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Mild boronic acid catalyzed Nazarov cyclization of divinyl alcohols in tandem with Diels–Alder cycloaddition

Hongchao Zheng, Michal Lejkowski, Dennis G. Hall *

Department of Chemistry, Gunning-Lemieux Chemistry Centre, 4-010 Centennial Centre for Interdisciplinary Science, University of Alberta, Edmonton, Alberta, Canada T6G 2G2

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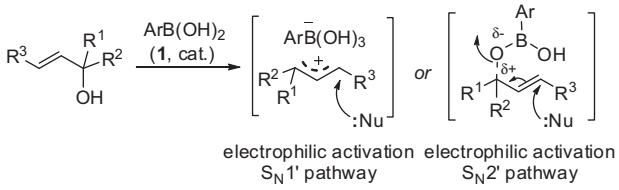
ABSTRACT

Boronic acid catalysis (BAC) was applied to a sequential Nazarov cyclization of divinyl alcohols/Diels–Alder cycloadditions leading to the preparation of highly functionalized bicyclic compounds in a highly diastereoselective fashion. In these one-pot transformations, highly functionalized dienes were generated in situ through boronic acid catalyzed Nazarov cyclizations of divinyl alcohols and were subsequently trapped with different dienophiles such as maleic anhydride and phenylmaleimide. The tandem reactions proceed directly from divinyl alcohols under very mild reaction conditions using air-stable catalysts, and as such this methodology represents a greener alternative to existing methods employing strong Lewis and Brønsted acids.

Hydroxyl is a poor leaving group and therefore pre-activation with recourse to intermediary functionalities such as halides and pseudo-halides (e.g., sulfonates, oxyphosphonium) is usually required for nucleophilic substitution.[1] The consideration of atom- and step-economy and the use of environmentally friendlier reactions are becoming a key theme in many research areas. In this regard, the *ACS Green Chemistry Institute Pharmaceutical Roundtable* ranked 'alcohol activation for nucleophilic substitution' as the second most important priority area for green chemistry research.[2] Highly Lewis acidic electron-deficient arylboronic acids **1** are emerging as a promising new class of organocatalysts for the direct activation of alcohols by facilitating the complete or partial ionization of the C–O bond (Scheme 1).[3–5] This concept of covalent hydroxyl activation has been successfully applied to a broad range of classical chemical transformations, including Friedel–Crafts alkylations,[3a–c] 1,3-transpositions of allylic alcohols,[3d] Meyer–Schuster rearrangements of propargylic alcohols,[3d] and a variety of cationic cyclizations of allylic alcohols.[3e] Faster reactions, milder reaction conditions, and increased selectivity are the main benefits provided by boronic acid catalysis (BAC). Inspired by these successful examples, we sought to expand the BAC concept to other synthetically useful organic reactions, such as the Nazarov cycloaddition, and further demonstrate its mildness and versatility.

The Nazarov cyclization is a widely employed chemical transformation allowing the synthesis of cyclopentenones such as **4** from divinyl ketone **2** (Scheme 2).[6] In the classical Nazarov reaction, upon activation with a Lewis or Brønsted acid, the divinyl ketone substrate **2** generates a hydroxyl-substituted pentadienyl cation **3** as a key intermediate, which then undergoes a 4π-electrocyclic ring closure to furnish the cyclopentenone **4** as the final product (Scheme 2).[6] It can be envisioned that a pentadienyl cation **6** can be generated from a different class of substrates, divinyl alcohols **5**, under boronic acid catalysis (Scheme 2). Subsequently, the formed pentadienyl cations **6** can undergo the Nazarov cyclization to provide synthetically useful cyclic dienes **8** via the elimination of cyclopentyl allylic cations **7** (Scheme 2). Although the Nazarov reactions of divinyl ketone substrates have been studied extensively,[6] there are only sporadic reports of using divinyl alcohols of type **5** as starting materials.[7] Moreover, nearly all methods in the literature require either strongly acidic or toxic metal based catalysts. Therefore, a milder and environmentally friendlier alternative is highly desirable. As part of our program aimed at exploring the use of boronic acids as catalysts and stoichiometric reaction promoters,[8] herein we report a mild and efficient Nazarov cyclization of divinyl alcohols in tandem with Diels–Alder cycloadditions to afford highly functionalized bicyclic compounds in a single operation.



Scheme 1. The concept of hydroxyl activation using boronic acid catalysis.

* Corresponding author. Tel.: +1 780 492 3141; fax: +1 780 492 8231.
E-mail address: dennis.hall@ualberta.ca (D.G. Hall).

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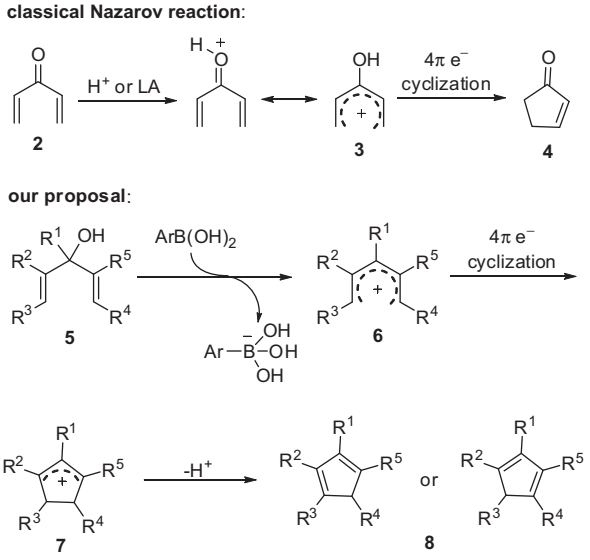
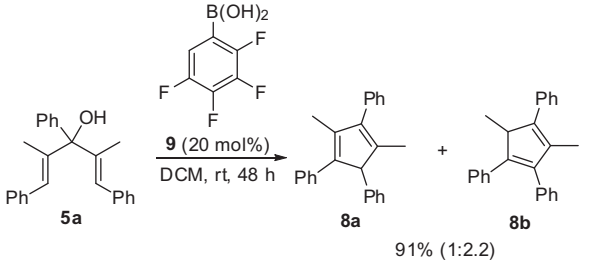


Scheme 2. Proposed boronic acid catalyzed Nazarov cyclizations.

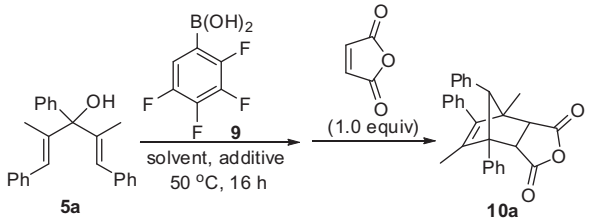


Scheme 3. A preliminary test for the boronic acid catalyzed Nazarov cyclization.

As a preliminary test, the Nazarov reaction of divinyl alcohol **5a** was found to proceed smoothly at room temperature using electron deficient arylboronic acid **9** as the catalyst, providing mixtures of polysubstituted cyclopentadienes **8a** and **8b** in excellent yield (Scheme 3). This result showed the suitability of electron deficient arylboronic acid **9** as a catalyst to promote the Nazarov reaction.

Maleic anhydride is a remarkably good dienophile and as such it was employed as a model partner to trap the formed dienes **8** (Table 1). Although the Nazarov reactions of divinyl alcohols could proceed smoothly at room temperature (Scheme 3), a slightly higher reaction temperature (50 °C) was necessary to ensure the completion of the subsequent Diels–Alder cycloaddition within a reasonable time (Table 1). In the first round of optimization, several solvents were evaluated in the sequential Nazarov cyclization/Diels–Alder trapping of model divinyl alcohol **5a** catalyzed by **9** (Table 1). Although some non-polar aprotic or halogenated solvents like toluene, hexanes, or 1,2-dichloroethane were quite effective, the highly polar aprotic solvent nitromethane was superior (Table 1, entry 8). A lower yield was obtained when a lower catalyst loading was employed (Table 1, entries 9 and 10). Furthermore, the use of dehydrating agents such as molecular sieves was detrimental, while excess water showed a subtle influence on the reaction (Table 1, entries 11 and 12). Then, a number of simple additives were screened but none provided any observable rate acceleration (Table 1, entries 13 and 14). Interestingly, when a strong Brønsted acid like *p*-TsOH was used as the additive or as the catalyst, the formed cycloadduct **10a** could further undergo hydrolysis to provide the corresponding dicarboxylic acid as the major product (Table 1, entries 14 and 15). This result provides evidence for the mildness of our BAC methodology. Finally, a control

Table 1
Optimization of reaction conditions in the boronic acid catalyzed sequential Nazarov cyclization/Diels–Alder reaction[a]



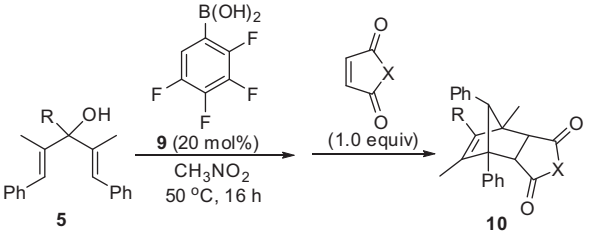
Entry	Solvent	Catalyst (mol %)	Additive	Yield[b] (%)
1	DMF	20	No additive	12
2	EtOAc	20	No additive	16
3	THF	20	No additive	31
4	Acetone	20	No additive	58
5	Hexanes	20	No additive	85
6	DCE	20	No additive	88
7	Toluene	20	No additive	90
8	**CH_3NO_2**	**20**	**No additive**	**95**
9	CH_3NO_2	10	No additive	71
10	CH_3NO_2	5	No additive	41
11	CH_3NO_2	20	4 Å Molecular sieves[c]	32
12	CH_3NO_2	20	H_2O (1.0 equiv)	83
13	CH_3NO_2	20	$ZrCl_4$ (20 mol %)	—[d]
14	CH_3NO_2	20	TsOH (20 mol %)	31[e]
15	CH_3NO_2	20	TsOH (20 mol %)	39[f]
16	CH_3NO_2	20	No additive	0[g]

[a] Reaction conditions: Unless specified, the reaction was performed with divinyl alcohol **5a** (0.2 mmol), maleic anhydride (0.2 mmol), and tetrafluorophenylboronic acid **9** (0.01–0.04 mmol) at 50 °C in a solvent (1 mL) for 16 h.
[b] Isolated yields of product **10a** after purification by silica gel column chromatography.
[c] 4 Å Molecular sieves (200 mg) were employed as the additive.
[d] A complex mixture was obtained.
[E] Sixty percentage of hydrolysis product (dicarboxylic acid) was isolated as the side product.
[f] The reaction was performed in the absence of boronic acid catalyst **9** and 55% of hydrolysis product (dicarboxylic acid) was isolated as the side product.
[g] The reaction was performed in the absence of boronic acid catalyst **9**.

run in the absence of boronic acid catalyst **9** led to no product formation (Table 1, entry 16).

Using the optimal conditions of entry **8**,[9] the scope of substituted divinyl alcohols was explored using maleic anhydride as the dienophile (Table 2, entries 1–6). In the event, a wide selection of substituted divinyl alcohols was tolerated. In all cases, the desired cycloadduct **10** was obtained in excellent yield as a single isomer (Table 2, entries 1–5). However, a trivinyl alcohol afforded a low yield of the desired product due to the competition between two possible Nazarov cyclizations (Table 2, entry 6). Phenylmaleimide is also suitable as a dienophile for trapping the formed cyclopentadienes **8** (Table 2, entries 7–10). Compared with maleic anhydride, it exhibited lower efficiency for the sequential Nazarov cyclization/Diels–Alder trapping (Table 2, entries 7–10). NMR experiments were performed on **10d** to determine the relative stereochemistry of the cycloadducts. From the ^{1}H NMR spectrum, H_a, H_b, and H_c could be identified as the signals at 2.99, 3.52, and 4.22 ppm, respectively. Then the strong NOE correlations of $H_a \leftrightarrow H_b$ and $H_a \leftrightarrow H_c$ clearly indicated that the produced cycloadducts **10** corresponded to the endo isomer (Fig. 1). To address the origin of the stereoselectivity in this sequential process, a control experiment was conducted (Scheme 4). When one isomer **8b** was re-subjected to the reaction conditions, a mixture of two isomers was obtained. This result confirms that a thermodynamic equilibration between two isomers is occurring under the reaction conditions, likely via 1,5-H shift. The subsequent Diels–Alder reaction is most likely under kinetic control and favored with the less sterically hindered isomer **8a**, thus providing the cycloadduct **10a** as the exclusive diastereomer (Scheme 4).

Table 2
Substrate scope in the boronic acid catalyzed sequential Nazarov cyclization/Diels–Alder reaction[a]



Entry	R	X	Product	Yield[b] (%)
1	Ph	O	**10a**	95
2	*n*-Bu	O	**10b**	88
3	Me	O	**10c**	91
4	$CH_2CH{=}CH_2$	O	**10d**	85
5	C≡CPh	O	**10e**	87
6	$CH{=}CH_2$	O	**10f**	30
7	Ph	NPh	**10g**	58
8	*n*-Bu	NPh	**10h**	62
9	Me	NPh	**10i**	60
10	$CH_2CH{=}CH_2$	NPh	**10j**	55

[a] Unless specified, the reaction was performed with divinyl alcohol **5** (0.2 mmol), maleic anhydride or phenylmaleimide (0.2 mmol), and tetrafluorophenylboronic acid **9** (0.04 mmol) at 50 °C in nitromethane (1 mL) for 16 h.
[b] Isolated yields of product **10** after purification by silica gel column chromatography.

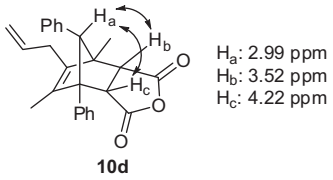
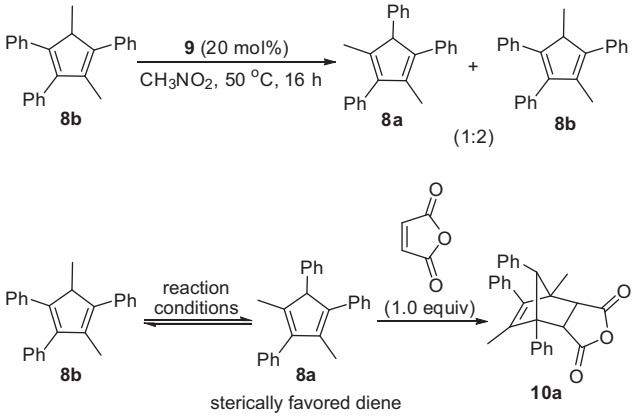


Figure 1. Illustration of NOE correlations for **10d**.



Scheme 4. Control experiment to address the origin of the stereoselectivity in the boronic acid catalyzed sequential Nazarov cyclization of divinyl alcohols/Diels–Alder reaction.

In summary, we have reported the application of boronic acid catalysis for the direct activation of allylic alcohols in a sequential Nazarov cyclization/Diels–Alder reaction involving divinyl alcohols as the substrates. These Nazarov cyclizations produce highly functionalized cyclic dienes and bicyclic cycloadducts effectively using an air-stable boronic acid catalyst under mild reaction conditions. Therefore, it represents an environmentally advantageous alternative to existing methods employing strong Lewis and Brønsted acids. Further studies of this reaction process will be aimed at applying the BAC concept to 'interrupted' Nazarov cyclizations.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures, NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.100.

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9. *Typical experimental procedure for the boronic acid catalyzed sequential Nazarov cyclization of divinyl alcohols*/Diels–Alder *trapping*: To a solution of the divinyl alcohol **5a** (68 mg, 0.2 mmol) and maleic anhydride (20 mg, 0.2 mmol) in nitromethane (1 mL) at room temperature was added 2,3,4,5-tetrafluorophenyl

boronic acid **9** (8 mg, 0.04 mmol). The resulting solution was stirred at 50 °C for 16 h. Upon evaporation of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (EtOAc/Hexanes = 1:10) to give the anhydride **10a** (80 mg, 95%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.37 (m, 2H), 7.36-7.16 (m, 11H), 7.03–6.98 (m, 2H), 4.35 (d, J = 8.2 Hz, 1H), 3.67 (d, J = 8.2 Hz, 1H), 3.22 (s, 1H), 1.75 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 170.2, 141.3, 139.9, 135.9, 135.4, 133.8, 130.4, 129.2, 129.2, 128.4, 128.2, 127.9, 127.58, 127.57, 127.4, 78.4, 67.8, 60.6, 54.7, 52.3, 16.5, 14.6; IR (Microscope, cm^{-1}) 3059, 3030, 2968, 2930, 1859, 1778, 1560, 1494, 1448; HRMS (EI) for $C_{29}H_{24}O_3$: calcd 420.1726; found 420.1733.