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Catalysis by Temporary Covalent Activation. A Novel Catalysis of Unactivated Diels-Alder Reactions

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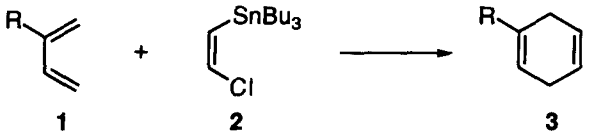
Abstract: Diels-Alder reactions of *cis*-2-chlorovinyltributylstannane are greatly accelerated by the presence of catalytic amounts of haloboranes. Mechanistic studies support a mechanism for the catalysis involving an intermediate boron-activated dienophile. A similar but simpler catalysis of Diels-Alder reactions of unactivated alkynes, via a hydroboration - Diels-Alder - dehydroboration mechanism, is also described. © 1997 Elsevier Science Ltd.

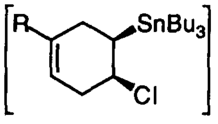
A major limitation of the Diels-Alder reaction is the intrinsic lethargy and inefficiency of reactions of electronically neutral addends. This has resulted in considerable interest in methods for catalyzing unactivated Diels-Alder reactions. Successful approaches include electron-transfer catalyzed reactions occurring via cation-radicals,[1] proton-catalyzed reactions involving allylic cations,[2] and transition-metal catalyzed reactions,[3] the last being more effective in intramolecular examples.[4,5] We report here a conceptually new method for catalysis of Diels-Alder reactions in which an electron-withdrawing activating group is temporarily covalently bound to the dienophile during the catalytic cycle.

Lewis acids can considerably enhance the reactivity and selectivity of Diels-Alder reactions of dienophiles already activated by carbonyl or nitrile groups, but usually have no effect on unactivated dienophiles. We were therefore intrigued by our observations with the Diels-Alder reaction of *cis*-2-chlorovinyltributylstannane (**2**). The dienophile **2** was of interest as an acetylene equivalent due to a facile elimination from the assumed intermediate **4** to form **3**. However, **2** is very unreactive and its direct reaction with dienes under forcing conditions affords only low yields of **3**. In surprising contrast, the Diels-Alder reactions of **2** proceed readily at room temperature in hexanes in the presence of 15 mol % BCl_3.

Insight into this result came from a variety of observations. 1. Two other haloborane-based Lewis acids, 9-bromo- and 9-chloro-9-borabicyclononane (Br-BBN and Cl-BBN), were effective catalysts in methylene chloride. However, no product was formed with diethylaluminum chloride as catalyst. 2. Tris(*p*-bromophenyl)aminium hexachloroantimonate, a common initiator for electron-transfer mediated reactions, did not catalyze the reaction. 3. BCl_3 did not react with the diene under the reaction conditions in the absence of **2**. In the absence of diene, BCl_3 appeared by ^1H NMR to react with **2** to form a complex mixture of materials. However, Cl-BBN appeared by NMR to react cleanly with **2** to form a new material. A



1 **2** **3**



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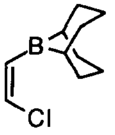
R = Ph		R = *t*-Bu	
140 °C, 24 h	3%	80 °C, 120 h	5%
15 mol % BCl_3 48 h, 25 °C	71%	15 mol % BCl_3 96 h, 25 °C	74%
15 mol % Br-BBN 144 h, 60 °C	78%	20 mol % Cl-BBN 240 h, 80 °C	73%

preparative reaction of **2** with stoichiometric Cl-BBN afforded 9-(*cis*-2-chlorovinyl)-9-BBN (**5**). 4. None of **3** was formed when *cis*-2-iodovinyltributylstannane (**6**) was used in place of **2**.[6] Notably, no direct reaction between **6** and BCl_3 or Cl-BBN could be observed. 5. The reaction of the pre-formed **5** with dienes under the reaction conditions afforded **3**.



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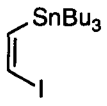

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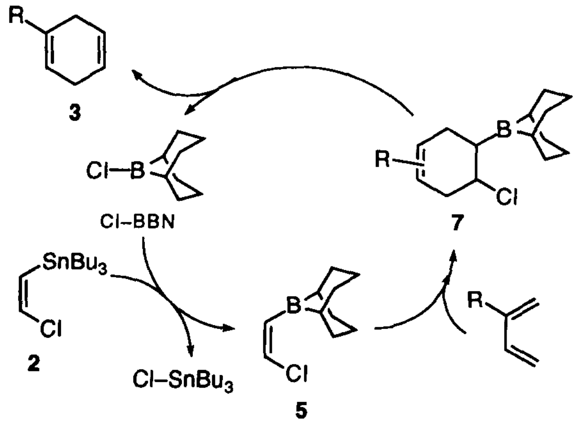
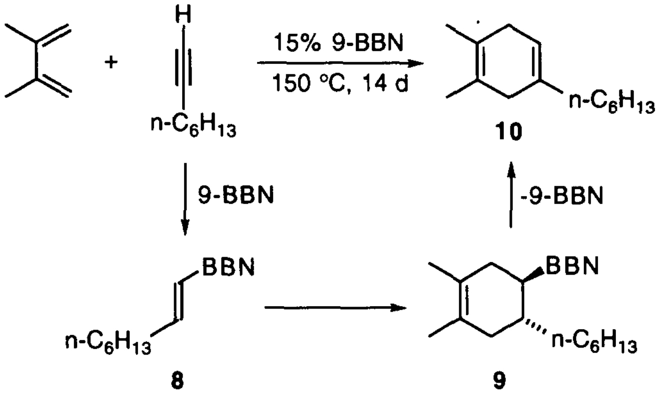
These observations suggest the catalytic cycle shown in Scheme I for the simplest case of catalysis by Cl-BBN, in which the haloborane acts not as a Lewis acid but as the source of the dienophile's activating group. Boron-tin transmetallation[7] between **2** and Cl-BBN would produce **5**. Since **5** is now an activated dienophile,[8] it can react with the diene to form **7**, which could then eliminate the haloborane to afford the product **3** and continue the catalytic cycle. The reactions of BCl_3 may be complicated by the possibility of varying levels of boron-tin transmetallation but could follow an overall similar mechanism.

Scheme I



To check this mechanism, the kinetics of the individual steps were determined in NMR experiments and compared with the overall catalytic reaction. The boron-tin transmetallation of **2** with Cl-BBN is fast at 25 °C, fitting the rate law: rate = k_{tm}•[**2**][Cl-BBN] with k_{tm} = $4.5 \pm 0.5 \times 10^{-4}$ $M^{-1}s^{-1}$. The rate of elimination of haloborane from **7** was assumed to be fast since **7** could not be observed under any conditions. The reaction of pre-formed **5** with 2-*tert*-butylbutadiene fit the rate law: rate = k_{DA}•[**5**][diene] with k_{DA} = $5.5 \pm 0.5 \times 10^{-6}$ $M^{-1}s^{-1}$ at 80 °C. With this reaction as the slow step, the initial rate of the catalytic reaction would be expected to be: k_{DA}•[Cl-BBN_{init}][diene]. Fitting of experimental data for the catalytic reaction at 80 °C to the equation k_{app}•[Cl-BBN_{init}][diene] gives $k_{app} \approx 2.3 \times 10^{-6}$ $M^{-1}s^{-1}$. That $k_{app} \leq k_{DA}$ shows that the mechanism in Scheme I is a kinetically competent catalytic cycle.

We have explored briefly the potential for a simpler catalytic reaction. Control experiments indicate that the neat reaction of 1-octyne with 2,3-dimethylbutadiene proceeds very slowly at 150 °C - a neat equimolar reaction went to <2% completion in 18 hours. However, the addition of 15 mol % 9-BBN in THF accelerates the reaction, despite an ≈2-fold dilution, to 21% completion in 18 hours. After 14 days a 65% yield of the cyclohexadiene **10** was formed. A plausible mechanism involves an initial hydroboration to generate the activated dienophile **8** followed by a Diels-Alder reaction to form **9** and final dehydroboration to form **10** and reform the catalytic 9-BBN. Both the Diels-Alder step and the dehydroboration to form the 1,4-cyclohexadiene occur when isolated intermediates, prepared in stoichiometric reactions, are subjected to the reaction conditions.



Although the prolonged heating required in this last example is daunting, the catalysis by hydroboration suggests considerable generality to the idea of temporary covalent activation. We plan to continue exploring this idea with the goal of developing mild catalyzed reactions of unactivated dienophiles.

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