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## $\alpha$ -Hydroxyacids accelerate the Diels-Alder reaction of dibutyl vinylboronate with cyclopentadiene: experimental results and mechanistic insights

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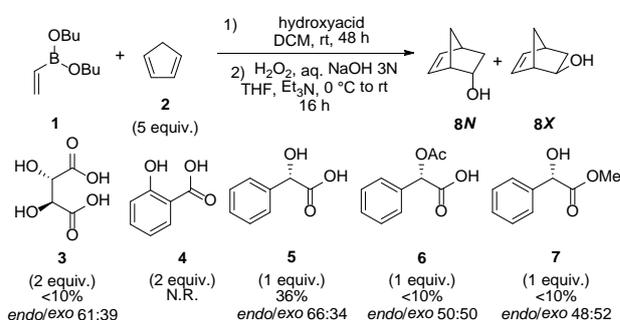
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We have found that  $\alpha$ -hydroxyacids accelerate the Diels-Alder reaction of dibutyl vinylboronate with cyclopentadiene. When stoichiometric quantities are used excellent yields are obtained, while catalytic activities are moderate. DFT calculations suggested that activation of the dienophile occurs by ligand exchange with both functionalities of the  $\alpha$ -hydroxyacid.

Recent years have witnessed a growing interest in the Diels-Alder (DA) reaction of boron-activated dienophiles.<sup>1-11</sup> We have been devoted to the development of an organocatalytic version of the DA reactions of alkenylboronates. Initial attempts using chiral biphenols were unsuccessful. In 2010, Sugiura and coworkers reported the first example of the use of chiral  $\alpha$ -hydroxyacids as enantioselective organocatalysts in boronic acids reactions.<sup>12</sup> Since then, an increasing amount of publications that extended this approach have appeared in the literature.<sup>13-19</sup> We figured that  $\alpha$ -hydroxyacids could accelerate the DA reactions of unsaturated boronates.

We evaluated this strategy for the DA reaction of dibutyl vinylboronate (**1**) with cyclopentadiene (**2**) (Scheme 1). The diastereomeric cycloadducts were oxidized to the alcohols under standard conditions due to the lability of the dibutyl boronate moiety.<sup>7</sup> (*S,S*)-Tartaric acid (**3**) gave the same yield as the background reaction (<10%, *endo/exo* 47:53). We then tested salicylic acid (**4**) as a  $\beta$ -hydroxyacid without detecting the formation of the desired product. Fortunately, (*S*)-mandelic acid (**5**) afforded a 36% yield. Next, we evaluated the use of (*S*)-*O*-acetylmandelic acid (**6**) and (*S*)-methyl mandelate (**7**). Since both compounds gave much lower yields than **5** (<10%), we demonstrated that both functional groups of the  $\alpha$ -hydroxyacid are necessary.



Scheme 1. Initial screening of hydroxyacids

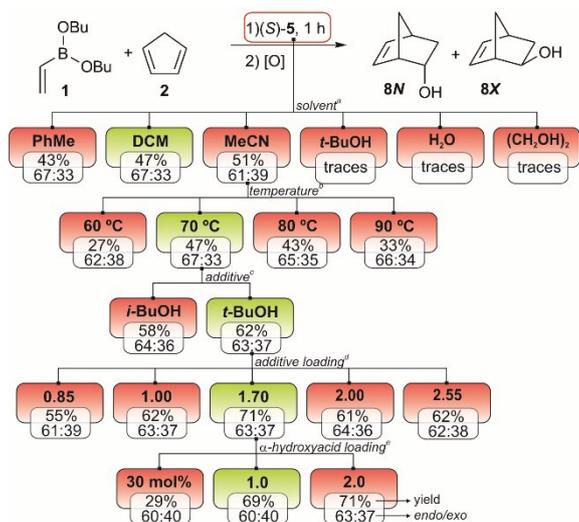
We next optimized the reactions conditions using (*S*)-mandelic acid (**5**). Based on previous results from our group, we first investigated the use of microwave heating.<sup>6</sup> A slightly higher yield (47%) was obtained in 1 h at 70 °C with 2 equivalents of **5**. We then screened the solvent, the temperature, the addition of an alcohol,<sup>20</sup> and the number of equivalents of **5** (Scheme 2). Best yields were obtained adding 1.7 equivalents of *t*-BuOH at 70 °C in DCM under microwave irradiation.<sup>21</sup> Protic solvents generated traces of the product, which may be due to competitive intermolecular interactions or ligand exchange reactions.

Next, we decided to analyze the effect of the substituent at the  $\alpha$  carbon atom of the  $\alpha$ -hydroxyacid. A variety of structurally related  $\alpha$ -hydroxyacids was evaluated in both catalytic and stoichiometric conditions (Table 1). All  $\alpha$ -hydroxyacids generated greater yields than the background reaction under all conditions. The increase in the reaction time from 1 to 2 hours, considerably improved the yields in all cases. Overall, best yields were obtained using 1 equivalent of  $\alpha$ -hydroxyacid (up to 93% with (*S*)-**5**). When 30 mol% was used yields up to 64% were obtained, which proved that the reaction can be catalyzed with this type of compounds. We evaluated the increase of the reaction time to 3 h with 30 mol% of (*S*)-**5** but the yield only raised to 72%. Unfortunately, enantiomeric excesses were below 20%.<sup>22</sup> It is worth noting that to obtain comparable yields of alcohols **8** in the absence

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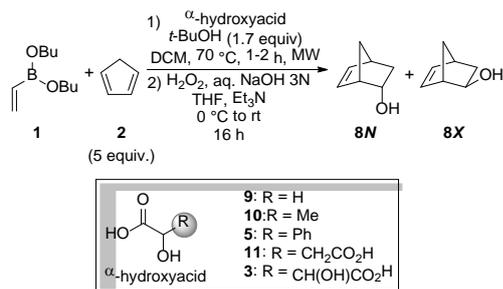
Electronic Supplementary Information (ESI) available: Experimental section, <sup>11</sup>B NMR spectra; computational methods; shapes and energies of the FMOs of the reactants; optimized geometries of transition structures not included in the paper; cartesian coordinates, absolute energies including zero-point energy corrections, free energies and number of imaginary frequencies of all the stationary points reported in the paper and values of imaginary frequencies of all transition structures.. See DOI: 10.1039/x0xx00000x

of  $\alpha$ -hydroxyacids the studied DA reaction has to be performed at 150 °C with MW irradiation for 1 h (91%, *endo/exo* 41:59).<sup>7,23</sup>



**Scheme 2.** Reaction conditions: <sup>a</sup> solvent (1 mL), 70 °C, (S)-5 (2 equiv.), MW; <sup>b</sup> DCM (1 mL), (S)-5 (2 equiv.), MW; <sup>c</sup> DCM (1 mL), 70 °C, alcohol (1 equiv.), (S)-5 (2 equiv.), MW; <sup>d</sup> DCM (1 mL), 70 °C, (S)-5 (2 equiv.), MW; <sup>e</sup> DCM (1 mL), 70 °C, *t*-BuOH (1.70 equiv.), MW.

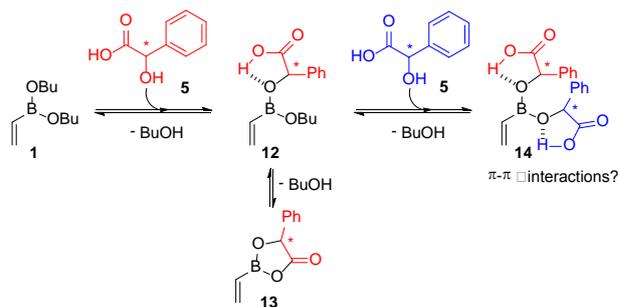
**Table 1.** Evaluation of  $\alpha$ -hydroxyacids



Entry	$\alpha$ -hydroxyacid	Yield (%) ( <i>endo/exo</i> ) <sup>a</sup>			
		30 mol%		1 equiv.	
		1 h	2 h	1 h	2 h
1	-	10 (43:57)	13 (42:58)	10 (43:57)	13 (42:58)
2	<b>9</b>	27 (60:40)	31 (61:39)	41 (56:44)	55 (62:38)
3	(S)- <b>10</b>	44 (60:40)	61 (59:41)	10 (43:57)	82 (60:40)
4	(S)- <b>5</b>	29 (60:40) <sup>b</sup>	64 (60:40)	69 (60:40)	93 (60:40)
5	(S)- <b>11</b>	41 (51:49)	60 (53:47)	75 (61:39)	79 (54:46)
6	(S,S)- <b>3</b>	22 (56:44)	51 (58:42)	21 (56:44)	50 (56:44)

<sup>a</sup> Determined by <sup>1</sup>H NMR integration. <sup>b</sup> *i*-BuOH (1 equiv.) was used instead of *t*-BuOH (1.7 equiv.)

To get a better understanding of the reaction mechanism, we proposed all the plausible species that could be generated by the combination of dibutyl vinylboronate (**1**) and (S)-mandelic acid (**5**) (Scheme 3). The <sup>11</sup>B NMR spectrum of a mixture of **1** and **5** showed a new signal after 2 h under MW irradiation at 70 °C in DCM, which may be an indication of ligand exchange and formation of a new boron-activated dienophile (see the Supporting Information).



**Scheme 3.** Formation of possible dienophiles.

With the aim to identify the key intermediate species of the reaction, we performed a theoretical study at the B3LYP/6-311++G\*\* level of theory using methyls instead of the butyl groups in the starting boronate to reduce the number of atoms.

Frontier Molecular Orbital (FMO) calculations of the optimized dienophiles showed that all reactions are normal electron-demand DA reactions (Table 2). Dioxaborolane **13** is the only thermodynamically favored structure and also has the lowest energy LUMO, which would indicate that this is the most activated dienophile. An analysis of the LUMO coefficients suggested that the carbonyl group might be responsible for the activation of this dienophile. Global properties are also gathered in Table 2.<sup>24</sup> Electrophilicity indices are in line with FMO results and reveal that **13** is the only dienophile that can be considered a strong electrophile.

**Table 2.** Free energies from reactants, HOMO<sub>dienne</sub>-LUMO<sub>dienophile</sub> gaps and global properties

Compound	$\Delta G$ (Kcal/mol)	FMO gap (eV)	$\eta^a$ (au)	$\mu^b$ (au)	$\omega^c$ (eV)	$\Delta N_{\max}^d$ (e)
<b>1</b>	-	-5.16	0.24	-0.15	1.37	0.65
<b>12</b>	3.92	-5.06	0.22	-0.15	1.38	0.69
<b>13</b>	-0.40	-4.36	0.20	-0.16	1.87	0.83
<b>14</b>	9.15	-4.91	0.21	-0.15	1.47	0.72
<b>2</b>	-	-	0.20	-0.13	1.12	0.65

<sup>a</sup>  $\eta$ : chemical hardness. <sup>b</sup>  $\mu$ : electronic chemical potential. <sup>c</sup>  $\omega$ : global electrophilicity. <sup>d</sup>  $\Delta N_{\max}$ : the maximum amount of electronic charge that the system might accept

All transition structures (TS) exhibit classical [4 + 2] geometries and are asynchronous (Figure 1). The non-classical [4+3] carbon-boron interactions are weak (C-B distances: 2.95-3.12 Å, Wiberg Bond Indices (WBI): 0.05-0.03) and very similar for the *endo* and *exo* approaches.<sup>25,26</sup> Also, **14** does not present  $\pi$ - $\pi$  stacking interactions as expected.

Table 3 gathers the activation free energies for the most stable conformers corresponding to the *endo* and *exo* approaches of each possible dienophile and the corresponding calculated *endo/exo* and *Re/Si* selectivities.<sup>27</sup>

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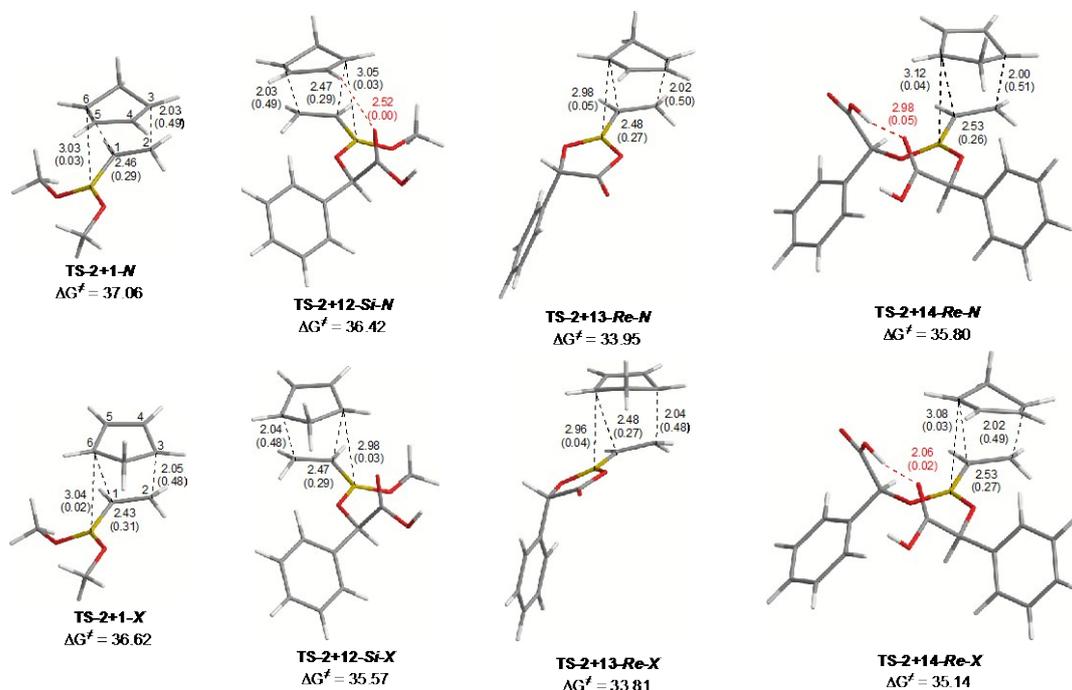
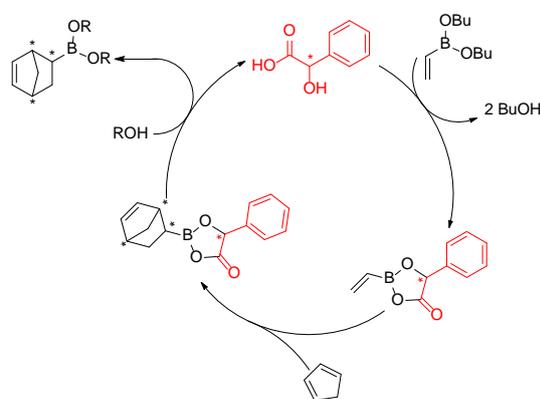


Figure 1. Most stable TSs for each approach of all possible dienophiles. Energy in Kcal/mol. Distances in Å and WBI between parentheses.

**Table 3.** Calculated activation free energies and selectivities

Entry	Dienophile	TS	$\Delta G^\ddagger$ (Kcal/mol)	<i>endo/exo</i>	<i>Re/Si</i>
1	1	<i>endo</i>	37.06	34:66	-
		<i>exo</i>	36.62		
2	12	<i>Re_endo</i>	36.67	21:79	43:57
		<i>Re_exo</i>	35.76		45:55
		<i>Si_exo</i>	35.57		
		<i>Si_endo</i>	36.42		
3	13	<i>Re_endo</i>	33.95	47:53	54:46
		<i>Si_endo</i>	34.09		58:42
		<i>Re_exo</i>	33.81		
		<i>Si_exo</i>	34.11		
4	14	<i>Re_endo</i>	35.80	19:81	74:26
		<i>Si_endo</i>	36.71		53:47
		<i>Re_exo</i>	35.14		
		<i>Si_exo</i>	35.23		

Once more, based on free energy barriers **13** was computed to be the most reactive dienophile. Therefore, we propose the catalytic cycle depicted in Scheme 4. This concurs with previous studies of this kind of organocatalysts.<sup>28</sup>



**Scheme 4.** Proposed catalytic cycle.

It should be noted that the computed energy barrier for **13** is less than 3 Kcal/mol lower than that of the background reaction with **1**, which might be an indication of the low catalytic activity of (*S*)-mandelic acid (**5**) and also explain the unsuccessful results obtained in preliminary experiments with other dienes and/or alkenylboronates. Also, calculations correctly predicted the poor enantioselectivities observed experimentally in the reactions of (*S*)-**5**. Nevertheless, we believe that the experimental and theoretical results presented herein provide essential information to further

develop an improved methodology both in terms of yields and enantioselectivities and are now working towards such goal.

In conclusion, we have found that  $\alpha$ -hydroxyacids accelerate the DA reaction of dibutyl vinylboronate with cyclopentadiene. Under stoichiometric conditions (1 equivalent), (S)-mandelic acid (**5**) gives 93% yield of the oxidized cycloadducts, though lower yields are observed with catalytic quantities (30 mol%). The computational study of the reaction suggested that the mechanism proceeds through a dioxaborolane intermediate which is activated by the presence of the carbonyl group. Further studies on the use of  $\alpha$ -hydroxyacids in the DA reactions of alkenylboronates are currently underway and will be reported in due course.

## Experimental

### Typical procedure for the tandem Diels–Alder reaction of dibutyl vinylboronate - oxidation (Table 1)

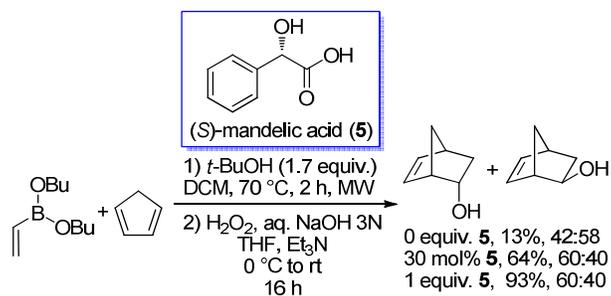
To an oven-dried 10 mL reaction vial equipped with a stirring bar were added  $\alpha$ -hydroxyacid (0.3 – 2 equivalents), dry DCM (1 mL), *tert*-butanol (81  $\mu$ L, 1.7 equivalents), dibutyl vinylboronate (**1**) (113  $\mu$ L, 0.5 mmol) and cyclopentadiene (206  $\mu$ L, 2.5 mmol) under argon atmosphere. The resulting reaction mixture was stirred at 70 °C under microwave irradiation for 1, 2 or 3 h. The reaction mixture was diluted with THF (3 mL), and transferred to a 25 mL round-bottom flask. After the addition of Et<sub>3</sub>N (1 mL), the solution was cooled to 0 °C and treated alternately with aq. NaOH 3 N (3 mL) and 30% H<sub>2</sub>O<sub>2</sub> (3 mL) under argon atmosphere, and then allowed to warm to room temperature and stirred overnight (16 h). The reaction mixture was diluted with water (10 mL) and extracted with Et<sub>2</sub>O (3 x 15 mL). The combined organic layers were washed with saturated NH<sub>4</sub>Cl (15 mL) and brine (15 mL) and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure at 0 °C, and the crude was purified by column chromatography (pentane-Et<sub>2</sub>O) to afford 5-norbornen-2-ol (**8**) with NMR spectra identical to the commercial material.

## Acknowledgements

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- It is worth noting that all reactions with mandelic acid generate a 60:40 *endo/exo* ratio, while in the absence of  $\alpha$ -hydroxyacid this ratio is 42:58.
- For the reaction that generates 93% yield, the *Re/Si* selectivity obtained was 43:57 for the *endo* adduct and 49:51 for the *exo* adduct. Similar yields were obtained when racemic acid was used.
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Dibutyl vinylboronate reacts with cyclopentadiene under mild conditions in the presence of (S)-mandelic acid probably via an activated dioxaborolane intermediate.