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Boronic Acid Catalysis for Mild and Selective [3+2] Dipolar Cycloadditions to Unsaturated Carboxylic Acids

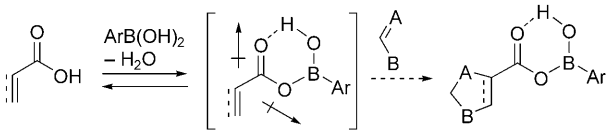
Hongchao Zheng,[a] Robert McDonald,[b] and Dennis G. Hall*[a]

Abstract: Herein, the concept of boronic acid catalysis (BAC) for the activation of unsaturated carboxylic acids is applied in several classic dipolar [3+2] cycloadditions involving azides, nitrile oxides, and nitrones as partners. These cycloadditions can be used to produce pharmaceutically interesting, small heterocyclic products, such as triazoles, isoxazoles, and isoxazolidines. These cycloadducts are formed directly and include a free carboxylic acid functionality that can be employed for further transformations, thereby avoiding prior masking or functionalization. In all cases, BAC provides faster reactions, under milder conditions, with much improved product yields and regioselectivities. In some instances, such as triazole formation from the reaction of azides with 2-alkynoic acids, catalysis with *ortho*-nitrophenylboronic acid circumvents the undesirable product decarboxylation observed when using thermal activation. By using NMR spectroscopic studies, the boronic acid catalyst was shown to provide activation by a LUMO-lowering effect in the unsaturated carboxylic acid, likely via a monoacylated hemiboronic ester intermediate.

Keywords: boronic acids · carboxylic acids · dipolar cycloadditions · heterocycles · homogeneous catalysis

Introduction

The quest for new ways of catalyzing important organic reactions is of utmost importance to expand the substrate scope or selectivity of existing transformations and to allow new bond-forming processes to occur. The activation of substrates by transition metals,[1] cyclic amines,[2] and gold complexes[3] exemplify the possibilities enabled by new catalysts for the production of small organic molecules that are of interest to medicine and materials science. For several important classes of substrate catalytic activation is difficult to achieve due to of the inherent chemical properties of the functional group of interest. For example, carboxylic acids tend to be difficult substrates due to their acidic character, which can create chemical compatibility issues. As a result, the carboxylic acid functionality is usually handled in a masked format, such as a suitable carboxylic ester, which necessitates additional synthetic steps. A direct method for the electrophilic (or LUMO-lowering) activation of unsaturated carboxylic acids towards cycloadditions would be advantageous in terms of both atom- and step-economy (Scheme 1). We recently demonstrated this concept with [4+2] cycloadditions of acrylic acid by using catalysis by arylboronic acids.[4] Herein, we present a significant expansion of this concept of boronic acid catalysis (BAC) into several classic dipolar [3+2] cycloadditions of unsaturated carboxylic acids to produce small heterocyclic products containing a free carboxylic acid functionality. Faster reactions, milder conditions, and increased regioselectivity are the main benefits provided by BAC.[5] In several instances, the resulting cycloadducts are not readily accessible by using thermal activation. The resulting O- and N-containing small heterocycles



Scheme 1. The concept of electrophilic (LUMO-lowering) activation of unsaturated carboxylic acids using BAC.

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[a] H. Zheng, Prof. D. G. Hall
Department of Chemistry, Gunning-Lemieux Chemistry Centre
University of Alberta, Edmonton, Alberta, T6G 2G2 (Canada)
Fax: (+1) 780-492-8231
E-mail: dennis.hall@ualberta.ca

[b] Dr. R. McDonald
X-ray Crystallographic Laboratory
Department of Chemistry, Gunning-Lemieux Chemistry Centre
University of Alberta, Edmonton, Alberta, T6G 2G2 (Canada)

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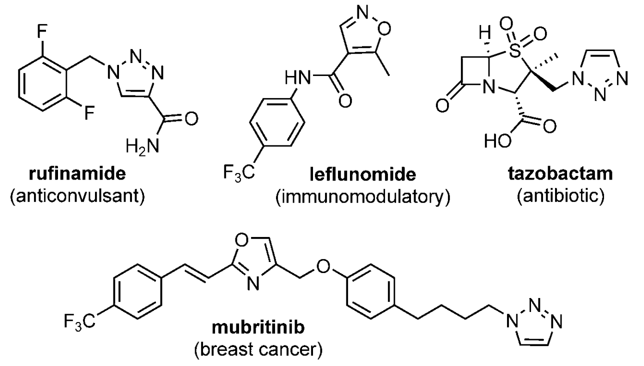
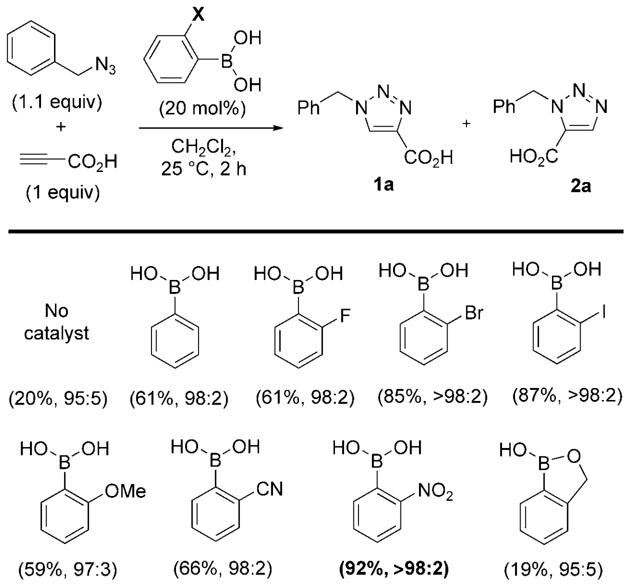
are important components of numerous pharmaceutical agents (some examples are shown below).



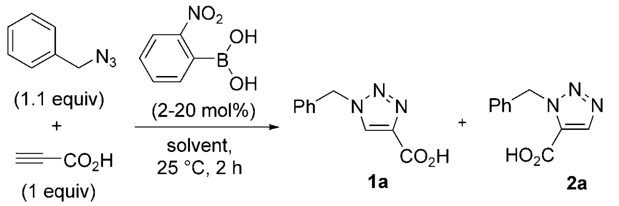
Results and Discussion

Optimization of catalyst and solvent: Because *ortho*-halo-substituted arylboronic acids were previously found to be potent catalysts in [4+2] cycloadditions of acrylic acid,[4] our initial screening of potential catalysts focused on this class of compounds. Thus, a large number of *ortho*-substituted arylboronic acids were evaluated for their ability to accelerate the Huisgen azide–alkyne [3+2] cycloaddition.[6] The thermal Huisgen azide–alkyne cycloaddition of propiolic acid is known to require elevated temperatures that lead to substantial decarboxylation of the 1,2,3-triazene cycloadduct formed.[7] It was hoped that milder conditions employing BAC at room temperature could help to suppress this undesirable process. In the event, all the arylboronic acids tested for their potential to accelerate the cycloaddition between benzyl azide and propiolic acid provided a significant increase in the reaction yield when used at 20 mol% loading, after two hours of stirring at room temperature, in dry dichloromethane (Scheme 2). Whereas the uncatalyzed process gave only 20% yield, the best catalyst identified, *ortho*-nitrophenylboronic acid, led to a yield of 92% of triazene product **1a** as a single regioisomer observed. By using *ortho*-nitrophenylboronic acid at 20 mol% loading, a solvent optimization study was completed (see Table 1) and showed that halogenated compounds are superior solvents for this reaction. Thus, 1,2-dichloroethane provided a near-quantitative yield and only a single observable regioisomer (Table 1, entry 9). As in our previous report on [4+2] cycloadditions, a substoichiometric amount of water (formed in situ from the condensation between the boronic acid and the carboxylic acid) is necessary to ensure catalyst turnover, which is confirmed by the low product yield in the presence of molecular sieves (Table 1, entry 10). On the other hand, stoichiometric quantities of water lead to reduced yields (Table 1, entries 11 and 12). Further optimization of catalyst loading revealed that catalysis was still effective at only 5 mol% (Table 1, entry 14); however, a further decrease to 2 mol% led to a significant reduction in the yield (Table 1, entry 15).



Scheme 2. Survey of *ortho*-functionalized arylboronic acids for catalytic activity in a model azide–alkyne cycloaddition.

Table 1. Optimization of solvent and catalyst loading for the BAC of a model azide–alkyne cycloaddition.[a]

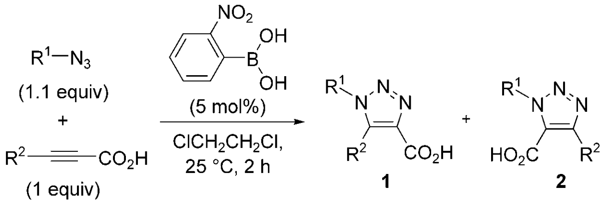


	Solvent[b]	Catalyst [mol%]	Yield[c] [%]	Regioselectivity[d] **1a**:**2a**
1	Et_2O	20	18	95:5
2	THF	20	40	95:5
3	CH_3CN	20	33	96:4
4	acetone	20	58	96:4
5	EtOH	20	38	95:5
6	DMF	20	70	97:3
7	toluene	20	81	>98:2
8	CH_2Cl_2	20	90	>98:2
9	$ClCH_2CH_2Cl$	20	95	>98:2
10[e]	$ClCH_2CH_2Cl$	20	18	95:2
11[f]	$ClCH_2CH_2Cl$	20	75	>98:2
12[g]	$ClCH_2CH_2Cl$	20	26	95:2
13	$ClCH_2CH_2Cl$	10	95	>98:2
14	$ClCH_2CH_2Cl$	5	94	>98:2
15	$ClCH_2CH_2Cl$	2	61	98:2

[a] Reaction conditions: propiolic acid (1.0 mmol) and the catalyst (0.02–0.2 mmol) were mixed in the indicated solvent (2 mL), stirred at 25 °C for 10 min, followed by the addition of benzyl azide (1.1 mmol) and stirred at 25 °C for 2 h. [b] Dry, distilled solvent was employed. [c] Isolated yields of the product after purification by simple filtration. [d] Measured by ^{1}H NMR spectroscopy of the crude reaction product. [e] With 4 Å molecular sieves. [f] With water (1.0 equiv) added. [g] With water (10 equiv) added.

Substrate scope for alkyne–azide cycloadditions: With the optimal conditions in hand (Table 1, entry 14: 5 mol% *o*-$NO_2C_6H_4B(OH)_2$ in $ClCH_2CH_2Cl$ at 25 °C), we then examined the azide and alkyne substrate scope of this [3+2] cycloaddition. The results in Table 2 display the yield and re-

Table 2. Substrate scope for the BAC of azide–alkyne cycloadditions.[a]

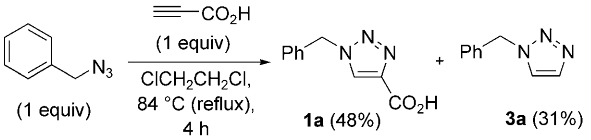


	R^1	R^2	T [°C]	t [h]	Yield[b] [%]		Regioselectivity[c] **1**:**2**	
1	$PhCH_2$	H	25	4	**1a**: 96	(23)	>98:2	(95:5)
2	PhCH(Me)	H	25	24	**1b**: 84	(22)	>98:2	(95:5)
3	EtO_2CCH_2	H	25	4	**1c**: 92	(21)	>98:2	(>98:2)
4	$MeO_2CCH(Me)$	H	25	24	**1d**: 92	(21)	>98:2	(>98:2)
5	EtO_2CCMe_2	H	25	96	**1e**: 71	(4)	>98:2	(>98:2)
6	$NCCH_2$	H	25	4	**1f**: 96	(15)	>98:2	(9:1)
7	Ph	H	25	24	**1g**: 82	(18)	>98:2	(6:1)
8	4-tolyl	H	25	48	**1h**: 85	(19)	16:1	(5:1)
9	2-tolyl	H	25	72	**1i**: 78	(9)	>98:2	(9:1)
10	2-naphthalene	H	25	72	**1j**: 80	(15)	>98:2	(95:5)
11	$4-MeOC_6H_4$	H	25	24	**1k**: 93	(17)	5:1	(1.5:1)
12	$2-MeOC_6H_4$	H	25	24	**1l**: 87	(13)	>98:2	(15:1)
13	$4-ClC_6H_4$	H	25	72	**1m**: 73	(12)	>98:2	(3:1)
14	$2-ClC_6H_4$	H	25	72	**1n**: 63	(8)	>98:2	(7:1)
15	$PhCH_2$	Me	40	48	**1o**: 70	(12)	>98:2	(6:1)
16	$PhCH_2$	Ph	40	96	**1p**: 68	(15)	5:1	(1.4:1)
17	$PhCH_2$	CO_2Me	25	24	**1q**: 73	(16)	>4.5:1[d]	(1.1:1)
18[e]	$PhCH_2$	CO_2H	25	24	**1r**: 92	(25)		
19	tosyl	H	40	48	**1s**: 0	(0)		

[a] Values in parentheses refer to the uncatalyzed process; reaction conditions: alkynoic acid (1.0 mmol) and the catalyst (0.02–0.2 mmol) were mixed in distilled 1,2 dichloroethane (2 mL) and stirred at the specified temperature for 10 min followed by addition of benzyl azide (1.1 mmol) and stirred for the specified time. [b] Isolated yields of the product after purification by simple filtration. [c] Measured by ^{1}H NMR spectroscopy of the crude reaction product; regioisomers were identified by a combination of NMR experiments, comparison with known compounds (**1o** and **1p** were compared with their corresponding known ethyl esters), and X-ray crystallography (**1r**)[8] (see Supporting Information). [d] An additional result, with 20 mol% catalyst: 76% yield and >98:2 regioselectivity. [e] Solvent was THF.

gioselectivity of both the boronic acid catalyzed reactions, and the uncatalyzed reactions. For the azide component, it is clear that a very wide variety of both aliphatic (Table 2, entries 1–6) and aromatic substrates (Table 2, entries 7–14) can be employed. To our surprise, not only did the o-$NO_2C_6H_4B(OH)_2$-catalyzed variant give greatly improved yields over the uncatalyzed reaction, but the regioselectivity was also significantly improved, to the point of avoiding isomer separation in most cases. Thus, 1,2,3-triazenes **1a–n** were obtained in yields as high as 96%, whereas, in the absence of the catalyst, the same cycloadditions typically occurred with yields of less than 20%. Satisfactorily, it was found that 3-substituted 2-alkynoic acids can also be successfully utilized provided a slightly elevated temperature or longer time period is used (Table 2, entries 15–18).[8] The single unsuccessful reaction of an azide was for p-toluenesulfonyl azide (Table 2, entry 19). Likewise, alkenoic acids are unsuitable substrates, as indicated by the failure of acrylic acid to react with benzyl azide (not shown).

The boronic acid catalyzed Huisgen cycloaddition of unsaturated carboxylic acids does not just display an interesting substrate scope, it also circumvents the decarboxylation problem that plagues the thermal, uncatalyzed variant.[7] For example, when run in typical conditions of refluxing 1,2-dichloroethane for just a few hours, the initial product in the reaction of benzyl azide and propiolic acid, **1a**, was accompanied by as much as 31% of the decarboxylated adduct **3a** (Scheme 3).

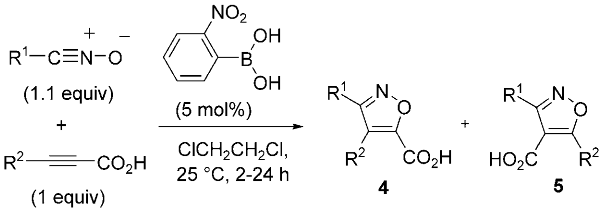


Scheme 3. Huisgen cycloaddition of propiolic acid under thermal conditions.

Substrate scope for nitrile oxide cycloadditions: The generality of this concept for activation of unsaturated carboxylic acids by using BAC was then assessed for other types of [3+2] cycloaddition, starting with nitrile oxides as the dipolar partners.[9] Remarkably, nitrile oxides were found to add to alkynoic acids under catalysis with o-$NO_2C_6H_4B(OH)_2$ in much improved yields and regioselectivities compared with the corresponding thermal, uncatalyzed reactions (Table 3). The sterically favored carboxyisoxazole isomers **4** were isolated from aromatic (Table 3, entry 1), unsaturated (Table 3, entry 2), and aliphatic (Table 3, entry 3) nitrile oxides as single products in good to high yields. 3-Substituted alkynoic acids can also be employed with success, but, conversely, give the alternative regioisomers **5** (Table 3, entries 4 and 5) as the major isomer, apparently under electronic control.[10] Acrylic acid and its 3-substituted derivatives were also found to be suitable substrates in reactions with nitrile oxides, giving dihydroisoxazole products **6** in greatly improved yields and regioselectivities compared with the uncatalyzed cycloadditions (Table 4).

Substrate scope for nitrone cycloadditions: The feasibility of these dipolar cycloadditions in reactions with nitrones was examined next.[11] In the event, the dipolar cycloaddition of nitrones to 2-alkynoic acids presented an extra challenge caused by the acid-catalyzed Beckmann rearrangement,

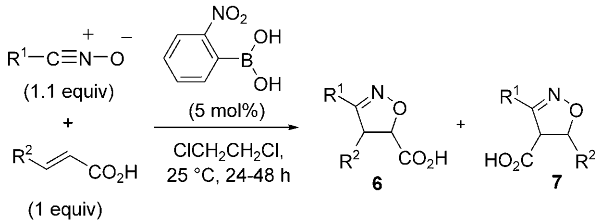
Table 3. Substrate scope for BAC of nitrile oxide cycloadditions to 2-alkynoic acids.[a]



	R^1	R^2	T [°C]	t [h]	Yield[b] [%]	Regio-selectivity[c]		
1	Ph	H	25	2	87 (15)	**4a**:**5a**	>98:2	(9:1)
2	PhCH=CH	H	25	24	71 (4)	**4b**:**5b**	>98:2	(6:1)
3	$PhCH_2CH_2$	H	25	24	73 (5)	**4c**:**5c**	>98:2	(6:1)
4	Ph	Me	25	24	78 (10)	**4d**:**5d**	1:16[d]	(1:5)
5	Ph	Ph	25	24	69 (5)	**4e**:**5e**	1:6[e]	(1:1.2)

[a] Values in brackets refer to the uncatalyzed process; reaction conditions: to nitrile oxide (1.1 mmol) in 1,2-dichloroethane (4 mL) was added a solution of alkynoic acid (1.0 mmol) and the catalyst (0.05 mmol) in 1,2-dichloroethane (4 mL). [b] Isolated yields of products purified by acid–base extraction. [c] Measured by ^1H NMR spectroscopy of the crude reaction product; regioisomers were identified by a combination of NMR experiments, comparison with known compounds (**5d**), and X-ray crystallography (**5e**;[8] see Supporting Information). [d] Additional result with 20 mol% catalyst: 75% yield and <2:98 regioselectivity. [e] Additional result with 20 mol% catalyst: 80% yield and <2:98 regioselectivity.

Table 4. Substrate scope for BAC of nitrile oxide cycloadditions to 2-alkenoic acids.[a]

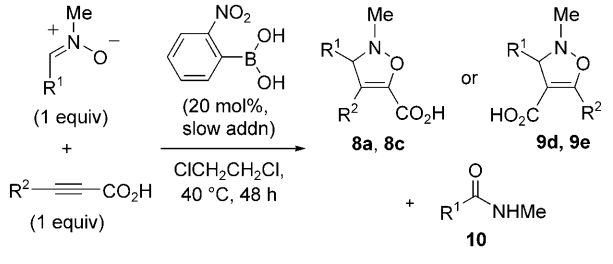


	R^1	R^2	T [°C]	t [h]	Yield[b] [%]	Regioselectivity[c]		
1	Ph	H	25	24	67 (7)	**6a**:**7a**	>98:2	(95:5)
2	PhCH=CH	H	25	48	67 (6)	**6b**:**7b**	>98:2	(10:1)
3	$PhCH_2CH_2$	H	25	48	65 (3)	**6c**:**7c**	>98:2	(5:1)
4	Ph	Me	25	24	77 (10)	**6d**:**7d**	<2:98[d]	(<2:98)
5	Ph	Ph	25	24	65 (10)	**6e**:**7e**	<2:98[e]	(<2:98)

[a] Values in brackets refer to the uncatalyzed process; reaction conditions: to nitrile oxide (1.1 mmol) in 1,2-dichloroethane (4 mL) was added a solution of alkynoic acid (1.0 mmol) and the catalyst (0.05 mmol) in 1,2-dichloroethane (4 mL). [b] Isolated yields of products purified by acid–base extraction. [c] Measured by ^1H NMR spectroscopy of the crude reaction product; regioisomers were identified by a combination of NMR experiments, comparison with known compounds (**7d** and **7e** were compared with their corresponding known methyl esters; see Supporting Information). [d] Diastereomeric ratio: 5:1 *anti*:*syn*. [e] Diastereomeric ratio: 40:1 *anti*:*syn*.

which leads to decomposition of the nitrone into an amide product.[12] While this reaction is unavoidable under thermal uncatalyzed conditions, we found that it could be suppressed by slow addition of the carboxylic acid, so as to keep it in the neutral, catalyst-activated form necessary for the dipolar cycloaddition. In the event, isoxazolecarboxylic acids **8a** and **8c** and **9d** and **9e** were isolated in moderate yields and pure regioisomeric forms with only traces of amides **10** synthesized (Table 5).

Table 5. Substrate scope for BAC of nitrone cycloadditions with 2-alkynoic acids.[a]



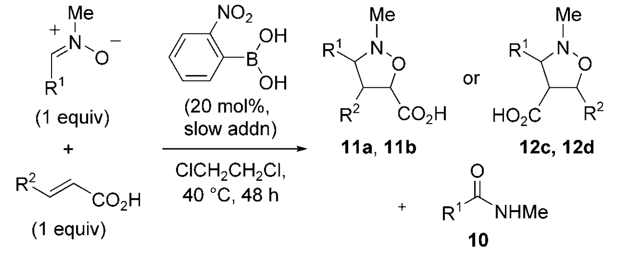
	R^1	R^2	T [°C]	t [h]	Yields [%]			
1	Ph	H	40	48	**8a**:[b]	71, (0)	**10a**:	<2 (41)
2	PhCH=CH	H	40	48		–[c](0)	**10b**:	– (43)
3	$PhCH_2CH_2$	H	40	48	**8c**:[b]	62, (<2)	**10c**:	<5 (60)
4	Ph	Me	40	48	**9d**:[b]	52, (<5)	**10a**:	<2 (54)
5	Ph	Ph	40	48	**9e**:[b]	50, (<2)	**10a**:	0 (54)

[a] Values in brackets refer to the uncatalyzed process; reaction conditions: to a solution of nitrone (1.0 mmol) in distilled 1,2-dichloroethane (4 mL) was slowly added, by syringe pump, a solution of propiolic acid (1.0 mmol) and the catalyst (0.2 mmol) in distilled 1,2-dichloroethane (4 mL). [b] Isolated yield of products purified by flash column chromatography on a short column; entries 1 and 3: products **8a** and **8c** were obtained as single regioisomers and identified by NMR spectroscopy; entries 4 and 5: products **9d** and **9e** were obtained as single isomers; regioisomers were identified by a combination of NMR experiments and comparison with known compounds (**9d** and **9e** were compared with the corresponding known methyl esters; see Supporting Information). [c] A complex mixture was obtained.

As with nitrile oxides, acrylic acid and its 3-substituted derivatives were found to be suitable substrates in the cycloadditions of nitrones, giving isoxazolidine products **11** or **12** in greatly improved yields and regioselectivities compared with the uncatalyzed cycloadditions (Table 6). The same slow addition procedure employed for the alkynoic acids also prevented amides **10** from forming during these reactions. The major regioisomeric cycloadducts were similar to those observed with alkynoic acids: propiolic acid gives sterically controlled formation of **11a** and **11b**, whereas 2-butynoic acid affords **12c** and **12d** through electronic control. The structure of the predominant *anti*:*syn* diastereomer of **11a** was ascertained by X-ray crystallography,[8] which helped support the stereochemical assignments of the other cycloadducts (see Supporting Information).

Mechanistic investigation: Preliminary experiments were conducted in order to understand the mechanism of the activation provided by the boronic acid catalyst. Because no rate acceleration for methyl acrylate was observed in the presence of $o\text{-}NO_2C_6H_4B(OH)_2$, dehydrative borylation of the carboxylic acid must be an essential step. Therefore, the two most viable activated intermediates that can be formed between the unsaturated carboxylic acid and *o*-nitrophenyl-

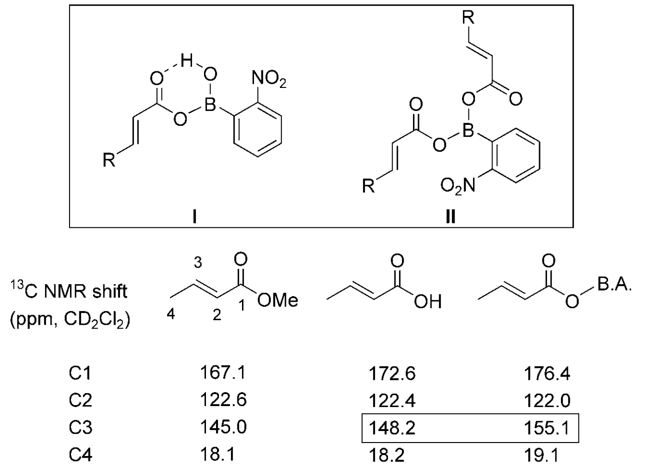
Table 6. Substrate scope for BAC of nitrone cycloadditions with 2-alkenoic acids.[a]



	R^1	R^2	T [°C]	t [h]	Yields [%]			
1	Ph	H	40	48	**11a**:[b,c]	75, (<2)	**10a**:	<2 (36)
2	$PhCH_2CH_2$	H	40	48	**11b**:[b,d]	73, (<2)	**10c**:	<2 (40)
3	Ph	Me	40	48	**12c**:[b,e]	66, (<2)	**10a**:	<2 (50)
4	$PhCH_2CH_2$	Me	40	48	**12d**:[b,f]	69, (<2)	**10c**:	<2 (41)
5	Ph	Ph	40	48	**11e/12e**:	<10, nd[g]	**10a**:	0 (53)
6	$PhCH_2CH_2$	Ph	40	48	**11f/12f**:	<10, nd[g]	**10c**:	0 (45)

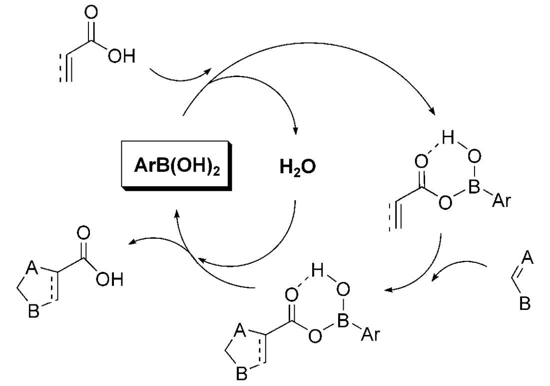
[a] Values in brackets refer to the uncatalyzed process; reaction conditions: to a solution of nitrone (1.0 mmol) in distilled 1,2-dichloroethane (4 mL) was slowly added, by syringe pump, a solution of 2-alkenoic acid (1.0 mmol) and the catalyst (0.2 mmol) in distilled 1,2-dichloroethane (4 mL). [b] Isolated yields of products purified by flash column chromatography on a short column; regioselectivities are >95:5 and were quantified by ^{1}H NMR spectroscopy of the crude reaction products; regioisomers were identified by a combination of NMR experiments and X-ray crystallography[8] (**11a**; see Supporting Information). [c] Diastereomeric ratio: 23:1 *anti*:*syn*. [d] Diastereomeric ratio: 2:1 *anti*:*syn*. [e] Diastereomeric ratio: 3:2.5:1:0. [f] Diastereomeric ratio: 3.5:1:0:0. [g] Diastereomeric ratio: not determined.

boronic acid are the hydrogen-bonded, monoacylated, hemiboronic ester **I** and the diacylated species **II** (Scheme 4).[13] Attempts were made to isolate the intermediates by condensing (*E*)-crotonic acid with *o*-$NO_2C_6H_4B(OH)_2$ under strictly anhydrous conditions, by using molecular sieves. It is notable that no adduct was formed without a dehydrating agent, implying that the dehydrative borylation is unfavorable and that the activated intermediate must exist in a very small concentration under the reaction conditions. This proposal is supported by the retardation effect of water on the cycloaddition (see Table 1, entries 11 and 12). Stoichiometric condensation experiments were planned with a varying ratio of (*E*)-crotonic acid to the boronic acid (1:1, 1:2, 2:1). Regardless of the ratio used, even with excess crotonic acid, only a single species and leftover crotonic acid were observed. No crotonic anhydride was detected by ^{1}H NMR spectroscopy. This result suggests that the activated intermediate is the monoacylated hemiboronic ester **I**. This claim is also supported by the poor activity of the cyclic benzoboroxole (see Scheme 2), which is incapable of the internal hydrogen bonding in intermediate **I**. Using the Childs method,[14] we observed a large increase of 6.9 ppm for the ^{13}C NMR chemical shift of the β carbon (C3) of the monoacylated intermediate **I**. The extent of this chemical shift increase is similar to that observed in the complexation of methyl crotonate with moderate Lewis acids, such as $SnCl_4$.[14] Under the same conditions the boronic acid had a negligible effect on the ^{13}C NMR chemical shifts of methyl crotonate (not shown). According to these results, *o*-$NO_2C_6H_4B(OH)_2$ catalyzes the dipolar cycloadditions through a powerful LUMO-lowering activation of the dipolarophile by the formation of a covalent adduct with the unsaturated carboxylic acid. Combined with the role of water described above, this preliminary mechanistic study leads to the proposed catalytic cycle depicted in Scheme 5, in which both *o*-$NO_2C_6H_4B(OH)_2$ and water are recycled in the cycloaddition process.



C1	167.1	172.6	176.4
C2	122.6	122.4	122.0
C3	145.0	$\boxed{148.2}$	$\boxed{155.1}$
C4	18.1	18.2	19.1

Scheme 4. Preliminary mechanistic experiments to address the origin of the activation in the BAC reactions of dipolar cycloadditions.



Scheme 5. The proposed catalytic cycle for the boronic acid catalyzed dipolar cycloadditions of unsaturated carboxylic acids.

Conclusion

In summary, we have reported the concept of BAC for the activation of unsaturated carboxylic acids toward several classical dipolar [3+2] cycloadditions involving azides, nitrile oxides, and nitrones as partners. These cycloadditions can directly produce pharmaceutically interesting, small heterocyclic products that contain a free carboxylic acid functionality. This carboxylate can be employed for further transformations, thereby avoiding prior masking or functionalization of the reagents. In all cases, BAC provides faster reactions, under milder conditions, with much improved product yields and regioselectivities. In some instances, such as triazole formation from azides and 2-alkynoic acids, catalysis with *ortho*-nitrophenylboronic acid circumvents the undesirable product decarboxylation observed when only using thermal activation. By using NMR spectroscopic studies, the boronic acid catalyst was shown to provide activation by lowering the LUMO of the unsaturated carboxylic acid likely via a monoacylated hemiboronic ester intermediate.

Experimental Section

Typical procedure for the boronic acid catalyzed cycloaddition of azides to unsaturated carboxylic acids: benzyl-1*H*-1,2,3-triazole-4-carboxylic acid (1a; Table 2, entry 1): *ortho*-Nitrophenylboronic acid (8 mg, 0.05 mmol) was added to a solution of propiolic acid (70 mg, 1 mmol) in 1,2-dichloroethane (2 mL), and the resulting solution was stirred at room temperature (25 °C) for 10 min. Benzyl azide (146 mg, 1.1 mmol) was then added and the resulting mixture was stirred at room temperature for 4 h. The solvent was then removed under vacuum, at room temperature. The residue was washed with Et_2O (3×5 mL) and filtered to give pure triazole **1a** (195 mg, 96 %) as a white solid. The characterization data for this compound matched that of previous reports.[15] Products **1b–r** were prepared using a similar procedure and then fully characterized (see the Supporting Information).

Typical procedure for the boronic acid catalyzed cycloaddition of nitrile oxides to unsaturated carboxylic acids: 3-phenylisoxazole-5-carboxylic acid (4a; Table 3, entry 1): Triethylamine (111 mg, 1.1 mmol) was added to an ice-cooled (0 °C), stirred solution of phenylhydroximic acid chloride (171 mg, 1.1 mmol) in 1,2-dichloroethane (2 mL); after 3 min, the mixture was washed with water (2×4 mL) and dried over Na_2SO_4. The resulting solution was filtered to remove the Na_2SO_4 and give a solution of benzonitrile oxide (around 4 mL). A solution of propiolic acid (70 mg, 1 mmol) and *ortho*-nitrophenylboronic acid (8 mg, 0.05 mmol) in 1,2-dichloroethane (4 mL) was added to the benzonitrile oxide solution prepared in this way. After stirring for 2 h at room temperature (25 °C), the solvent was removed under vacuum, at room temperature. Then, NaOH (1 M, 5 mL) was added to the residue and this mixture was washed with Et_2O (3×5 mL). The aqueous layer was adjusted to pH 4 by adding HCl (6 M), dropwise. The resulting aqueous layer was extracted with EtOAc (3×10 mL) and the organic layer was dried over Na_2SO_4. Filtering off the Na_2SO_4 and removing the solvent gave pure isoxazole product **4a** (165 mg, 87 %) as a white solid. The regiochemistry was assessed by using 2D NMR experiments (HMBC and HSQC, see the Supporting Information). ^1H NMR (400 MHz, [D$_6$] DMSO, 25 °C): $\delta = 14.30$ (brs, 1H), 7.97–7.92 (m, 2H), 7.77 (s, 1H), 7.55–7.49 ppm (m, 3H); ^{13}C NMR (100 MHz, [D$_6$] DMSO, 25 °C): $\delta = 162.7$, 161.7, 157.6, 130.6, 129.1, 127.6, 126.7, 107.5 ppm; IR (microscope): $\tilde{\nu} = 3400$–2100 (br), 1705, 1595, 1579 cm^{-1}; HRMS (ESI): m/z calcd for $C_{10}H_6NO_3$: 188.03532; found: 188.03545. Products **4a–c**, **5d** and **5e**, **6a–c**, and **7d** and **7e** were prepared by using a similar procedure and then characterized (see the Supporting Information).

Typical procedure for the boronic acid catalyzed cycloaddition of nitrones to unsaturated carboxylic acids: 2-methyl-3-phenyl-2,3-dihydroisoxazole-5-carboxylic acid (8a; Table 5, entry 1): A solution of propiolic acid (70 mg, 1 mmol) and *ortho*-nitrophenylboronic acid (33 mg, 0.2 mmol) in 1,2-dichloroethane (4 mL) was slowly added by syringe pump, over 6 h, to a stirred solution of (*Z*)-*N*-benzylidenemethanamine oxide (135 mg, 1 mmol) in 1,2-dichloroethane (4 mL) maintained at 40 °C. After the mixture was stirred at 40 °C for 48 h, the solvent was removed under vacuum and the crude product was purified by flash column chromatography (EtOAc/hexanes = 1:2) to give pure isoxazolecarboxylic acid **8a** (146 mg, 71 %) as a white solid. The regiochemistry was assessed by using 2D NMR experiments (HMBC and HSQC, see the Supporting Information). ^1H NMR (400 MHz, [D$_6$] DMSO, 25 °C): $\delta = 13.36$ (brs, 1H), 7.38–7.24 (m, 5H), 5.97 (d, $J = 3.0$ Hz, 1H), 4.97 (d, $J = 2.9$ Hz, 1H), 2.81 ppm (s, 3H); ^{13}C NMR (125 MHz, [D$_6$] DMSO, 25 °C): $\delta = 160.0$, 144.8, 140.7, 128.4, 127.6, 126.7, 109.8, 74.8, 46.6 ppm; IR (microscope): $\tilde{\nu} = 3400$–2100 (br), 1714, 1642, 1555 cm^{-1}; HRMS (ESI): calcd for $C_{11}H_9NO_3$: 204.06662; found: 204.06635. Without 2-nitrophenylboronic acid as the catalyst, this reaction gave *N*-methylbenzamide (**10a**) in 41 % yield. Products **8a** and **8c**, **9d** and **9e**, **11a** and **11b**, and **12c** and **12d** were prepared using a similar procedure and then characterized (see the Supporting Information).

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[1] a) V. Michelet, P. Y. Toullec, J.-P. Genet, *Angew. Chem.* **2008**, *120*, 4338–4386; *Angew. Chem. Int. Ed.* **2008**, *47*, 4268–4315; b) T. Satyanarayana, S. Abraham, H. B. Kagan, *Angew. Chem.* **2009**, *121*, 464–503; *Angew. Chem. Int. Ed.* **2009**, *48*, 456–494; c) M. Rubin, M. Rubina, V. Gevorgyan, *Chem. Rev.* **2007**, *107*, 3117–3179; d) S. Diez-Gonzalez, N. Marion, S. P. Nolan, *Chem. Rev.* **2009**, *109*, 3612–3676; e) D. M. Homden, C. Redshaw, *Chem. Rev.* **2008**, *108*, 5086–5130.

[2] a) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569; b) D. W. C. MacMillan, *Nature* **2008**, *455*, 304–308; c) A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416–5470; d) M. J. Gaunt, C. C. C. Johansson, *Chem. Rev.* **2007**, *107*, 5596–5605; e) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716–4739; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638–4660.

[3] a) E. Jimenez-Nunez, A. M. Echavarren, *Chem. Commun.* **2007**, 333–346; b) A. Fürstner, P. W. Davies, *Angew. Chem.* **2007**, *119*, 3478–3519; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410–3449; c) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180–3211; A. S. K. Hashmi, G. J. Hutchings, *Angew. Chem.* **2006**, *118*, 8064–8105; *Angew. Chem. Int. Ed.* **2006**, *45*, 7896–7936; d) A. Arcadi, *Chem. Rev.* **2008**, *108*, 3266–3325; e) E. Jimenez-Nunez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326–3350; f) Z. Li, C. Brouwer, C. He, *Chem. Rev.* **2008**, *108*, 3239–3265; g) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351–3378; h) D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395–403.

[4] R. Al-Zoubi, O. Marion, D. G. Hall, *Angew. Chem.* **2008**, *120*, 2918–2921; *Angew. Chem. Int. Ed.* **2008**, *47*, 2876–2879.

[5] I. Georgiou, G. Ilyashenko, A. Whiting, *Acc. Chem. Res.* **2009**, *42*, 756–768.

[6] a) M. Meldal, C. W. Tornoe, *Chem. Rev.* **2008**, *108*, 2952–3015; b) C. R. Becer, R. Hoogenboom, U. S. Schubert, *Angew. Chem.* **2009**, *121*, 4998–5006; *Angew. Chem. Int. Ed.* **2009**, *48*, 4900–4908.

[7] a) R. Alvarez, S. Velazquez, A. San-Felix, S. Aquaro, E. De Clercq, C.-F. Perno, A. Karlsson, J. Balzarini, M. J. Camarasa, *J. Med. Chem.* **1994**, *37*, 4185–4194; b) B. A. Salameh, H. Leffler, U. J. Nilsson, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3344–3346.

[8] CCDC-750311 (**1r**), 750312 (**5e**), and 756956 (**11a**) contain the crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[9] a) T. M. V. D. Pinho e Melo, *Curr. Org. Chem.* **2005**, *9*, 925–958; b) B. J. Wakefield, *Science of Synthesis: Houben–Weyl Methods of Molecular Transformations, Vol. 11* (Ed.: E. Shaumann), Thieme, Stuttgart, **2001**, pp. 229–288.

[10] V. Jager, P. A. Colinas, *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products, Vol. 59* (Ed.: A. Padwa), Wiley, New York, **2002**, pp. 361–472.

[11] K. V. Gothelf, K.-A. Jørgensen, *Chem. Rev.* **1998**, *98*, 863–909.

[12] a) I. A. Grigoriev, *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis* (Ed.: H. Feuer), Wiley, New York, **2008**, pp. 129–434; b) J. Hamer, A. Macaluso, *Chem. Rev.* **1964**, *64*, 473–495.

[13] a) K. Ishihara, S. Ohara, H. Yamamoto, *J. Org. Chem.* **1996**, *61*, 4196–4197; b) T. Maki, K. Ishihara, H. Yamamoto, *Tetrahedron* **2007**, *63*, 8645–8657.

[14] R. F. Childs, D. L. Mulholland, A. Nixon, *Can. J. Chem.* **1982**, *60*, 801–808.

[15] a) T. L. Mindt, R. Schibli, *J. Org. Chem.* **2007**, *72*, 10247–10250; b) L. S. Campbell-Verduyn, L. Mirfeizi, R. A. Dierckx, P. H. Elsinga, B. L. Feringa, *Chem. Commun.* **2009**, 2139–2141; c) A. Maisonial, P. Serafin, M. Traikia, E. Debiton, V. Thery, D. J. Aitken, P. Lemoine, B. Viossat, A. Gautier, *Chem. Eur. J.* **2008**, *14*, 298–305.

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