

Aqua-aminoorganoboron Catalyst: Engineering Single Water Molecule to Act as an Acid Catalyst in Nitro Aldol Reaction

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We have disclosed the catalytic potential hidden behind a series of aqua-aminoorganoboron compounds in the formation and reaction of nitronate species. The pivotal role of a single-coordinated water molecule in the catalyst was demonstrated by comparison with the D₂O-analogue. The present results provide a new strategy for the design of metal-free catalysts which function via elaborative hydrogen-bonding networks involving water.

Naturally occurring enzymes frequently contain water in their catalytic active sites, where the water plays a crucial role in the catalysis.¹ In contrast, attempts to impose catalytic function onto a water molecule represents a challenge in the development of artificial molecular catalysts.² We herein report that aqua-aminoorganoboron compounds³ exhibit unique catalytic activities in the nitro aldol reaction.⁴ The reaction pathways involve subtle interplay between the multiple functions of the catalyst.

A series of aqua-aminoorganoboron compounds **1a–1c** (Figure 1) were readily prepared according to literature procedure³ with small modification. Single-crystal X-ray diffraction analyses of **1a**,³ **1c**,⁵ and **2**⁵ identified a single water molecule as a common feature. The boron-coordinated water bridges two of the three nitrogens via formation of two hydrogen bonds (Figure 1), with the third amine remaining free from any detectable interactions. In contrast, the solution structures of **1a–1c** exhibited dynamic behavior in corresponding ¹H NMR spectra, consistent with intramolecular N...H(OH) exchange. Accordingly, this rapid positional exchange of the N...HOH...N bridge makes the three nitrogens indistinguishable on the NMR time scale.⁵

Treatment of a 1:3 mixture of PhCHO and CH₃NO₂ in THF with a 1 mol % of **1a** at 25 °C for 8.5 h gave nitro aldol product **4a** in 90% yield (Entry 1, Table 1). In contrast, compound **2**, having a structure similar to **1a** but lacking one of the three amino-residues, showed no catalytic activity (Entry 4). When a 1:1 mixture of **2** and Et₃N was used instead of **1a** (Entry 5), the reaction proceeded although at a significantly slower rate. The BPh₃/

Table 1. Catalyst screening in the reaction of CH₃NO₂ with PhCHO^a

CH ₃ NO ₂ + PhCHO (3 equiv) (1 equiv)		catalyst (1 mol %) additive THF, 25 °C, 8.5 h	PhCH(OH)CH ₂ NO ₂ 4a
Entry	Catalyst	Additive (mol %)	Yield ^b /%
1	1a	—	90 (93) ^c
2	1b	—	80
3	1c	—	0
4	2	—	0
5	2	Et ₃ N (1)	29
6	BPh ₃	Et ₃ N (3)	29
7	BPh ₃	Et ₃ N (3), H ₂ O (10)	26
8	—	Et ₃ N (1)	11
9	—	Me ₂ NBn (3)	<5

^aUnless otherwise specified, reaction was performed using 1 mol % of catalyst with respect to the amount of PhCHO in anhydrous THF at 25 °C for 8.5 h. ^bOf isolated, purified product. ^cWith 70 mg/mL of MS4A, which was dried at 150 °C under vacuum (1 mmHg) for 12 h.

Et₃N (1:3) catalyst neither improved the yield of **4a** under anhydrous conditions nor in the presence of water (Entries 6 and 7). Et₃N (1 mol %) or *N,N*-dimethylbenzylamine (3 mol %) alone showed scant catalytic activity under otherwise identical conditions (Entries 8 and 9). The use of **1b**, which differs in steric size at the nitrogen-residue, was also effective, while the extremely bulky diisopropylamine derivative **1c** abolished the reactivity (Entries 2 and 3). These experiments clearly demonstrate that the three amino-residues worked in a cooperative fashion and were critical for generating catalytic activity within some steric restraints. Other examples listed in Tables 2 and 3 indicate the versatile nature of catalyst **1a** under protic or aprotic conditions. Solvent-free conditions (R¹CHO:CH₃NO₂ = 1:3) were beneficial resulting in significant rate acceleration (Table 2, Entry 1), although alcoholic solvents were the best choice for rate optimization (Table 3, Entries 2–5). The reaction showed substrate generality with respect to both nitroalkane and aldehyde components. Various functional groups were tolerated and self-dimerization of aldehydes was prevented owing to the mild (almost neutral pH) reaction conditions (Tables 2 and 3). The optimal results afforded aldol adducts in more than 90% yields in many cases and turnover numbers (TON) of up to 800 (generally 70–100).

The presence of a water molecule in the catalyst is pivotal for catalytic activity. Kinetic studies with the D₂O-derivative **3** (deuterium content: 75–80%) using CD₃NO₂ and hexanal in THF at 27 °C showed that the initial reaction rate (*k*_{obs}) is roughly 35 times faster than that with Et₃N alone (no water).⁶ The reaction proceeded with pseudo-first-order dependence on [hexanal]. Examination of reaction kinetic isotope effects

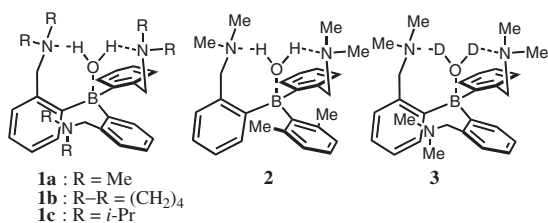


Figure 1. Aqua aminoorganoboron compounds.

Table 2. Nitro aldol reaction by use of various nitroalkanes^a

$$\text{RCH}_2\text{NO}_2 + \text{PhCHO} \xrightarrow[\text{no solvent}]{\text{1a (1 mol\%)}} \text{PhCH}^{\text{a}}(\text{OH})\text{CH}^{\text{b}}(\text{R})\text{NO}_2$$

4a : R = H
4b : R = CH₃
4c : R = Br
4d : R = (CH₂)₃CO₂CH₃

Entry	RCH ₂ NO ₂ (equiv)	Conditions °C, h	Product	Yield ^b /%
1	CH ₃ NO ₂ (3)	25, 1	4a	95
2	CH ₃ NO ₂ (3)	25, 24	4a	80 ^c
3	CH ₃ CH ₂ NO ₂ (3)	25, 1	4b	84 ^d
4	BrCH ₂ NO ₂ (2)	25, 1	4c	71 ^e
5	CH ₃ O ₂ C(CH ₂) ₄ NO ₂ (3)	25, 2	4d	77 ^f

^aUnless otherwise specified, reaction was performed using 1 mol % of **1a** with respect to the amount of PhCHO under indicated conditions. ^bOf isolated, purified product. ^c0.1 mol % of **1a** was used. ^dsyn:anti = 67:33, determined as previously described. ^esyn:anti = 69:31, determined by the coupling constant ($J_{\text{H}^{\text{a}}-\text{H}^{\text{b}}}$) of *syn* (8.5 Hz)-**4c** and *anti* (5.0 Hz)-**4c**. ^f*syn* ($J_{\text{H}^{\text{a}}-\text{H}^{\text{b}}} = 8.9$ Hz)-**4d**:*anti* ($J_{\text{H}^{\text{a}}-\text{H}^{\text{b}}} = 4.9$ Hz)-**4d** = 60:40.

Table 3. Nitro aldol reaction by use of CH₃NO₂ and various aldehydes^a

$$\text{CH}_3\text{NO}_2 + \text{R}^1\text{CHO} \xrightarrow[\text{solvent}]{\text{1a (1 mol\%)}} \text{R}^1\text{CH}(\text{OH})\text{CH}_2\text{NO}_2$$

5a : R¹ = (CH₂)₄CH₃
5b : R¹ = *c*-Hex
5c : R¹ = *t*-Bu
5d : R¹ = CH₂OH

Entry	R ¹ CHO	Conditions °C, h	Solvent	Product	Yield ^b /%
1	CH ₃ (CH ₂) ₄ CHO	50, 24	—	5a	97
2	CH ₃ (CH ₂) ₄ CHO	50, 8	MeOH	5a	91(94) ^c
3	CH ₃ (CH ₂) ₄ CHO	50, 8	MeOH	5a	91
3	<i>c</i> -HexCHO	50, 30	MeOH	5b	98 ^d
4	<i>t</i> -BuCHO	50, 48	MeOH	5c	77 ^d
5	HOCH ₂ CHO ^e	25, 24	MeOH	5d	99

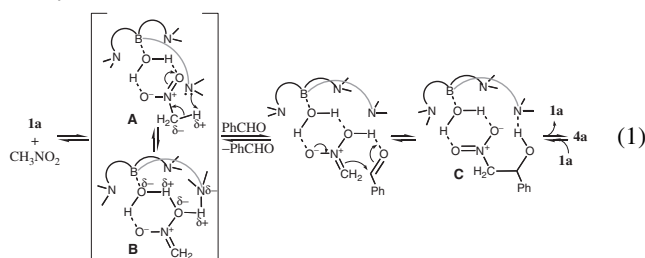
^aUnless otherwise specified, reaction was performed using 1 mol % of **1a** with respect to the amount of R¹CHO and CH₃NO₂ (1.5 equiv) under indicated conditions. ^bOf isolated, purified product. ^c*i*-PrOH was used as solvent instead of MeOH. ^dCH₃NO₂ (3.0 equiv) was used. ^eThe dimer was used.

(KIE) verified that the initial rate for **3** in CD₃NO₂ was ca. 1.5 times greater than that with **1a** in CH₃NO₂ ($k_{\text{H}}/k_{\text{D}} = 0.68$, $t = 6$ –15 min; conversion $\approx 5\%$).⁶

This suggests that the α -C–H bond cleavage is not the rate-determining step. In contrast, when each CH₃NO₂ and CD₃NO₂ was reacted in a separate experiment with hexanal in the presence of 10 mol % of Et₃N, the initial stage of the reaction ($t = 10$ –40 min; conversion $\approx 5\%$) conforms to $k_{\text{H}}/k_{\text{D}} = 1.19$,⁶ suggesting that deprotonation is rate-determining and that C–C bond formation is kinetically faster.⁷ The overall catalysis proceeds through different pathways with the interior H₂O and D₂O altering the rate-determining step.

Although a possibility of an extended transition state could not be fully ruled out, eq 1 summarizes our present understanding and mechanistic models for the overall catalysis during the initial reaction period.⁸ Presumably, one out of the three amino-residues served as a deprotonating agent for the generation of the nitronate **B** following attractive interaction of the O=N–O[−] functionality with the boron-coordinated H₂O molecule of the catalyst. Here the formation of (O)H $\cdots$ (O)(N) hydrogen bonds increases the acidity of the α -hydrogen (δ^+ , structure **A**). The D₂O-analogue stabilize more favorably the nitronate anion since D₂O and D⁺ are well accepted to make stronger hydrogen bonds than H₂O and H⁺, respectively.⁹ In any events, the rate acceleration by **3** (cf. **1a**) may result from a number of not fully under-

stood deuterium isotope effects,¹⁰ which facilitate the overall catalysis.



In summary, we have disclosed a catalytic potential hidden behind a series of aqua aminoorganoborons in the formation and reaction of nitronate species, where a single-coordinated water molecule plays a critical role. Catalyst **1a** is shelf-stable enough to obviate the need for a strict removal of water and air from reaction media. Thus the *aqua*-catalytic species persists throughout the overall process, giving a TON of as high as 800.¹¹

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Dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday.

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- The selected crystal data of **1c** and **2**, as well as ¹H NMR (600 MHz, CDCl₃) data of **1a**, **1b**, and **1c**, where a set of broad peaks appear, were summarized in the Supporting Information.
- We assume that retro-aldol reaction is negligible during the initial stages of reaction. The kinetic data were derived from calorimetric measurements (Omnicol Super CRC and Omnicol Insight). Details will appear in a full account (see also the Supporting Information).
- Deprotonation of CH(D)₃NO₂ was similarly found to be the rate-determining step for systems catalyzed by methane monooxygenase (KIE, $k_{\text{H}}/k_{\text{D}} = 8.1$), see: E. A. Ambundo, R. A. Friesner, S. J. Lippard, *J. Am. Chem. Soc.* **2002**, *124*, 8770.
- Complex **C** (1:1 mixture of **1a** and **4a**) was observed using ¹H NMR measured at −90 °C while complex **A** (**1a**–MeNO₂) and **B** (nitronate) were not detected. Accordingly, release of **4a** from **C** may be rate-determining with **C** as resting state. Related experiments will appear in a full account.
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- Supporting Information is also available electronically on the CSJ-Journal Web site, <http://www.csj.jp/journals/chem-lett/index.html>.