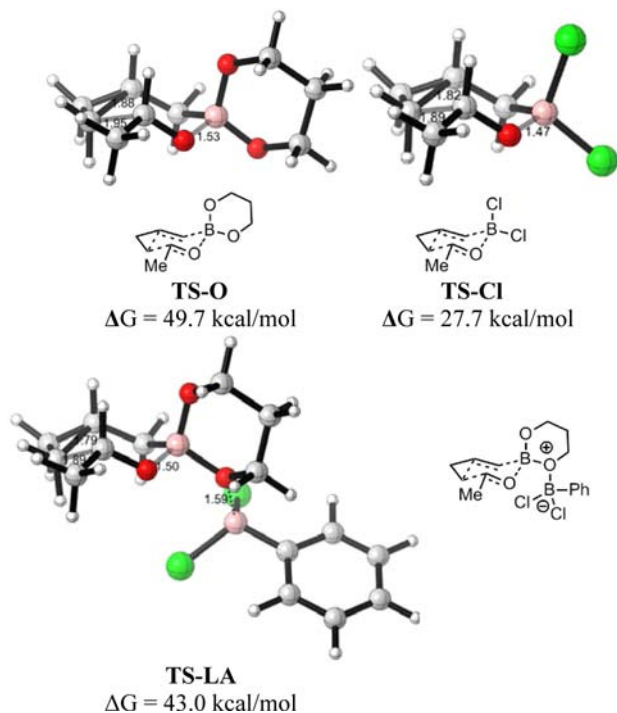

Figure 2. Zimmerman−Traxler transition states for homoallylations.

beginning with the proposed active species, dichlorocyclopropylcarbinylborane **15**. A six-membered chairlike homoallylation transition state, **TS-Cl**, was located with an activation barrier of 27.7 kcal/mol. We then compared this to the potential direct reaction of boronate **13** with acetaldehyde. This transition state, **TS-O**, is a normal chairlike TS, but the activation energy of 49.7 kcal/mol is very high; no reaction is expected, consistent with experiment. By analogy to allylation precedent, we next considered Lewis acid catalysis of homoallylation,[11] with PhBCl$_2$ complexation on the boronate oxygen. We located a transition state, **TS-LA**, with an activation energy of 43.0 kcal/mol, which was also very high. The remarkable energy difference between **TS-Cl** and **TS-O** is due to the stronger B−O coordination and higher electrophilicity of the dichloroborane. In **TS-Cl**, the forming bond distance between the carbonyl oxygen and the boron atom is 1.47 Å, which is shorter than that of **TS-LA** (1.50 Å) or **TS-O** (1.53 Å). The cyclopropane bond is stretched substantially in the concerted homoallylations. The fact that the energy of **TS-LA** is much closer to **TS-O** than to **TS-Cl** is partly due to the entropic cost of bringing together three rather than two molecules, which adds a $-T\Delta S$ term of 6 kcal/mol.[12]

To explore the origins of regio- and stereoselectivity, we performed theoretical calculations for the TSs of the dichloroborane derived from **1** (Scheme 2). **TS-2** (Figure 3)
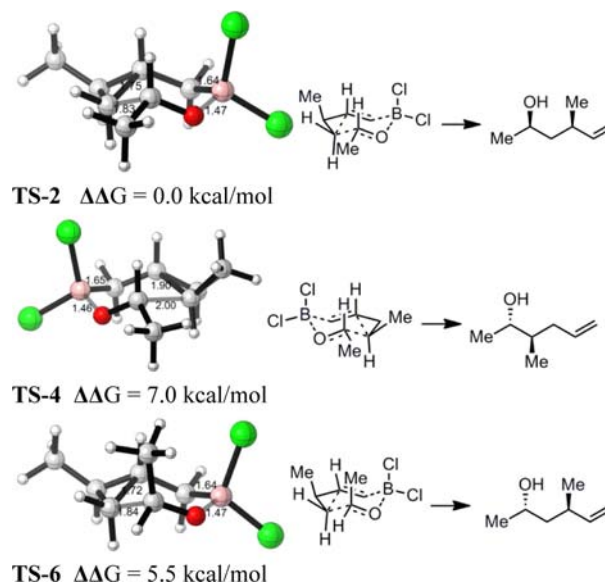

Figure 3. Optimized isomeric transition state structures proposed in Scheme 2.

is the most stable, 7.0 and 5.5 kcal/mol more stable than **TS-4** and **TS-6**, respectively. **TS-6** has an axial methyl and is destabilized in the normal Zimmerman−Traxler sense. **TS-4** is even higher in energy than **TS-2**, and the breaking cyclopropane bond is longer. This indicates steric hindrance to formation of the new bond at the substituted carbon of the cyclopropane, due to a gauche interaction.

In summary, we have developed the first enantioselective *syn* homocrotylation of aldehydes by applying the allylation logic to the homoallylation problem. NMR studies show that cyclopropylcarbinyldichloroboranes are generated by ligand exchange of cyclopropylcarbinylboronates with the PhBCl$_2$ activator. Theoretical calculations further support the theory that the active homoallylating species is a dichloroborane, which transfers the homoallyl group through a Zimmerman−Traxler transition state. We expect that this method will be amenable to enantioselective construction of other stereochemical patterns, and we will report those advances in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedure for preparation of **1**, general procedure for homocrotylation. and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

kraussi@brandeis.edu; houk@chem.ucla.edu

Notes

The authors declare no competing financial interest.

REFERENCES

(1) Reviews on allylation: (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207−2293. (b) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763−2794. (c) Lachance, H.; Hall, D. G. *Organic Reactions*; 73; John Wiley & Sons, Inc.: 2009. For seminal references on crotylation, see: (d) Hoffmann, R. W.; Zeiss, H. J. *Angew. Chem., Int. Ed.* **1979**, *18*, 306−307. (e) Hoffmann, R. W.; Zeiss, H. J. *J. Org. Chem.* **1981**, *46*, 1309−1314.

(2) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920−1923.

(3) Pei, W.; Krauss, I. J. *J. Am. Chem. Soc.* **2011**, *133*, 18514−18517.

(4) (a) Luithle, J. E. A.; Pietruszka, J. *Liebigs Ann. Chem.* **1997**, *1997*, 2297−2302. (b) Pietruszka, J.; Widenmeyer, M. *Synlett* **1997**, 977−979. (c) Luithle, J. E. A.; Pietruszka, J.; Witt, A. *Chem. Commun.* **1998**, 2651−2652. (d) Luithle, J. E. A.; Pietruszka, J. *J. Org. Chem.* **1999**, *64*, 8287−8297. (e) Luithle, J. E. A.; Pietruszka, J. *Eur. J. Org. Chem.* **2000**, *2000*, 2557−2562. (f) Zhou, S.-M.; Deng, M.-Z.; Xia, L.-J.; Tang, M.-H. *Angew. Chem., Int. Ed.* **1998**, *37*, 2845−2847. (g) Chen, H.; Deng, M.-Z. *Org. Lett.* **2000**, *2*, 1649−1651.

(5) Fujioka, Y.; Amii, H. *Org. Lett.* **2008**, *10*, 769−772.

(6) Aromatic aldehydes do not react cleanly in this system, and development of new promotors to overcome this challenge is the subject of further study.

(7) (a) Ghosh, A. K.; Xu, X. *Org. Lett.* **2004**, *6*, 2055−2058. (b) Chen, J.; Forsyth, C. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2148−2152. (c) Ferrié, L.; Reymond, S.; Capdevielle, P.; Cossy, J. *Org. Lett.* **2006**, *8*, 3441−3443. (d) Chandrasekhar, S.; Mahipal, B.; Kavitha, M. *J. Org. Chem.* **2009**, *74*, 9531−9534.

(8) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191−1224.

(9) Frazer, M. J.; Gerrard, W.; Lappert, M. F. *J. Chem. Soc. (Resumed)* **1957**, 739−744.

(10) Denmark, S. E.; Wynn, T.; Beutner, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 13405−13407.

(11) (a) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 11586−11587. (b) Ishiyama, T.; Ahiko, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 12414−12415. (c) Lachance, H.; Lu, X.; Gravel, M.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 10160−10161. (d) Gravel, M.; Lachance, H.; Lu, X.; Hall, D. G. *Synthesis* **2004**, 1290−1302. (e) Rauniyar, V.; Hall, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 4518−4519.

(12) The Lewis acidity of the various boron species and the strength of the incipient B−O bond formed in the transition state are reflected in $\Delta H^{\ddagger}$, which for **TS-LA** is half way between that of **TS-O** and **TS-Cl** ($\Delta H^{\ddagger}$ of **TS-O**, **TS-LA**, and **TS-Cl** are calculated as 36.9, 25.3, and 15.4 kcal/mol, respectively).