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 D_2O-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 compounds[3] 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 procedure[3] 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 ^{1}H 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 CH_3NO_2 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 Et_3N was used instead of **1a** (Entry 5), the reaction proceeded although at a significantly slower rate. The BPh_3/Et_3N (1:3) catalyst neither improved the yield of **4a** under anhydrous conditions nor in the presence of water (Entries 6 and 7). Et_3N (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 (R^1CHO:CH_3NO_2 = 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).

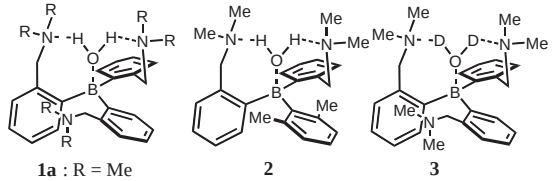


Figure 1. Aqua aminoorganoboron compounds.

Table 1. Catalyst screening in the reaction of CH_3NO_2 with PhCHO[a]

Entry	Catalyst	Additive (mol %)	Yield[b] /%
1	**1a**	—	90 (93)[c]
2	**1b**	—	80
3	**1c**	—	0
4	**2**	—	0
5	**2**	Et_3N (1)	29
6	BPh_3	Et_3N (3)	29
7	BPh_3	Et_3N (3), H_2O (10)	26
8	—	Et_3N (1)	11
9	—	Me_2NBn (3)	<5

[a]Unless 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. [b]Of isolated, purified product. [c]With 70 mg/mL of MS4A, which was dried at 150 °C under vacuum (1 mmHg) for 12 h.

The presence of a water molecule in the catalyst is pivotal for catalytic activity. Kinetic studies with the D_2O-derivative **3** (deuterium content: 75–80%) using CD_3NO_2 and hexanal in THF at 27 °C showed that the initial reaction rate (k_{obs}) is roughly 35 times faster than that with Et_3N alone (no water).[6] The reaction proceeded with pseudo-first-order dependence on [hexanal]. Examination of reaction kinetic isotope effects

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

RCH_2NO_2 + PhCHO —(**1a** (1 mol%), no solvent)→ $PhCH^a(OH)CH^b(R)NO_2$

4a : R = H
4b : R = CH_3
4c : R = Br
4d : R = $(CH_2)_3CO_2CH_3$

Entry	RCH_2NO_2 (equiv)	Conditions °C, h	Product	Yield[b] /%
1	CH_3NO_2 (3)	25, 1	**4a**	95
2	CH_3NO_2 (3)	25, 24	**4a**	80[c]
3	$CH_3CH_2NO_2$ (3)	25, 1	**4b**	84[d]
4	$BrCH_2NO_2$ (2)	25, 1	**4c**	71[e]
5	$CH_3O_2C(CH_2)_4NO_2$ (3)	25, 2	**4d**	77[f]

[a]Unless otherwise specified, reaction was performed using 1 mol % of **1a** with respect to the amount of PhCHO under indicated conditions. [b]Of isolated, purified product. [c]0.1 mol % of **1a** was used. [d]syn:anti = 67:33, determined as previously described.[4c] [e]syn:anti = 69:31, determined by the coupling constant ($J_{H^a-H^b}$) of *syn* (8.5 Hz)-**4c** and *anti* (5.0 Hz)-**4c**. [f]*syn* ($J_{H^a-H^b}$ = 8.9 Hz)-**4d**:*anti* ($J_{H^a-H^b}$ = 4.9 Hz)-**4d** = 60:40.

Table 3. Nitro aldol reaction by use of CH_3NO_2 and various aldehydes[a]

CH_3NO_2 (1.5 equiv) + R^1CHO (1.0 equiv) —(**1a** (1 mol%), solvent)→ $R^1CH(OH)CH_2NO_2$

5a : R^1 = $(CH_2)_4CH_3$
5b : R^1 = *c*-Hex
5c : R^1 = *t*-Bu
5d : R^1 = CH_2OH

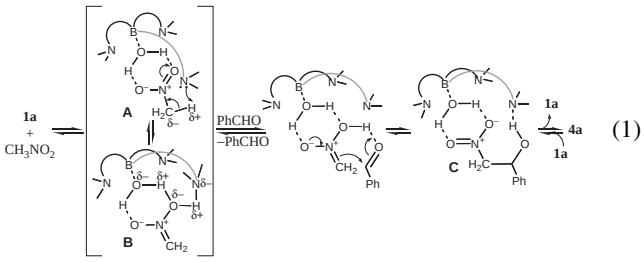
Entry	R^1CHO	Conditions °C, h	Solvent	Product	Yield[b] /%
1	$CH_3(CH_2)_4CHO$	50, 24	—	**5a**	97
2	$CH_3(CH_2)_4CHO$	50, 8	MeOH	**5a**	91(94)[c]
3	$CH_3(CH_2)_4CHO$	50, 8	MeOH	**5a**	91
3	*c*-HexCHO	50, 30	MeOH	**5b**	98[d]
4	*t*-BuCHO	50, 48	MeOH	**5c**	77[d]
5	$HOCH_2CHO$[e]	25, 24	MeOH	**5d**	99

[a]Unless otherwise specified, reaction was performed using 1 mol % of **1a** with respect to the amount of R^1CHO and CH_3NO_2 (1.5 equiv) under indicated conditions. [b]Of isolated, purified product. [c]*i*-PrOH was used as solvent instead of MeOH. [d]CH_3NO_2 (3.0 equiv) was used. [e]The dimer was used.

(KIE) verified that the initial rate for **3** in CD_3NO_2 was ca. 1.5 times greater than that with **1a** in CH_3NO_2 ($k_H/k_D = 0.68$, t = 6–15 min; conversion ≈5%).[6]

This suggests that the α-C–H bond cleavage is not the rate-determining step. In contrast, when each CH_3NO_2 and CD_3NO_2 was reacted in a separate experiment with hexanal in the presence of 10 mol % of Et_3N, the initial stage of the reaction (t = 10–40 min; conversion ≈5%) conforms to $k_H/k_D = 1.19$,[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 H_2O and D_2O 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 H_2O molecule of the catalyst. Here the formation of (O)H···O(N) hydrogen bonds increases the acidity of the α-hydrogen ($\delta+$, structure **A**). The D_2O-analogue stabilize more favorably the nitronate anion since D_2O and D^+ are well accepted to make stronger hydrogen bonds than H_2O and H^+, respectively.[9] In any events, the rate acceleration by **3** (cf. **1a**) may result from a number of not fully understood deuterium isotope effects,[10] which facilitate the overall catalysis.



(1)

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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5 The selected crystal data of **1c** and **2**, as well as ^{1}H NMR (600 MHz, $CDCl_3$) data of **1a**, **1b**, and **1c**, where a set of broad peaks appear, were summarized in the Supporting Information.
6 We assume that retro-aldol reaction is negligible during the initial stages of reaction. The kinetic data were derived from calorimetric measurements (Omnical Super CRC and Omnical Insight). Details will appear in a full account (see also the Supporting Information).
7 Deprotonation of $CH(D)_3NO_2$ was similarly found to be the rate-determining step for systems catalyzed by methane monooxygenase (KIE, k_H/k_D = 8.1), see: E. A. Ambundo, R. A. Friesner, S. J. Lippard, *J. Am. Chem. Soc.* **2002**, *124*, 8770.
8 Complex **C** (1:1 mixture of **1a** and **4a**) was observed using ^{1}H NMR measured at −90 °C while complex **A** (**1a**–$MeNO_2$) 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.
9 For example, the boiling and melting point of D_2O: 101.42 and 3.82 °C, respectively: a) *CRC Handbook of Chemistry and Physics*, 80th ed., ed. by D. R. Lide, CRC Press, Boca Raton, **1999**. b) S. Scheiner, M. Cuma, *J. Am. Chem. Soc.* **1996**, *118*, 1511. c) S. Scheiner, *Biochim. Biophys. Acta* **2000**, *1458*, 28.
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11 Supporting Information is also available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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