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Authors: Ming Zhang and Xiao-Chen Wang

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RESEARCH ARTICLE

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Bifunctional Borane Catalysis of a Hydride Transfer/Enantioselective [2+2] Cycloaddition Cascade

Ming Zhang, and Xiao-Chen Wang*

[*] M. Zhang, Prof. Dr. X.-C. Wang
State Key Laboratory and Institute of Elemento-Organic Chemistry, College of Chemistry, Nankai University
94 Weijin Road, Tianjin 300071 (China)
E-mail: xcwang@nankai.edu.cn
Homepage: http://www.wangnankai.com/

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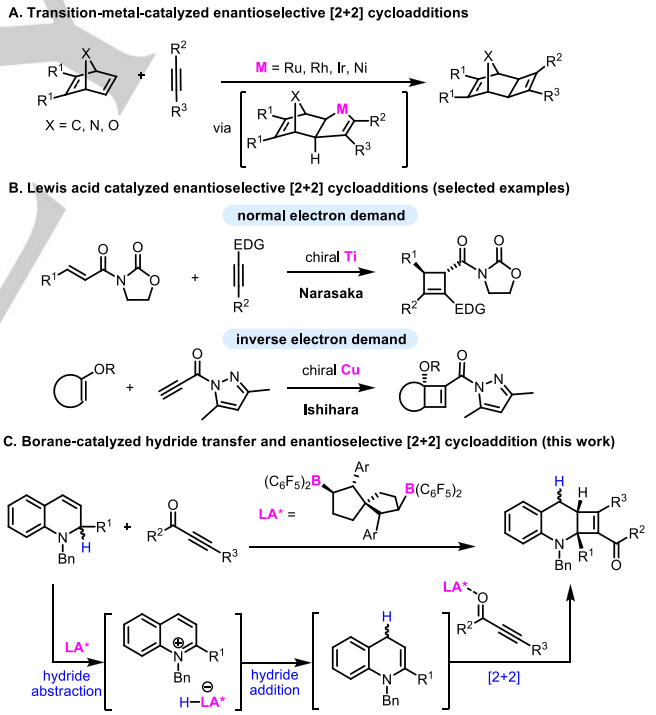
Abstract: Herein, we present a mild and efficient method for synthesizing enantioenriched tetrahydroquinoline-fused cyclobutenes through a cascade reaction between 1,2-dihydroquinolines and alkynones with catalysis by chiral spiro-bicyclic bisboranes. The bisboranes served two functions: first they catalyzed a hydride transfer to convert the 1,2-dihydroquinoline substrate to a 1,4-dihydroquinoline, and then they activated the alkynone substrate for an enantioselective [2+2] cycloaddition reaction with the 1,4-dihydroquinoline generated in situ.

Introduction

Chiral cyclobutene skeletons are prevalent in natural products and drugs.[1] The catalytic enantioselective [2+2] cycloaddition reaction between an alkyne and an alkene is one of the most direct and atom-economical methods for synthesizing enantioenriched cyclobutenes. Transition metals such as Ru, Rh, Ir, and Ni are known to promote these reactions via a sequential process involving alkene/alkyne oxidative coupling and reductive elimination, but enantioselective examples have been confined to highly reactive strained olefins, such as norbornene, norbornadiene, and aza- or oxa-bridged cyclic olefins (Scheme 1A).[2] There have also been sporadic reports of alternative mechanisms for transition-metal-catalyzed enantioselective cyclobutene formation, including the palladium-catalyzed Heck reaction[3] and nucleophilic addition of alkenes to gold-activated alkynes.[4] In addition, photocatalytic [2+2] cycloaddition is feasible,[5] but enantiocontrol is challenging.

In contrast, Lewis acid catalyzed [2+2] cycloadditions between alkynes and alkenes show promise for the generation of cylcobutenes.[6] However, there have been only a few reports of enantioselective reactions, most of which have involved substrates capable of bidentate coordination to the Lewis acid[7] (Scheme 1B). Such coordination facilitates substrate activation and decreases the conformational flexibility of the substrate, an effect that is essential for diastereo- and enantioselectivity. So far, there has been only one report of highly enantioselective cycloaddition reactions involving monodentate substrates: Feng, Liu, and co-workers carried out enantioselective [2+2] cycloaddition reactions of alkynones with cyclic silyl enol ethers with catalysis by a *N*,*N*'-dioxide-zinc(II) complex.[8]

Because of our ongoing interest in catalysis using Lewis acidic boranes,[9] we reasoned that chiral borane catalysts might promote enantioselective [2+2] cycloaddition reactions of alkenes with alkynes. In fact, we herein report a protocol for mechanistically novel borane-catalyzed reactions between 1,2-dihydroquinolines and alkynones (Scheme 1C). These reactions occurred via a cascade process promoted by a bifunctional pentafluorophenyl-substituted chiral borane, which first facilitated conversion of the 1,2-dihydroquinoline to a 1,4-dihydroquinoline via a hydride transfer and then activated the alkynone via monodentate coordination for enantioselective [2+2] cycloaddition with the 1,4-dihydroquinoline. These are the first examples of Lewis acid catalyzed enantioselective [2+2] cycloaddition reactions between electron-rich enamine intermediates and electron-deficient alkynes. Moreover, this is also a rare report of a chiral borane Lewis acid acting both as a conventional Lewis acid (to activate a carbonyl) and as an unconventional Lewis acid (to catalyze hydride transfer) in a single reaction.



Scheme 1. Enantioselective synthesis of cyclobutenes via [2+2] cycloaddition reactions

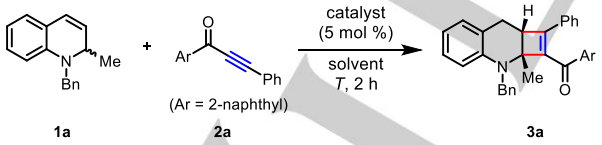
We chose pentafluorophenyl-substituted boranes because they have many unique and interesting activities attributable to their strong Lewis acidity and sterically hindered boron center.[10] For example, $B(C_6F_5)_3$ can mediate hydride abstraction from the α carbon of an amine to generate an iminium ion and a borohydride.[11] Recently, this activity has become a flourishing platform for the development of catalytic organic reactions, including transfer hydrogenations,[12] dehydrogenations,[13] Mannich-type reactions,[14] cyclizations,[15] and

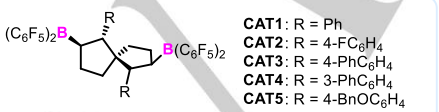
dehydrogenation/functionalization cascade reactions.[16] Intrigued by this activity, we hypothesized that boranes might perhaps convert 2-alkyl-substituted 1,2-dihydroquinolines (which can easily be prepared by reaction of an alkyllithium reagent with an unsubstituted quinoline) to 1,4-dihydroquinolines, which are much less synthetically accessible, via borane-mediated hydride transfer. Subsequently, if an alkynone was present, the boranes could activate the alkynone for an inverse-electron-demand [2+2] cycloaddition reaction with the 1,4-dihydroquinoline. Moreover, a chiral borane catalyst might be able to control the enantioselectivity.

Results and Discussion

To test our hypothesis, we began by carrying out reactions of 1,2-dihydroquinoline **1a** with alkynone **2a** at 30 °C in toluene in the presence of various Lewis acid catalysts (Table 1). First, we tested several commonly used Lewis acids—$Sc(OTf)_3$, $Zn(OTf)_2$, $Mg(OTf)_2$, $FeCl_3$, and $BF_3{\cdot}OEt_2$—but none of them were active under these conditions (entries 1–5). Encouragingly, however, when we used $B(C_6F_5)_3$ (10 mol %), the desired hydride transfer/[2+2] cycloaddition cascade occurred to afford tetrahydroquinoline-fused cyclobutene **3a** in 23% yield (entry 6). We then tested some chiral boranes with the goal of achieving an enantioselective reaction. Interestingly, chiral spiro-bicyclic bisborane[17] **CAT1** gave **3a** in a greatly improved yield (85%) with an ee of 68% (entry 7). Next, we tested four bisborane catalysts with substituted aryl rings (**CAT2**–**CAT5**, entries 8–11) and found that the enantioselectivity was markedly improved by a 4-benzoxyphenyl-substituted catalyst (**CAT5**), which gave an 81% yield and an 85% ee (entry 11). Changing the solvent to *n*-hexane or THF resulted in little to none of the desired product (entries 12 and 13). The yield was slightly higher in DCE than in toluene, but the enantioselectivity was slightly lower (entry 14). Performing the reaction in $CHCl_3$ gave the highest enantioselectivity (87% ee, entry 15). Moreover, adding 4 Å molecular sieves increased the ee to 89% (entry 16). The enantioselectivity improved further when we decreased the reaction temperature; at 0 °C, **3a** was obtained in 92% yield and 93% ee (entry 18).[18]

Table 1. Optimization of reaction conditions[a]



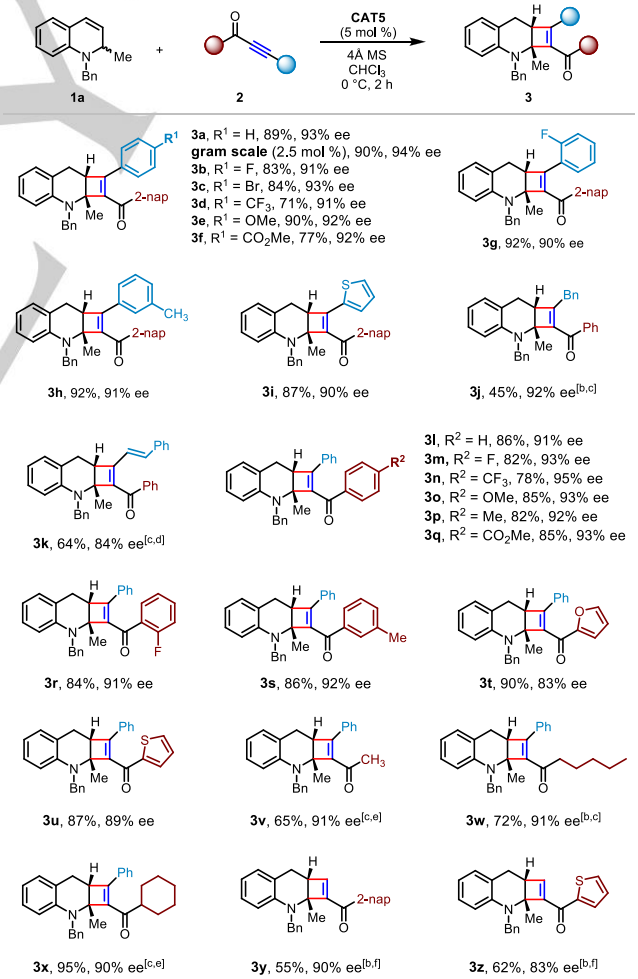


entry	catalyst	solvent	*T* (°C)	yield (%)[b]	ee (%)[c]
1	$Sc(OTf)_3$	toluene	30	n.d.	–
2	$Zn(OTf)_2$	toluene	30	n.d.	–
3	$Mg(OTf)_2$	toluene	30	n.d.	–
4	$FeCl_3$	toluene	30	n.d.	–
5	$BF_3{\cdot}OEt_2$	toluene	30	n.d.	–
6[d]	$B(C_6F_5)_3$	toluene	30	23	–
7	**CAT1**	toluene	30	85	68
8	**CAT2**	toluene	30	93	56
9	**CAT3**	toluene	30	82	75
10	**CAT4**	toluene	30	79	61
11	**CAT5**	toluene	30	81	85
12	**CAT5**	*n*-hexane	30	16	80
13	**CAT5**	THF	30	n.d.	–
14	**CAT5**	DCE	30	92	82
15	**CAT5**	$CHCl_3$	30	89	87
16[e]	**CAT5**	$CHCl_3$	30	90	89
17[e]	**CAT5**	$CHCl_3$	10	91	92
18[e]	**CAT5**	$CHCl_3$	0	92	93

[a] Unless otherwise noted, all reactions were performed with 5 mol % of a catalyst, 0.24 mmol of **1a**, and 0.20 mmol of **2a** in 2 mL of solvent for 2 h. [b] NMR yields; n.d. = not detected. [c] Determined by HPLC with a chiral column. [d] The amount of $B(C_6F_5)_3$ was 10 mol %, and the reaction time was 12 h. [e] Molecular sieves (4 Å, 50 mg) were added.

We then explored the substrate scope with respect to the alkynone by carrying out reactions with **1a** (Table 2). Alkynones with an electron-donating or electron-withdrawing substituent at the *para* position of the phenyl ring were well tolerated, giving the corresponding cyclobutenes (**3a**–**3f**) in moderate to high yields (71–90%) with excellent ee values (91–93%). *ortho*-

Table 2. Substrate scope with respect to the alkynone[a]

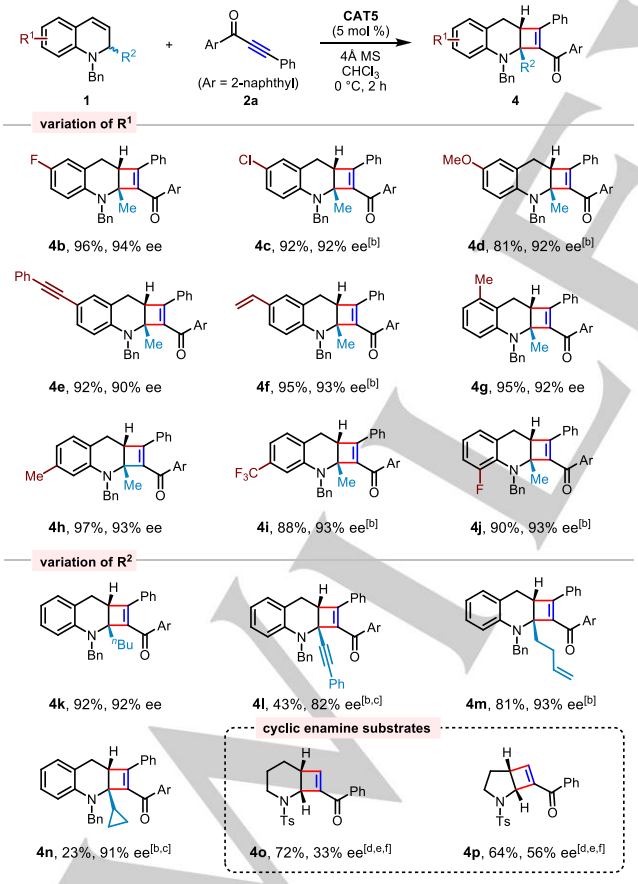


[a] Unless otherwise noted, all reactions were performed with 5 mol % of **CAT5**, 0.24 mmol of **1a**, 0.20 mmol of **2**, and 50 mg of 4 Å molecular sieves in 2 mL of $CHCl_3$ at 0 °C for 2 h; isolated yields are provided. [b] −20 °C. [c] 24 h. [d] −50 °C. [e] −30 °C. [f] 1 h.

Fluorophenyl-, *meta*-tolyl- and 2-thienyl-substituted alkynones were also compatible (**3g**–**3i**). When the alkyne was substituted with a benzyl or styryl group, the reaction occurred, but either the yield (**3j**) or the enantioselectivity (**3k**) decreased. As for the ketone substituent, substrates with an aryl ring bearing various groups were reactive, providing cyclobutenes **3l**–**3s** in 78–86% yields and 91–95% ee.[18] 2-Furyl and 2-thienyl compounds gave the corresponding products (**3t** and **3u**) with 83% ee and 89% ee, respectively. Ketones with an alkyl group (methyl, *n*-pentyl, or cyclohexyl) were also suitable, affording **3v**–**3x** with excellent enantioselectivities. Furthermore, the reaction was compatible with terminal alkynes (**3y** and **3z**).[19] Finally, a gram-scale reaction between **1a** and **2a** in the presence of only 2.5 mol % of catalyst gave **3a** in 90% yield with 94% ee.

Next, we explored the substrate scope with respect to the 1,2-dihydroquinoline by carrying out reactions with alkynone **2a** (Table 3). Substrates with a 6-fluoro, 6-chloro, or 6-methoxy substituent were tolerated, affording desired products **4b**–**4d** in good yields (81–96%) with high enantioselectivities (92–94% ee). Notably, unsaturated alkynyl and vinyl substituents were untouched by the reaction conditions; products **4e** and **4f** were obtained in excellent yields and enantioselectivities. Substrates with a 5-methyl, 7-methyl, 7-trifluoromethyl, or 8-fluoro substituent reacted smoothly to give desired products **4g**–**4j**, respectively, in 88–97% yields with 92–93% ee. Changing the 2-methyl group to a 2-butyl group was tolerated; **4k** was obtained

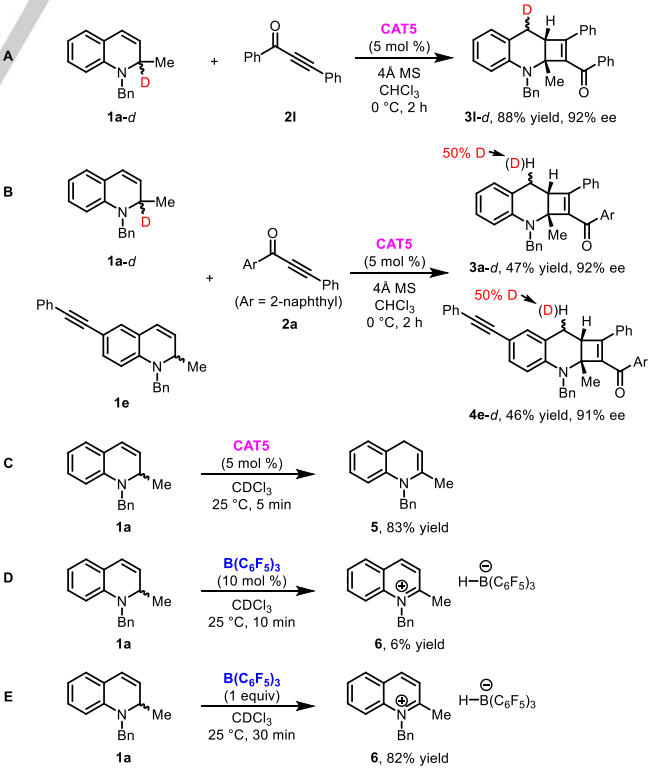
Table 3. Substrate scope with respect to the 1,2-dihydroquinoline[a]



[a] Unless otherwise noted, all reactions were performed with 5 mol % of **CAT5**, 0.24 mmol of **1**, 0.20 mmol of **2a**, and 50 mg of 4 Å molecular sieves in 2 mL of $CHCl_3$ at 0 °C for 2 h; isolated yields are provided. [b] 24 h. [c] 20 °C. [d] 0.3 mmol of **1**. [e] 4 h. [f] 25 °C.

in 92% yield with 92% ee. A 2-alkynyl 1,2-dihydroquinoline was less reactive, and the reaction was less selective, affording **4l** in 43% yield with 82% ee. When the 2-position was substituted with an alkyl group bearing a terminal olefin, the reaction gave **4m** in 81% yield and 93% ee. A sterically hindered 2-cyclopropyl substrate was much less reactive (**4n**, 23% yield), but the high enantioselectivity was maintained (91% ee). However, any substituent other than a hydrogen at the 3- or 4-position of the 1,2-dihydroquinoline greatly inhibited the reaction; either no reaction occurred at all, or only trace of product formed.[19] Subsequently, we tested six- and five-membered-ring enamines for the [2+2] cycloaddition, which afforded the corresponding products (**4o** and **4p**) with 33% ee and 56% ee, respectively.

We then studied the mechanism of the reaction by performing several control experiments. A reaction of a 2-deuterium-labeled 1,2-dihydroquinoline (**1a**-*d*) with **2l** catalyzed by **CAT5** gave **3l**-*d*, the product arising from deuterium transfer to the 4-position of the *N*-heterocyclic ring (Scheme 2A). This result demonstrates that the hydride transfer occurred prior to the cycloaddition. Furthermore, the deuterium in **3l**-*d* was evenly split between the two faces of the heterocyclic ring, indicating the absence of enantiocontrol during the hydride transfer. A competition experiment involving **1a**-*d* and **1e** gave **3a**-*d* and **4e**-*d* in 47% and 46% yields, respectively, with deuterium evenly distributed to the two products (Scheme 2B); this result suggests that the hydride transfer proceeds in an intermolecular fashion. Treatment of **1a** with 5 mol % **CAT5** for 5 min gave 1,4-dihydroquinoline **5** in 83% yield, accompanied by decomposition of the remainder of the starting material (Scheme 2C). Interestingly, when we tested the more acidic borane $B(C_6F_5)_3$ (10 mol %) in a reaction with **1a**, the hydride transfer product was not detected; instead, quinolinium borohydride intermediate **6** was generated in 6% yield, along with unchanged starting material (Scheme 2D). When the amount of $B(C_6F_5)_3$ was increased to 1 equiv, **6** was produced in 82% yield after 30 min



Scheme 2. Control experiments

(Scheme 2E). These results show that the chiral boranes efficiently promoted the hydride transfer; whereas $B(C_6F_5)_3$ was effective for hydride abstraction but not for hydride addition.

To improve our understanding of the hydride transfer process, we performed density functional theory (DFT) calculations for processes involving **CAT1** and $B(C_6F_5)_3$ (Figure 1).[20] Because **1a** is racemic, the hydride abstraction catalyzed by chiral borane **CAT1** can proceed via one of two transition states (**TSA-*R*** or **TSA-*S***), each derived from one of the two enantiomers. These transition states had similar moderate energies (14.8 kcal/mol for **TSA-*R*** and 15.1 kcal/mol for **TSA-*S***), which explains the efficient hydride abstraction for both enantiomers. The free energy of the resulting prochiral quinolinium intermediate stabilized by **CAT1**–hydride anion (**7**, −0.4 kcal/mol) was similar to the energy of **1a**. The subsequent hydride addition reaction (formation of **5** from **7**) was exothermic (−1.8 kcal/mol), and the energy barriers to addition from the top and bottom faces were almost the same (**TSB-1**, 12.2 kcal/mol; **TSB-2**, 12.6 kcal/mol); these results agree qualitatively with the observed absence of enantiocontrol during the hydride addition (Scheme 2A). The thermodynamic stability of **5** may have been the driving force for hydride transfer. In contrast, when $B(C_6F_5)_3$ was used as the catalyst, the hydride abstraction proceeded via **TSA'** (15.2 kcal/mol), a process that was very exothermic because the quinolinium intermediate stabilized by the $B(C_6F_5)_3$–hydride anion (**6**) had a relatively low energy (−3.9 kcal/mol). This result is qualitatively in agreement with our experimental results showing that the reaction of **1a** with $B(C_6F_5)_3$ predominantly produced **6** instead of **5** (Scheme 2E) because **6** is thermodynamically more stable than **5**. Formation of the cycloaddition product with $B(C_6F_5)_3$ (Table 1, entry 6) may have resulted from a trace amount of **5**, and the cycloaddition reaction would shift the equilibrium between **6** and **5** toward **5**.

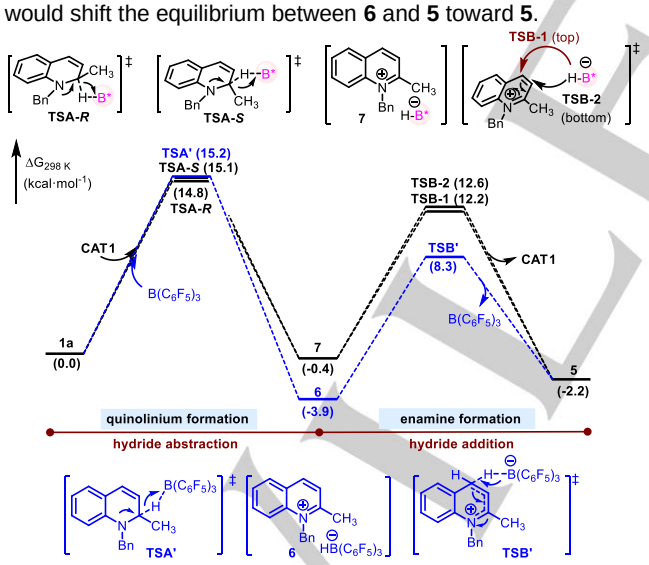


Figure 1. Energy profiles of hydride transfer reactions catalyzed by **CAT1** and $B(C_6F_5)_3$ at 298 K. The DFT calculations were performed using ω-B97XD/def2-TZVPP/SMD(chloroform)//ω-B97XD/6-31G(d).

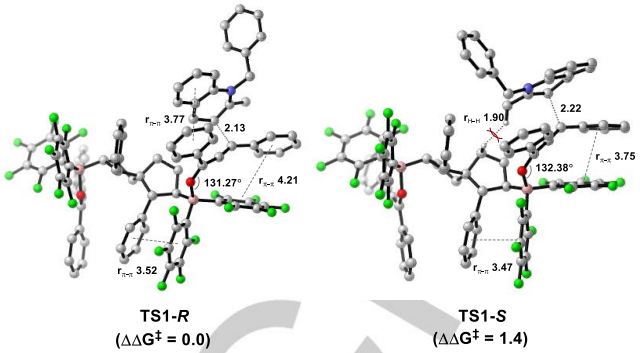


Figure 2. Optimized transition states in the stereo-determining step of the [2+2] cycloaddition reaction between **5** and **2l** catalyzed by **CAT1** at 273 K. The DFT calculations were performed using ω-B97XD/def2-TZVPP/SMD(chloroform)//ω-B97XD/6-31G(d). Energies are given in kcal/mol. Bond lengths are given in Å.

In addition, we also studied the **CAT1**-catalyzed enantioselective [2+2] cycloaddition reaction between **5** and **2l** by means of DFT calculations (Figure 2). The two most stable transition states for generation of the two enantiomers were **TS1-*R*** and **TS1-*S***, which differ in free energy by 1.4 kcal/mol, a result that is in good agreement with the observed 86% ee of **3l** (with **CAT1**). After coordination to one of the boron atoms, an alkynone would occupy the open space between a BAr^F_2 group of one cyclopentane ring and a phenyl group of the other cyclopentane ring. The position of the alkynone would be fixed by a π–π stacking interaction between the phenyl ring adjacent to the alkyne and an Ar^F group. The 1,4-dihydroquinoline would react with the alkynone at a position fixed by the π–π stacking interaction with the alkynone (**TS1-*R***); the reaction with a flipped 1,4-dihydroquinoline would be disfavored by the absence of the π–π stacking interaction and by steric repulsion (**TS1-*S***). Furthermore, we evaluated the possibility of cooperation between two boron atoms of one catalyst molecule (e.g., one boron atom activates the alkynone while the other captures the 1,4-dihydroquinoline). However, the sterics of the catalyst would prevent such interactions (the DFT calculations showed no viable models). Because the catalyst is C_2-symmetric, the two boron atoms are equivalent and presumably function independently. Indeed, racemic monocyclic *trans*-2-phenyl-1-$B(C_6F_5)_2$-cyclopentane was also found to be very active for this cascade reaction (see Supporting Information).

Conclusion

In summary, we have developed a protocol for enantioselective synthesis of fully substituted cyclobutenes by means of a cascade process comprising a borane-catalyzed hydride transfer and an enantioselective [2+2] cycloaddition. This protocol has the following advantages due to the use of a chiral spiro-bicyclic bisborane catalyst: the strong Lewis acidity of the catalyst activated the substrates, enabling reactions with sterically hindered compounds (internal alkynes and trisubstituted alkene); the combination of the steric bulk of the catalyst and its strong Lewis acidity resulted in excellent enantiocontrol of the reactions of monodentate substrates (alkynones). In addition, the catalyst showed unique activity; that

is, it catalyzed hydride transfer. We are currently evaluating chiral borane catalysts in additional enantioselective reactions that are traditionally catalyzed by conventional Lewis acids to see whether the use of chiral boranes will uncover new reactivities or circumvent the limitations of existing methods.

Acknowledgements

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Keywords: asymmetric catalysis • boron • hydride transfer • cycloaddition • heterocycles

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[18] CCDC 2058710 (**3q**) and 2058712 (**3a**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

[19] For a discussion of the limitations of this cascade reaction, see Supporting Information.

[20] To simplify the computational models, we performed calculations on **CAT1** instead of **CAT5**. The reactions in Scheme 2A and 2C were also tested with **CAT1**; they gave similar results as **CAT5**. See Supporting Information for details.

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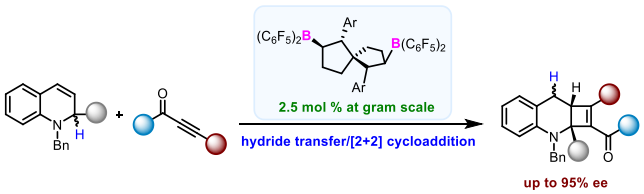

Bifunctional Borane Catalyst. A borane-catalyzed cascade reaction between a benzyl-protected 1,2-dihydroquinoline and an alkynone has been developed. The reaction consists of hydride transfer and enantioselective [2+2] cycloaddition, which are both promoted by the spiro-bicyclic bisborane catalysts.