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Enantioselective Homocrotylboration of Aliphatic Aldehydes

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

Kendall N. Houk: houk@chem.ucla.edu; Isaac J. Krauss: kraussi@brandeis.edu

[†]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

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 homoal-lyl/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 6-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 chair-like transition state model. We recently showed that this logic can be extended to homoallylation reactions (Scheme 1), in which the alkene 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 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 non-racemic reagent

Correspondence to: Kendall N. Houk, houk@chem.ucla.edu; Isaac J. Krauss, kraussi@brandeis.edu.

Notes

The authors declare no competing financial interests.

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.

synthesis (Scheme 3). Whereas we previously obtained homocrotylation reagents by cyclopropanation of crotylboronates, we suspected that enantioselective cyclopropanation could more easily be achieved on vinyl-boronates. 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 diazome-thane/ $Pd(OAc)_2$. 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 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). Enantioselectivities (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 non-racemic 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 homocrotyl product.

To help delineate the nature of activation by $PhBCl_2$, we initiated spectroscopic studies. Unsubstituted cyclopropyl reagent **13** was treated with 0.5 equiv. of $PhBCl_2$ in $CDCl_3$ and the reaction was monitored by ^1H NMR (Figure 1A). In 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 cyclopropyl-carbinylborondichloride **15**, and the remaining peaks as a mixture of monochloride species **14**. After addition of pivaldehyde, no C**H**O 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 $RBCl_2$ adducts of the aldehyde, **16** and **17**. Similar adducts with $BC1_3$ have been proposed by Lappert,[9] and more recently $SiCl_4$ 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), 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 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) is 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 cyclopropyl-carbinyldichloroboranes are generated by ligand exchange of cyclopropylcarbinylboronates with $PhBCl_2$ 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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11674750] (e) Luithle JEA, Pietruszka J. Eur J Org Chem. 2000; 2000:2557–2562.(f) Zhou SM, Deng MZ, Xia LJ, Tang MH. Angew Chem Int Ed. 1998; 37:2845–2847.(g) Chen H, Deng MZ. Org Lett. 2000; 2:1649–1651. [PubMed: 10880192]

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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 at 36.9, 25.3 and 15.4 kcal/mol, respectively).

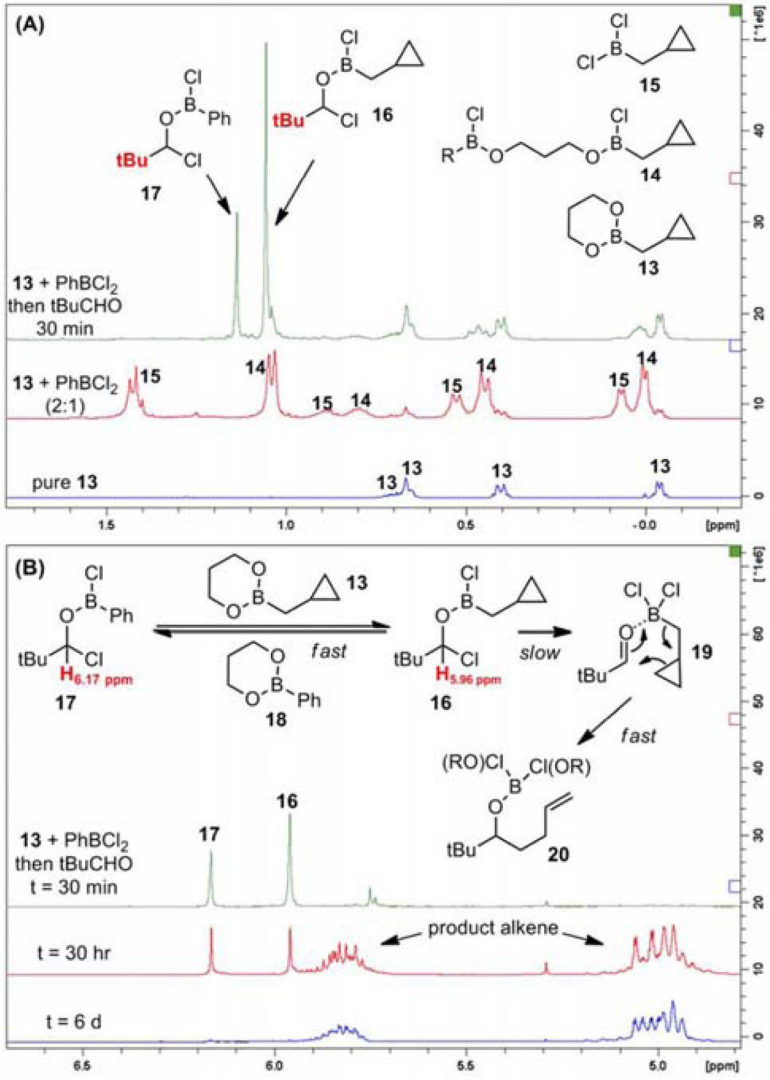


Figure 1.

^{1}H NMR of (A) Addition of 0.5 equiv. $PhBCl_2$ to boronate **13** in $CDCl_3$, followed by addition of 0.5 equiv. ^{t}BuCHO. (B) The final mixture from 30 min until completion of the reaction.

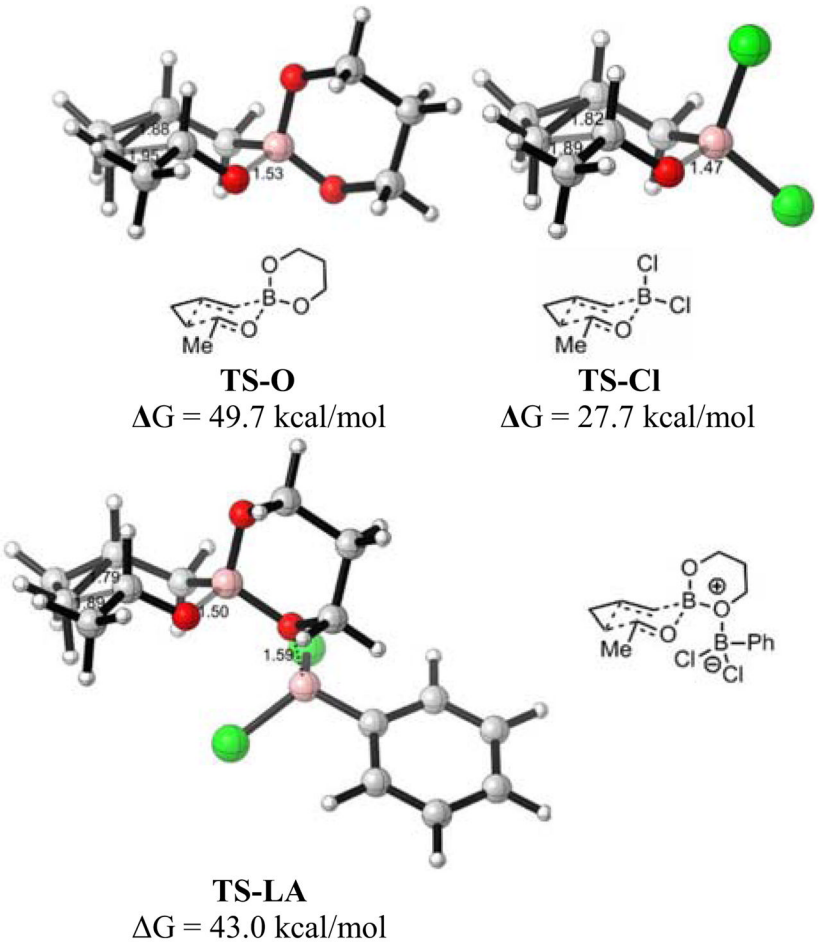


Figure 2.
Zimmerman-Traxler transition states for homoallylations.

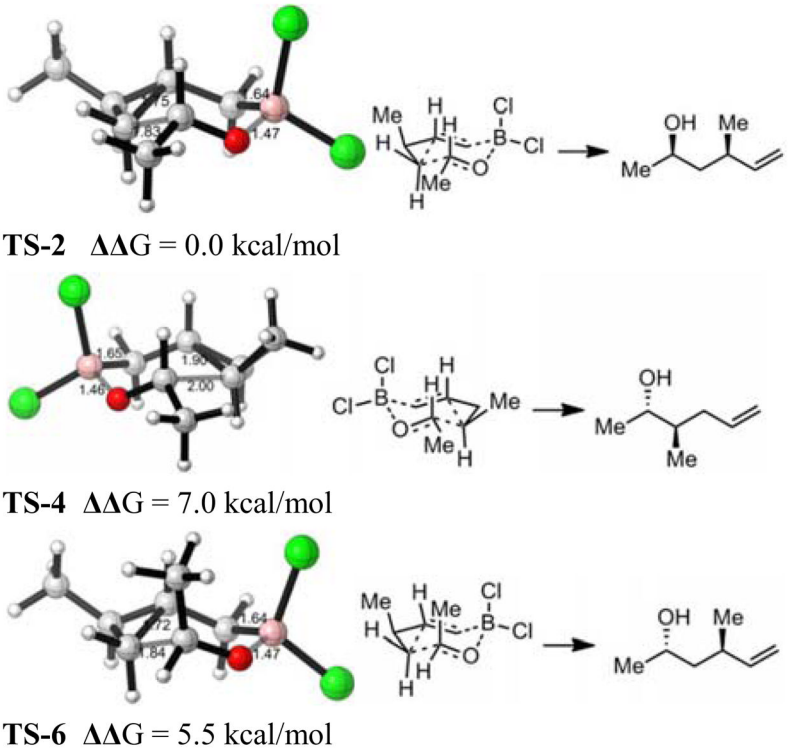
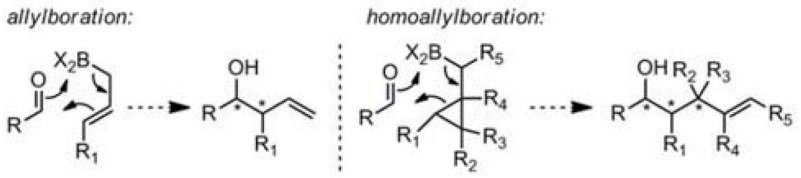
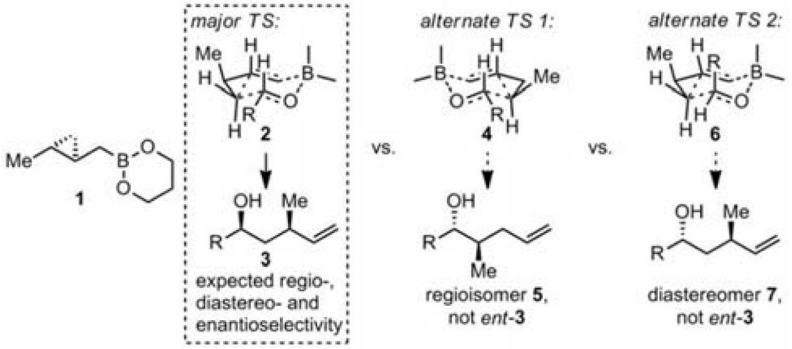


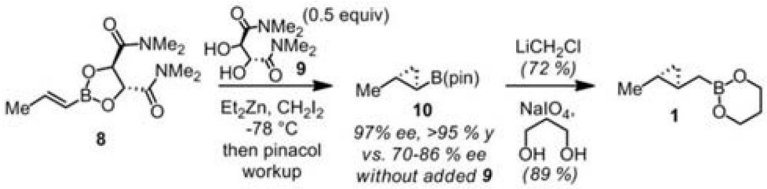
Figure 3.
Optimized isomeric transition state structures proposed in Scheme 2.



Scheme 1.
Homoallylation Using Allylation Logic



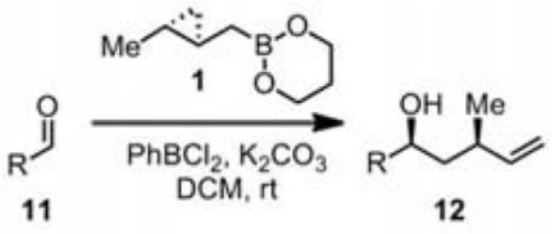
Scheme 2.
Prediction of Highly Enantioselective Homocrotylation

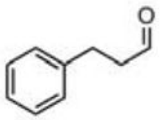
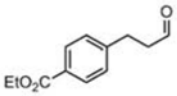
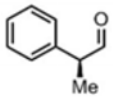
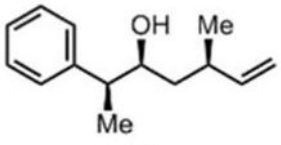
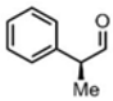
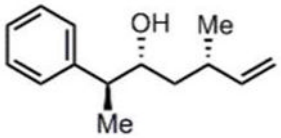


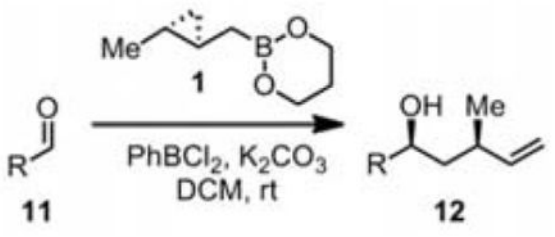
Scheme 3.
Synthesis of Homocrotylation Reagent

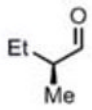
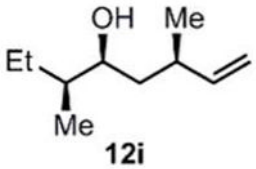
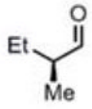
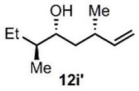
Table 1

Enantioselective Homocrotylation Scope[a]



entry	aldehyde	time	% y	% ee[b] product/dr
1	 (**11a**)	14 h	83	97
2	*n*-hept-CHO (**11b**)	14 h	89	97
3	(C_6H_{11})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	$PhCH_2CHO$ (**11f**)	14 h	82	97
7	 (**11g**)	14 h	89	97
8	 (**11h**)	48 h	83	 **12h** >20:1 dr[d]
9[c]	 (**11h**)[c]	48 h	78	 **12h'** >20:1 dr[d]



entry	aldehyde	time	% y	% ee[b] product/dr
10	 (**11i**)	90 h	76 (87)	 **12i** >99:1[d]
11[c]	 (**11i**)[c]	90 h	81 (96)	 **12i'** >99:1[d]

[a] 3.0 equiv **1** and 1.5 equiv $PhBCl_2$. 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.