Homogeneous Catalysis

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Boronic Acid Catalysis as a Mild and Versatile Strategy for Direct Carbo- and Heterocyclizations of Free Allylic Alcohols**

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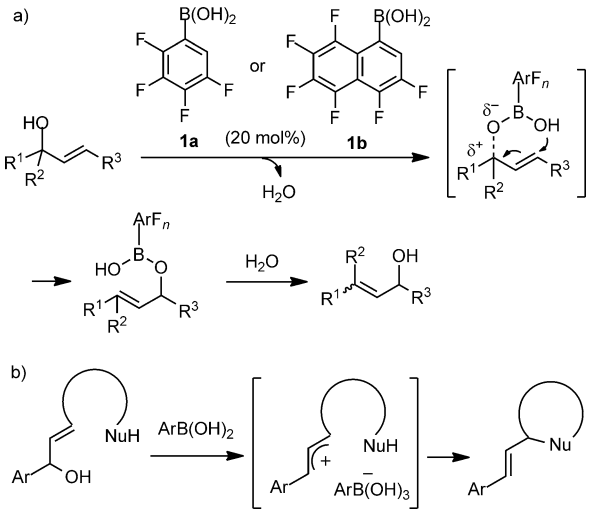
The ability to activate simple electrophilic functional groups directly without recourse to intermediary functionalities like halides and pseudohalides (e.g., sulfonates, oxyphosphonium) has become an important goal of modern organic chemistry.[1] Boronic acid catalysis (BAC) is emerging as a mild and effective strategy for the direct, covalent activation of alcohols and carboxylic acids.[2] Important reactions such as direct esterification and amidation,[3] intramolecular anhydride formation,[4] imine hydrolysis,[5] epoxide opening,[6] the Biginelli reaction,[7] Diels–Alder[8] and dipolar cycloadditions,[9] aldol condensations,[10] ene reactions,[11] Friedel–Crafts alkylations,[12] and transpositions of allylic/propargylic alcohols[13] have all been performed recently under BAC. Faster reactions, milder reaction conditions, and increased selectivity are some of the benefits provided by BAC. These attributes are highlighted in recent reports from McCubbin and co-workers on mild Friedel–Crafts-type alkylations by activation of allylic and benzylic alcohols with electron-poor boronic acids.[12] Inspired by this approach, we devised mild and effective reaction conditions for stereoselective 1,3-transpositions of allylic and propargylic alcohols in the absence of an external nucleophile (Scheme 1 a).[13] The successful development of these reactions unveiled boronic acids **1a** and **1b** as superior catalysts for the activation of hydroxy groups. We reasoned that under conditions favoring a strong polarization or full ionization of allylic alcohols, a suitably placed nucleophilic functionality on the substrate could lead to the formation of cyclic products under unusually mild reaction conditions (Scheme 1 b). Indeed, the pK_a of boronic acids is in the range of 5–9,[14] which is significantly higher than that of the strong protic acids usually required in cationic cyclizations. Herein, we demonstrate the versatility and mildness (low temperature, functional group tolerance) of boronic acid catalysis over traditional methods employing strong Lewis and Brønsted acids.[15]



Scheme 1. Boronic acid catalysis of 1,3-transposition of allylic alcohols (a)[13] and the proposed carbo- and heterocyclizations (b).

In the first round of optimization, several solvents were evaluated in the Friedel–Crafts cyclization of model alcohol **2a** catalyzed by **1a** (Table 1). Although some nonpolar solvents like toluene and hexanes were quite effective, the highly polar aprotic solvent nitromethane was superior (entry 8). The catalyst was effective even at room temperature (entry 9), however a lower yield was obtained when using a lower catalyst loading (entries 10–11). A comparison with pentafluorophenylboronic acid (entry 12) confirmed that **1a** (entry 9) is a superior catalyst.[16] Furthermore, a control run without molecular sieves (entry 13) showed that there were no advantages to using this dehydrating agent or any other such as $MgSO_4$ (data not shown). It is noteworthy that the reaction in entry 9 was repeated on a larger scale (1 g of **2a**) to give a 95% yield of **3a** with a 96% recovered yield of the catalyst **1a**. Thus, **1a** is stable to protodeboronation under the reaction conditions and is recyclable.

The scope of substrates was explored using the optimal reaction conditions: 20 mol% catalyst **1a** in nitromethane (Table 2). Most substrates provided cyclic products at room temperature but reaction times can be reduced significantly by performing the reactions at 50°C. Both benzopyrans **3a** and **3b** were obtained in high yield, thus demonstrating that a single phenyl group in **2b** is sufficient to promote effective activation by the catalyst (entries 1 and 2). Remarkably, the unactivated arene substrate **2c** was successfully cyclized, thus affording a 72% yield of product **3c** with catalyst **1c** (entries 3–5). This result suggests that the design of boronic acids that are even more electronically impoverished could

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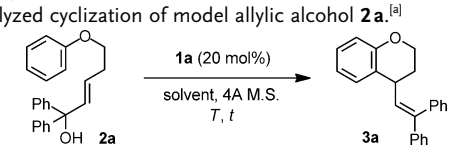
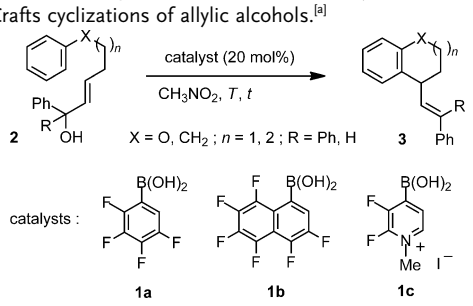
Table 1: Optimization of solvent and reaction conditions in the boronic acid catalyzed cyclization of model allylic alcohol **2a**.[a]

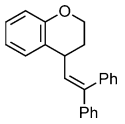
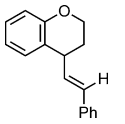
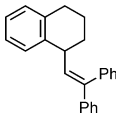
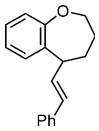


Entry	Cat. loading [mol%]	Solvent[b]	T [°C]	t [h]	Yield[c] [%]
1	20	DMF	50	48	< 5
2	20	EtOAc	50	48	< 5
3	20	THF	50	48	19
4	20	1,4-dioxane	50	48	23
5	20	CH_3CN	50	48	30
6	20	toluene	50	48	55
7	20	hexanes	50	48	67
8	20	CH_3NO_2	50	48	92
9	20	CH_3NO_2	RT	60	97
10	10	CH_3NO_2	RT	60	67
11	5	CH_3NO_2	RT	60	8
12	20	CH_3NO_2	RT	60	68[d]
13	20	CH_3NO_2	RT	60	97[e]

[a] Reaction conditions: The boronic acid catalyst (0.04 mmol) was added to a solution of alcohol substrate (0.2 mmol) in nitromethane (1 mL) containing activated 4 A molecular sieves (M.S.; 200 mg). The solution was stirred at the indicated temperature for the indicated period of time. [b] Dry solvents were employed. [c] Yields of isolated product purified by column chromatography on silica gel. In most cases, other materials are minor amounts of leftover substrate, as well as elimination and 1,3-transposition products. [d] Using pentafluorophenylboronic acid (20 mol%) as the catalyst. [e] No molecular sieves were used. DMF = *N*,*N*′-dimethylformamide, THF = tetrahydrofuran.

Table 2: Substrate scope in the boronic acid catalyzed intramolecular Friedel–Crafts cyclizations of allylic alcohols.[a]



Entry	Catalyst	T [°C]	t [h]	Product[b]		Yield[c] [%]
1	**1a**	RT	60		**3a**	97
2	**1a**	RT	48		**3b**	79
3	**1a**	50	48		**3c**	50
4	**1b**	50	48		**3c**	60
5	**1c**	50	48		**3c**	72
6	**1a**	50	48		**3d**	21
7	**1c**	50	48		**3d**	60

[a] Reaction conditions: The boronic acid catalyst (0.04 mmol) was added to a solution of alcohol substrate (0.2 mmol) in nitromethane (1 mL). The solution was stirred at the indicated temperature for the indicated period of time. [b] *E*/*Z* isomer ratio > 20:1 for **3b** and **3d**. [c] Yields of isolated product purified by column chromatography on silica gel. In most cases, other materials obtained are minor amounts of leftover substrate, as well as elimination and 1,3-transposition products.

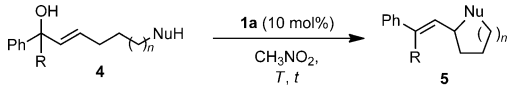
further increase the substrate scope of these Friedel–Crafts-type cyclizations. For example, the use of the new and more active catalyst, 2,3-difluoro-4-methylpyridiniumboronic acid (**1c**), was necessary for effecting a medium ring closure affording **3d** in a reasonable yield of 60% compared to only 21% with catalyst **1a** (entries 6 and 7).

Boronic acid catalyzed cationic cyclizations are not limited to C–C bond formation. Heteroatom cyclizations with diols and amino alcohols are possible, as shown with the isolation of tetrahydrofurans **5a**,**b** (Table 3, entries 1–3), pyrans **5c**,**d** (entries 4-5), oxepan **5e** (entry 6), pyrrolidine **5f** (entry 7), and piperidine **5g** (entry 8). Secondary alcohols were employed successfully (entries 9 and 10), with pyran **5i** formed in excellent yield with very high diastereoselectivity. The desired heterocyclic products were all obtained in high yields. The mildness and effectiveness of these BAC procedures are remarkable. When attempted under standard protic conditions (20 mol% *p*-TsOH under various reaction conditions, see the Supporting Information), the same transformations led to products **3c** (Table 2), **5b**, **5f**, and **5i** (Table 3) in very low maximum yields of 21, 27, 13, and 24%, respectively.

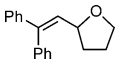
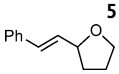
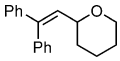
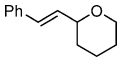
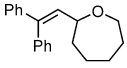
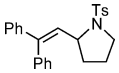
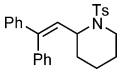
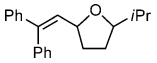
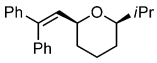
Several other variants of the above cationic cyclizations demonstrate the versatility of boronic acid catalysis in promoting ring-forming reactions (Scheme 2). The example of diol **6** shows that benzylic alcohols are suitable substrates (Scheme 2a). Diol **8** also led to a high yield of cyclized product **9** with intact phenolic silyl ethers (Scheme 2a), and thus bears testimony to the functional group compatibility of these reaction conditions. Indeed, the *p*-TsOH-catalyzed reaction gave product in only 61% as the doubly deprotected bisphenol (see the Supporting Information). The tertiary nonstabilized alcohol **10** afforded the desired product **11**, albeit in modest yield using a higher temperature (Scheme 2b). The benzopyran **13** was formed in high yield by cyclization of a phenol as the nucleophile (Scheme 2c). The remarkable cascade polycyclization of substrate **14** provided the desired tricycle **15** in high diastereoselectivity (Scheme 2d), while the use of a ketone as nucleophile led to an efficient spiroketalization reaction (Scheme 2e).

The scope of substrates of these cyclizations of nucleophile-tethered allylic alcohols is consistent with a mechanism involving complete or near-complete ionization into an allylic carbocation. For example, while substrate **4b** undergoes a smooth and high-yielding reaction to give tetrahydrofuran **5b** at room temperature [Eq. (1), Scheme 3], the isomeric allylic alcohol **4b′** is inert and reacts slowly only at a temper-

Table 3: Substrate scope in the boronic acid catalyzed heterocyclizations of allylic alcohols.[a]



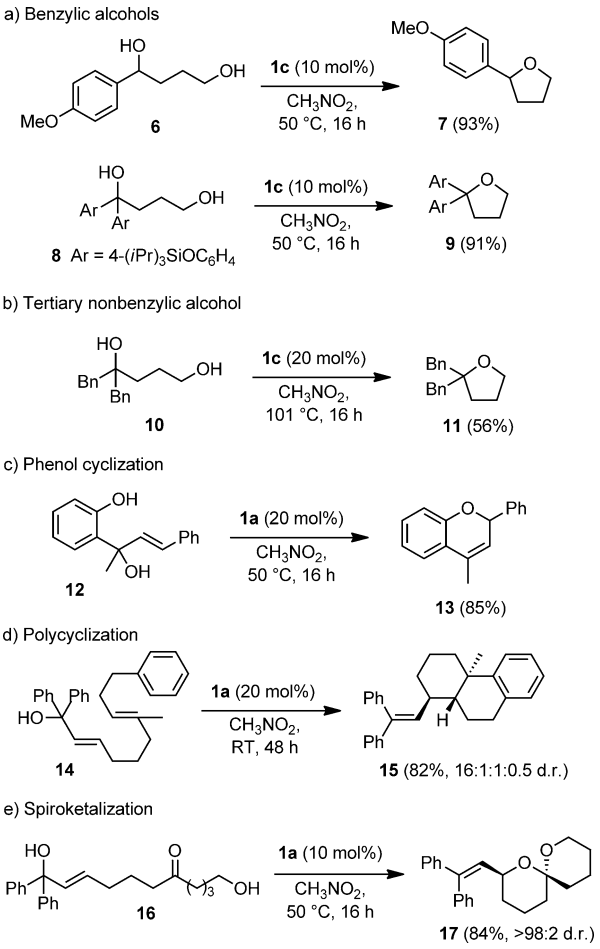
NuH = OH, NHTs ; n = 1, 2, 3 ; R = Ph, H

Entry	T [°C]	t [h]	Product[b]		Yield[c] [%]
1	RT	24		**5a**	95
2	50	16	**5a**		99
3	50	16		**5b**	89
4	50	16		**5c**	87[d]
5	50	48		**5d**	94
6	50	16		**5e**	62[e]
7	50	16		**5f**	88
8	50	16		**5g**	85
9	50	16		**5h**	88 (55:45 d.r.)
10	50	24		**5i**	90 (95:5 d.r.)

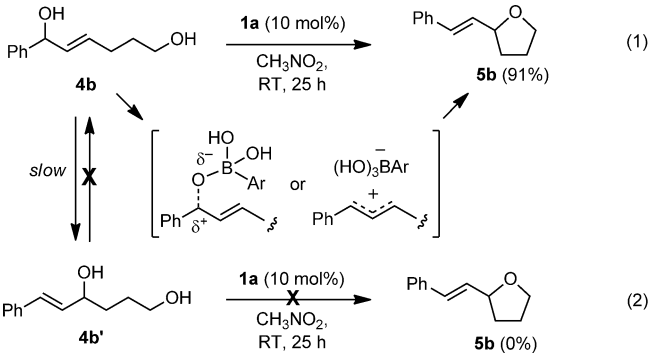
[a] Reaction conditions: The boronic acid catalyst **1a** (4 mg, 0.02 mmol) was added to a solution of alcohol substrate (0.2 mmol) in nitromethane (1 mL). The solution was stirred at the indicated temperature for the indicated period of time. [b] *E*/*Z* isomer ratio > 20:1 for **5b** and **5d**. [c] Yields of isolated product purified by column chromatography on silica gel. In most cases, other materials obtained are minor amounts of leftover substrate, as well as elimination and 1,3-transposition products. [d] 5% of S_N2 product (eight-membered ring) was isolated. [e] 30% of 1,3-hydroxy transposition product was isolated. Ts = 4-toluenesulfonyl.

ature of 80°C [Eq. (2)]. Because ionization of **4b** is greatly facilitated by the benzylic nature of this alcohol, this outcome is consistent with an S_N1' mechanism. Given that **4b′** does not cyclize readily, cyclization of **4b** must be significantly faster than the 1,3-allylic hydroxy transposition giving isomer **4b′** through an S_N2'-like mechanism.[13] Likewise, reverse transposition of **4b′** into **4b** is obviously not occurring under these reaction conditions (see the Supporting Information for more experiments). Altogether these results support the formation of carbocation-like intermediates, of which formation is highly favored in the polar aprotic solvent nitromethane.

In summary, we have reported the application of boronic acid catalysis for the direct carbo- and heterocyclizations of allylic alcohols. The versatility of this concept was convincingly demonstrated by the broad range of cyclic and polycyclic products which can be obtained in high yields with this new type of catalysis. In addition to avoiding the use of reactive leaving groups like sulfonates or halides, BAC provides operationally simple reactions using air-stable catalysts under very mild reaction conditions compared to traditional Lewis or protic acid catalysis.



Scheme 2. Other examples of boronic acid catalyzed cyclizations of nonallylic (a, b) and allylic alcohols (c–e).



Scheme 3. Mechanistic control experiments with alcohols **4b**, **4b′**.

Experimental Section

Typical procedure for the boronic acid catalyzed cyclization of allylic alcohols: 4-(2,2-Diphenylvinyl)chroman (**3a;** Table 2, entry 1): 2,3,4,5-Tetrafluorophenylboronic acid (**1a**; 8 mg, 0.04 mmol) was added to a solution of (*E*)-5-phenoxy-1,1-diphenylpent-2-en-1-ol (**2a**;

66 mg, 0.2 mmol) in CH_3NO_2 (1 mL) at room temperature. The resulting solution was stirred at room temperature for 60 h. Upon evaporation of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (EtOAc/hexanes = 1:20) to give the chroman **3a** (60.5 mg, 97%) in pure form. A larger scale reaction (1 g of **2a**) gave a 95% yield of **3a** with a 96% recovered yield of the catalyst **1a**. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.48–7.24 (m, 10H), 7.22–7.10 (m, 2H), 6.93–6.81 (m, 2H), 6.12 (d, J = 10.2 Hz, 1H), 4.34 (dt, J = 10.9, 4.1 Hz, 1H), 4.12–4.02 (m, 1H), 3.78–3.66 (m, 1H), 2.12–2.00 ppm (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.4, 142.7, 142.0, 139.8, 131.6, 129.7, 129.6, 128.6, 128.2, 127.8, 127.37, 127.35, 127.3, 124.9, 120.4, 116.8, 65.1, 35.5, 29.6 ppm. IR (Microscope): $\tilde{\nu}$ = 3056, 3023, 2947, 2876, 1603, 1580, 1487, 1450 cm^{-1}. HRMS (EI) for $C_{23}H_{20}O$: calcd. 312.1514; found 312.1517. Products **3a**–**3d**, **5a**–**5i**, **7**, **9**, **11**, **13**, **15**, and **17** were prepared using a similar procedure and then fully characterized (see the Supporting Information).

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Keywords: allylic compounds · boron · carbocycles · cyclization · heterocycles

[1] For example, the *ACS Green Chemistry Institute Pharmaceutical Roundtable* ranked "alcohol activation for nucleophilic activation" the second most important priority area for green chemistry research: D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer, R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks, T. Y. Zhang, *Green Chem.* **2007**, *9*, 411–420.

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[16] The inferior efficacy of pentafluoro- versus tetrafluorophenylboronic acid (**1a**) is not due to a difference in stability because both can be recovered intact after the reaction. One explanation is the possibility for additional substrate activation from the relatively acidic *ortho* C–H bond of **1a** (and **1b**, **1c**).