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Asymmetric Conjugate Addition of Alkynylboronates to Enones: Rationale for the Intriguing Catalysis Exerted by Binaphthols

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Catalytic asymmetric carbon−carbon bond forming reactions represent an extremely valuable synthetic procedure for preparing enantiomerically pure chiral compounds. Recently, Wu and Chong have reported that the asymmetric conjugate additions of *B*-1-alkynyldiisopropylboronates **2** to enones **1** catalyzed by binaphthols **3** occur smoothly, affording alkynes **4** with high yields and enantiomeric excesses (Scheme 1).[1,2] The development of this methodology constitutes a key contribution to the progress of modern asymmetric synthesis since it proves that the use of catalytic amounts of “exchangeable” chiral ligands on boron can be used to promote asymmetric transformations.

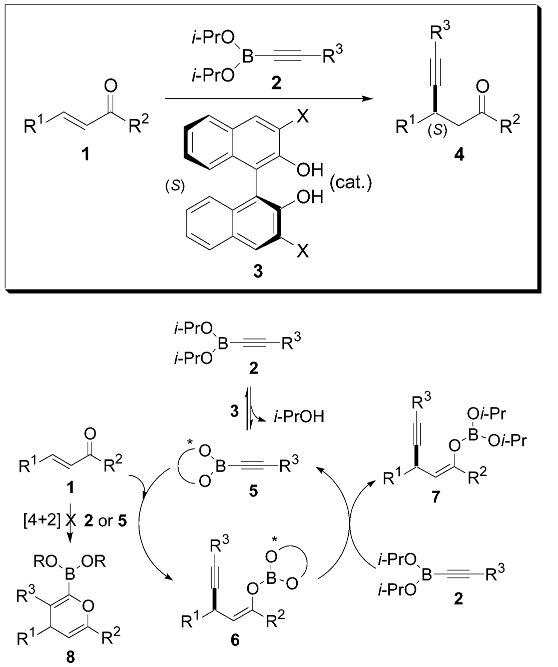
On the basis of experimental observations, the authors propose the catalytic cycle depicted in Scheme 1. The rapid equilibrium established between diisopropylboronate **2** and its chiral analogue **5** is followed by the conjugate addition of **5** to enone **1**, which appears to be the rate-determining step. The alkylated product (**6**) subsequently exchanges ligands with **2** to simultaneously yield diisopropoxyboron enolate **7** and regenerate **5**. Final protonation of **7** during workup affords the β-alkynyl ketone **4**.

This scheme will work only if the reactivity of the different components is finely balanced. First, **2** must not react with **1** to compete with the reaction of **5** with **1**. Second, however, **2** must also be reactive enough to allow the initial equilibrium (**2** to **5**) to be established and to convert **6** to **7** while regenerating **5**. Third, the chiral ligand must be small enough that the reaction of **5** with **1** goes smoothly, and yet hindered enough that it can stereodifferentiate the *Re* and *Si* faces of the enone to induce chirality in the conjugate addition. Fourth, these conditions must not lead to **8** through a [4 + 2] cycloaddition, which occurs for the analogous alkynylborane/diene system.[3,4]

To gain a deeper understanding of the factors responsible for the intriguing catalysis exerted by binaphthols, to investigate the limits on the variations possible for this process, and to explain the direction of the stereoinduction, we have performed a theoretical study at the B3LYP/lacvp* level of theory using *Jaguar* version 4.2.[5,6] We have investigated the reaction between enone **1a** ($R^1 = Ph$, $R^2 = CH_3$) and model alkynylboronate **2a** ($R^3 = CH_3$) using 3,3′-diiodo-2,2′-biphenol as a model for the most effective binaphthol catalyst **3a** ($X = I$), which would lead to chiral alkynylboronate **5a**. We have located the transition structures (TSs) for the conjugate addition of **2a** and **5a** to **1a** (Figure 1).

The calculations correctly reproduced the effect of catalysis produced by binaphthol **3a**, as well as the sense of asymmetric induction. The energy barrier for the reaction of **1a** with **2a** is much higher than that for **1a** with the chiral alkynylboronate **5a**.

Scheme 1



The boron atom of alkynylboronate **5a** binds tightly to enone **1a** and activates it effectively for the reaction. The boron in **2a** is less able to do this. This is illustrated by the B−O1 distances, which are considerably shorter in the TSs with **5a** than with **2a**, and is further demonstrated by the NBO analysis (see Supporting Information).[7] In addition, QRC analysis[8] of the TSs connects the reactants and the product for the reaction of **1a** with **2a**, but connects the products to a complex between the reactants **1a** and **5a**. The formation of a complex between enone **1a** and alkynylboronate **5a** lowers the energy of the LUMO of the enone moiety from −0.07 to −0.11 eV and so facilitates the conjugate addition process.

Wu and Chong also tested ethylene glycol and pinacol, and none of these gave the desired product.[1] The TSs for the corresponding propynylboronates (**9** and **10**, respectively) reacting with **1a** have also been found (see Supporting Information), and the barriers are similar to that for the reaction of **2a** (ca. 23 kcal mol^{-1}). We were not able to locate the complex between **1a** and **9** or **10**, and QRC analysis of the TSs leads directly to products and reactants, like **2a** and unlike **5a**. This lack of reactivity might be explained by steric effects for **2a** and **10**, but the ethylene glycol derived reagent (**9**) does not have great steric demands. The difference in reactivity may also be due to the ability of the oxygen lone pairs to donate into the vacant boron orbital. For isolated **2a**, **9**, and **10**, the C−O−B−C1′ angles are close to either 180 or 0°. For **5a**, however, this angle is 147°, twisted substantially from the plane and reducing

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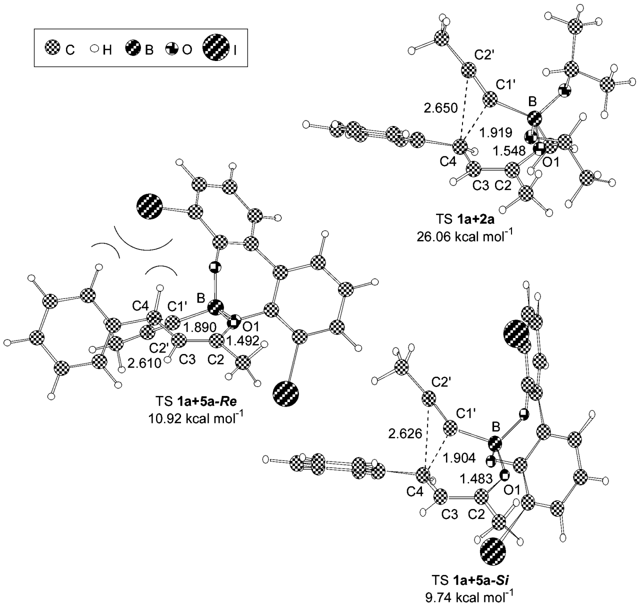


Figure 1. B3LYP/lacvp* transition structures of the conjugate additions of alkynylboronates **2a** and **5a** to enone **1a**. Selected distances (in Å) and B3LYP/lacvp* activation energies including zero-point energy (ZPE) corrections are shown.

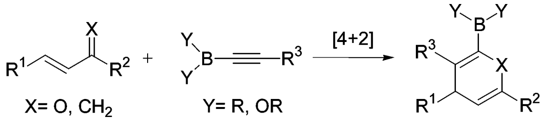
the oxygen lone pair's ability to donate into the vacant boron orbital. This is reinforced by the possibility of delocalization into the adjacent aromatic systems and by the presence of electron-withdrawing groups on the 3 and 3′ positions of the aromatic system, which further withdraw electron density from the oxygens, enhancing the Lewis acid character of the boron.

NBO values show that TSs **1a**+**5a**-***Re*** and -***Si*** present similar interactions. However, the former has two close contacts between one of the iodines of the chiral boronate and two hydrogens in the enone (3.14 and 3.17 Å, Figure 1). These destabilizing interactions can be invoked to account for the facial discrimination of compound **5a**. The energy difference computed between TSs **1a**+**5a**-***Re*** and -***Si*** (1.18 kcal mol^{-1}) predicts a 87:13 *S*/*R* ratio for product **4**, which agrees reasonably well with the experimental ratio for the reaction of **1a** using *B*-1-octynyldiisopropylboronate and catalyst **3a** (X = I) (97:3 *S*/*R*).

The reaction coordinates for the stoichiometric reaction of alkynylboronate **2a** and for the catalytic cycle proposed for binaphthol have also been inspected (Scheme 1, see Supporting Information). In addition, the influence of thermal effects on the kinetics and the thermodynamics of these processes has been taken into account. For alkynylboronate **5a**, the thermodynamic penalties of the initial coordination and the disproportionation suggest that these steps might be reversible. On the other hand, the alkynylboration product (**6a**) lies ca. 15 kcal mol^{-1} lower than the starting complex, shifting the equilibrium to the formation of the product. Therefore, the formation of a complex between **1a** and **5a** favors both the kinetics and the thermodynamics of the conjugate addition, playing a crucial role in the overall process.

We have also studied the hetero-Diels−Alder reactions of enone **1a** with alkynylboronates **2a** and **5a** (Scheme 2, X = O and Y = OR).[9] These competitive processes are related to the Diels−Alder reactions between alkynylboranes and 1,3-dienes (Scheme 2, X = CH_2 and Y = R).[3,4] Previous theoretical studies on these systems suggested that the [4 + 2] cycloaddition is kinetically favored over the 1,4-alkynylboration.[10] The Diels−Alder reaction can occur either through classical [4 + 2] TSs with [4 + 3] C−B secondary orbital interactions or through [4 + 3] TSs (DATSs).

Scheme 2



We have located the TSs for the competing hetero-Diels−Alder reaction of enone **1a** and alkynylboronates **2a** and **5a** (see Supporting Information). For **2a**, we have found the [4 + 2] TS (DATS **1a**+**2a**-**A**) and the [4 + 3] TS (DATS **1a**+**2a**-**B**), whereas for **5a**, only nonclassical TSs could be located (DATS **1a**+**5a**-**B**-***Re*** and -***Si***). All attempts to locate the [4 + 2] TSs merged in the [4 + 3] TSs. This could be attributed to the higher electrophilic character of the boron atom of **5a**. Again, the Diels−Alder TSs for **2a** connect the product and the reactants, while the TSs for **5a** connect the products to a complex between the reactants. In agreement with experimental results, the hetero-Diels−Alder reactions were predicted to be kinetically disfavored relative to the alkynylborations by about 10 kcal mol^{-1} for **5a**.

In summary, we have shown that the stringent requirements for Chong's catalytic cycle to work are consistent with the calculated reaction pathways. The inability of different achiral ligands to perform the conjugate addition reaction also fits this scheme. This demonstrates that the computational procedure is able to analyze this finely balanced reactivity, to distinguish between competing reaction pathways, and so guide the choice of potential reagents.

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Supporting Information Available: Geometries, Cartesian coordinates, absolute energies, and number of imaginary frequencies of all stationary points; imaginary frequencies of all transition structures; conformers for **2a** and derived transition structures; reaction coordinates for the reactions of **2a** and **5a**; energies and atomic coefficients of the frontier molecular orbitals of the reactants. This material is available free of charge via the Internet at http://pubs.acs.org.

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