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Mild and efficient boronic acid catalysis of Diels–Alder cycloadditions to 2-alkynoic acids

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ABSTRACT

The concept of boronic acid catalysis (BAC) for the activation of unsaturated carboxylic acids is applied to the Diels–Alder cycloaddition between 2-alkynoic acids as dienophiles and various dienes. These [4+2] cycloadditions produce cyclohexadienyl carboxylic acids, which can be oxidized in situ to produce polysubstituted aromatic carboxylic acids. The boronic acid catalyst is suspected to provide activation by a LUMO-lowering effect of the unsaturated carboxylic acid likely via a covalent, monoacylated hemiboronic ester intermediate.

The quest for new ways of catalyzing important organic reactions is of utmost importance in order to expand the substrate scope or the selectivity of existing transformations, or to allow new bond-forming processes to occur.[1] Catalytic activation of carboxylic acids is difficult to achieve because of the inherent chemical properties of this functional group. The acidic character of carboxylic acids can create chemical compatibility issues. As a result, the carboxylic acid functionality is usually handled in a masked form such as a suitable carboxylic ester, which requires additional synthetic steps. A direct method for electrophilic (or LUMO-lowering) activation of unsaturated carboxylic acids toward cycloadditions would be very advantageous in terms of atom- and step-economy. We recently demonstrated this concept in [4+2] cycloadditions of acrylic acid catalyzed by arylboronic acids (Fig. 1).[2] The same concept was also applied to several classical dipolar [3+2] cycloadditions.[3] Herein, we extend this concept to the use of 2-alkynoic acids in [4+2] cycloadditions to access polysubstituted cyclohexadienes and arenes functionalized with a carboxylic acid (Fig. 1). Faster reactions, milder conditions, and increased regioselectivity are the main benefits provided by boronic acid catalysis (BAC).[4]

ortho-Halo-substituted arylboronic acids were previously found to be potent catalysts in [4+2] cycloadditions of acrylic acid, therefore our initial screening of potential catalysts focused on the same class of boronic acids along with a few more electron-poor arylboronic acids (Table 1, entries 1–6). It was found that *ortho*-bromophenylboronic acid was the most efficient amongst the boronic acids tested (Table 1, entry 6). Solvent dependency was next examined and chlorinate solvent CH_2Cl_2 was found to be superior for this reaction (Table 1, entries 6–10), whereas the same cycloaddition gave only 3% yield in the absence of the boronic acid catalyst (Table 1, entry 13). It is noteworthy that a low yield was obtained in the presence of molecular sieves (Table 1, entry 11), which is in line with our previous reports on [4+2] cycloadditions[2] of acrylic acid and [3+2] dipolar cycloadditions.[3] Indeed, as depicted in Figure 1, a small amount of water formed by the condensation between the boronic acid and the carboxylic acid is necessary to allow the catalyst turnover. However, excess water reduced the product yield substantially (Table 1, entry 12).

Using the optimal conditions, the scope of diene was explored using propiolic acid as the dienophile (Table 2).[5] In the event, a wide selection of substituted butadienes was tolerated. In all cases, the boronic acid-catalyzed variant gave greatly improved yields.

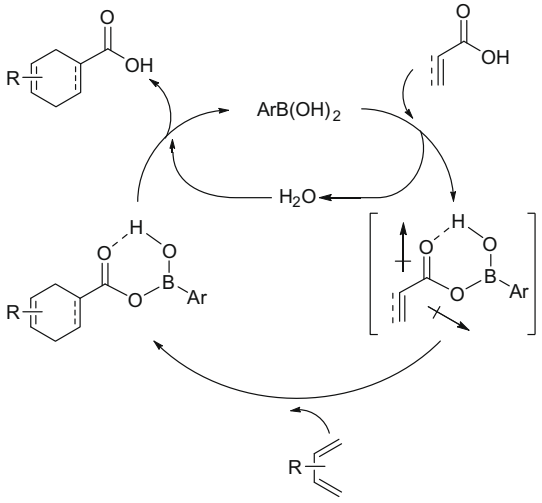

Figure 1. Catalytic cycle for the boronic acid-catalyzed Diels–Alder cycloadditions of unsaturated carboxylic acids.

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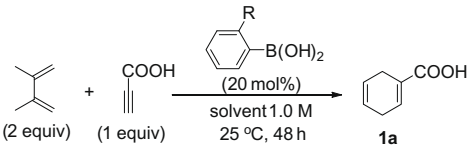
Table 1
Optimization of reaction conditions for the BAC of a model Diels–Alder cycloaddition with propiolic acid[a]



Entry	R=	Solvent[b]	Yield[c] (%)
1	I	CH_2Cl_2	80
2	F	CH_2Cl_2	52
3	Cl	CH_2Cl_2	71
4	CN	CH_2Cl_2	39
5	NO_2	CH_2Cl_2	82
6	**Br**	**CH_2Cl_2**	**86**
7	Br	Toluene	80
8	Br	MeOH	6
9	Br	THF	59
10	Br	CH_3CN	24
11[d]	Br	CH_2Cl_2	20
12[e]	Br	CH_2Cl_2	71
13[f]	—	CH_2Cl_2	3

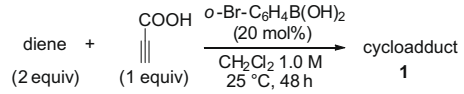
[a] Reaction procedure: propiolic acid (1.0 mmol) and boronic acid (0.2 mmol) were mixed in the indicated solvent (1 mL), stirred at 25 °C for 10 min, followed by the addition 2,3-dimethyl-1,3-butadiene (2.0 mmol), and stirred at 25 °C for 48 h.
[b] Dry, distilled solvents were employed.
[c] Isolated yields of product after purification by flash column chromatography.
[d] With 4 Å molecular sieves (1.0 g) added.
[e] With 1.0 equiv of water added.
[f] Control reaction: no boronic acid was added.

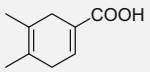
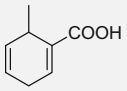
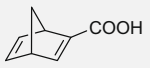
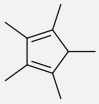
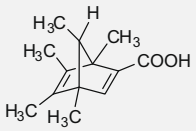
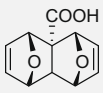
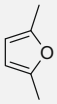
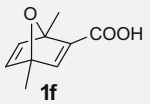
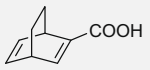
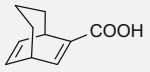
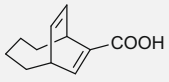
Acyclic dienes proceeded smoothly under optimized conditions (Table 2, entries 1 and 2). Interestingly, for the asymmetric diene, complete regioselectivity was realized under BAC (Table 2, entry 2). Compared to the linear dienes, cyclopentadiene reacted even more efficiently (Table 2, entry 3). In the case of a substituted cyclopentadiene, a mixture of diastereoisomers (3:1) was obtained (Table 2, entry 4). To our satisfaction, furans are also suitable substrates for this cycloaddition, the double Diels–Alder cycloadduct **1e** and the dienecarboxylic acid **1f** (not stable at room temperature after isolation) were obtained in excellent yields (Table 2, entries 5 and 6). The ring size of cyclic dienes played an important role in the reaction, the larger the ring size, the lower the reaction yield (Table 2, entries 3–9). For instance, only trace amount of product in the crude reaction mixture was detected with cycloocta-1,3-diene after 30 days (Table 2, entry 9).

To further expand this methodology, substituted 2-butynoic acids were employed as the dienophiles (Table 3). With 2,3-dimethyl-1,3-butadiene, the desired dienecarboxylic acids **2a–c** were obtained in acceptable yields using a slightly elevated temperature and longer reaction times (Table 3, entries 1–3). Compared to 2,3-dimethyl-1,3-butadiene, cyclopentadiene showed much better reactivity and could react with substituted 2-butynoic acids to provide the desired cycloadducts **2d–f** in excellent yields under relatively mild conditions (Table 3, entries 4–6).

The 1,4-cyclohexadienyl carboxylic acids **1** and **2** synthesized by this method could be conveniently converted to synthetically and biologically useful polysubstituted arylcarboxylic acids (Scheme 1).[6] Thus, DDQ-mediated aromatization of dienecarboxylic acid **1a** afforded the polysubstituted arene **3a** in nearly quantitative yield.[7] Based on this promising result, a one-pot sequential boronic acid-catalyzed Diels–Alder cycloaddition/aromatization was envisioned for maximizing step-economy and synthetic efficiency (Scheme 2). Following the one-pot procedure,[8] the polysubstituted arenes **3a–c** were obtained in good to excellent yields.

Table 2
Substrate scope for the BAC of Diels–Alder cycloadditions with propiolic acid[a]



Entry	Diene	t (h)	Product	Yield[b] (%)
1		48	 **1a**	86 (3)
2		48	 **1b**	83[c] (6[d])
3		8	 **1c**	91 (6)
4		6	 **1d**	92[e] (3[f])
5		6	 **1e**	98 (Trace)
6		2	 **1f**	96 (4)[g]
7		48	 **1g**	82 (Trace)
8		72	 **1h**	62 (Trace)
9		720	 **1i**	Trace (0)

[a] Reaction procedure: see Table 1.
[b] Isolated yields of product after purification by flash column chromatography. Yields in bracket represent the control reactions performed without boronic acid as the catalyst.
[c] Only one regioisomer was obtained.
[d] Regioisomeric ratio: 1:1.
[e] Diastereomeric ratio: 3:1.
[f] Diastereomeric ratio: 3:1.
[g] Product is unstable and decomposes quite rapidly at room temperature.

Although the underlying mechanism remains to be elucidated, previous mechanistic NMR studies[3] using the Childs method[9] showed that this concept of BAC of Diels–Alder cycloadditions of 2-alkynoic acids most likely operates through a powerful LUMO-lowering activation of the dipolarophile by the formation of a covalent adduct between the boronic acid and the unsaturated carboxylic acid (Fig. 1).

In summary, we have reported the application of boronic acid catalysis (BAC) for the activation of propiolic acid and 2-butynoic acids in the classical [4+2] cycloaddition involving acyclic and cyclic