Aqueous Catalysis

DOI: 10.1002/ange.200704293

# A Catalytic Aldol Reaction and Condensation through In Situ Boron "Ate" Complex Enolate Generation in Water**

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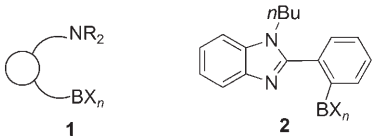
The development of new catalytic processes for C–C bond formation that can either be carried out in water or are water tolerant is an important goal in the pursuit of environmentally benign chemical synthesis.[1] Of the water-tolerant catalytic C–C bond-forming reactions known, there are several examples of catalytic aldol reactions;[2] however, very few of these are mediated by boron enolates.[3] Indeed, the in situ generation of boron enolates in water is rare.[4] Therefore, we were interested in determining whether boron enolates could be generated in situ under aqueous conditions and confirmed, for example, by trapping with an aldol reaction.

Our goal was to develop a water-based catalytic system that was capable of generating a boron enolate intermediate in water. A possibility for generating the intermediate would be through the cooperative intramolecular interaction between a basic and a boronate function. The hypothesis is that deprotonation of a ketone, for example, proximal to a boronate group, would result in immediate trapping of the boron enolate by esterification. The potential for success of such a process is supported by reports from the 1960s in which cooperation between intramolecular amino and boronic acid functions was used to achieve catalytic effects. For example, Letsinger et al. demonstrated rate enhancement in chlorohydrin hydrolysis.[5] The proposed mechanism involved an equilibrium-mediated boronic acid esterification process, followed by intramolecular amine-assisted hydrolysis.[6] Hence, we proposed that aminoboronates[7] and their complexes[7d] might have potential as bifunctional catalysts for a range of reactions, such as in situ generation of boron enolates and subsequent trapping of the enolate species with an aldehyde, thus resulting in aldol products. Herein, we report preliminary results to show that it is indeed possible to demonstrate the cooperative effect of intramolecular amine and boronate functions to generate boron enolate species in water.

A series of bifunctional aminoboronate systems of general type **1**[7] were examined for their in situ effectiveness at



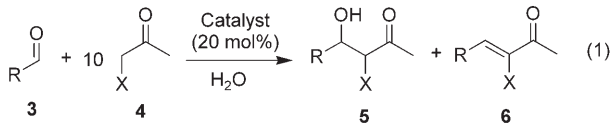

**1**

**a**: $BX_n$=$B(OH)_2$
**b**: $BX_n$=$B(OH)_3^-$

**2**

**a**: $BX_n$=$B(OH)_2$
**b**: $BX_n$=$B(OH)_3Na$

enolization of hydroxyacetone and acetone through formation of the corresponding boron enolate. Ketone enolization was initially demonstrated by reaction with benzaldehyde to give the corresponding condensation product(s). Of the several potential analogues for model aminoboronate catalyst **1** examined, benzimidazolylphenylboronic acid **2a**[6a] was inactive. However, its "ate" complex **2b**[7d] showed high catalytic activity in water at 20 mol% for Equation (1); solely




(1)

**3**

**a**: R=Ph
**b**: R=4-$NO_2$Ph
**c**: R=4-MeOPh
**d**: R=(*E*)-CH=CHPh
**e**: R=Et
**f**: R=*t*Bu

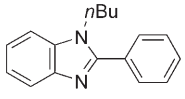
**4**

**a**; X=OH
**b**; X=H

**5**

**a**: R=Ph, X=OH
**b**: R=4-$NO_2$Ph, X=OH
**c**: R=4-MeOPh, X=OH
**d**: R=(*E*)-CH=CHPh, X=OH
**e**: R=Et, X=OH
**f**: R=*t*Bu, X=OH
**g**: R=Ph, X=H
**b**: R=4-$NO_2$Ph, X=H
**h**: R=4-MeOPh, X=H
**i**: R=(*E*)-CH=CHPh, X=H
**j**: R=Et, X=H
**k**: R=*t*Bu, X=H

**6**




**7**

aldol adducts **5** were produced with hydroxyacetone (**4a**) in high conversion and moderate to high *syn* selectivity (Table 1, entries 1–6). In contrast, reactions of aldehydes **3a–d** with acetone (**4a**; Table 1, entries 7–10) mainly gave condensation products **6** (aldehydes **3e** and **3f** resulted in a complex mixtures of products). This observed activity of complex **2b**

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[**] We thank the EPSRC for research grants (GR/R24722/01, GR/S85368/01, and GR/T22759/01) and GlaxoSmithKline Pharmaceuticals for a CASE award (to A.R.B.). We also thank Dr. M. Crampton (Durham University) for helpful discussions and the EPSRC MS service, Swansea.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

***Table 1:*** Product ratios and yields for the aldol reactions outlined in Equation (1).

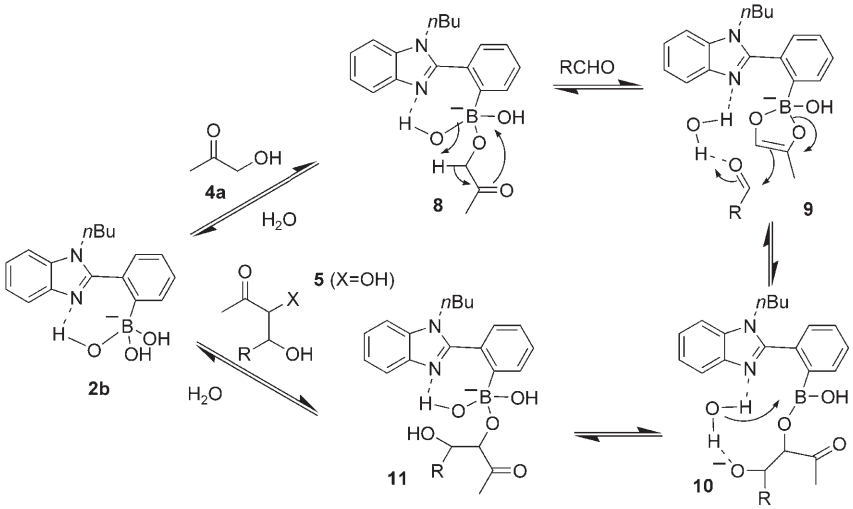
| Entry | Aldehyde | Ketone | Catalyst | *t* [h] | Conv. [%][a] | Yield of **5** [%][b] (*syn*:*anti*)[a] | Yield of **6** [%][b] |
|---|---|---|---|---|---|---|---|
| 1 | **3a** | **4a** | **2b** | 7 | >99 | 97(2.75:1) | 0 |
| 2 | **3b** | **4a** | **2b** | 7 | >99 | 76(5.5:1) | 0 |
| 3 | **3c** | **4a** | **2b** | 9 | ca. 70 | 46(2.2:1) | 0 |
| 4 | **3d** | **4a** | **2b** | 7 | >99 | 64(1.3:1) | 0 |
| 5 | **3e** | **4a** | **2b** | 7 | >99 | 68(2:1) | 0 |
| 6 | **3f** | **4a** | **2b** | 7 | >99 | 62(1:0) | 0 |
| 7 | **3a** | **4b** | **2b** | 7 | >99 | 19 | 77 |
| 8 | **3b** | **4b** | **2b** | 7 | >99 | 0 | 64 |
| 9 | **3c** | **4b** | **2b** | 9 | >93 | 10 | 81 |
| 10 | **3d** | **4b** | **2b** | 7 | >85 | 10 | 75 |
| 11 | **3a** | **4a** | A[c] | 7 | >99 | 49(2.3:1) | 0 |
| 13 | **3a** | **4a** | B[d] | 7 | <2 | – | – |
| 14 | **3a** | **4a** | C[e] | 7 | <2 | – | – |
| 15 | **3a** | **4a** | D[f] | 7 | <2 | – | – |
| 16 | **3a** | **4b** | A[c] | 7 | >99 | 0 | 99 |

[a] Based on crude $^1$H NMR data. [b] Yield of isolated products after purification by column chromatography using silica gel. [c] Conditions A: 20 mol% aq 16 M NaOH. [d] Conditions B: 20 mol% $PhB(OH)_2$. [e] Conditions C: 20 mol% aq 16 M NaOH and aq $PhB(OH)_2$. [f] Conditions D: 20 mol% aq 16 M NaOH, aq $PhB(OH)_2$, and **7**.

raises the question of the origin of its reactivity, and whether it acts as a source of hydroxide ions. Significantly, **2b** can be isolated as an analytically pure ate complex (see the Supporting Information) showing a single $^{11}$B NMR chemical shift at $\delta = 0.3$ ppm. Alternatively, **2b** can be generated in situ in water from the corresponding boroxine ($\delta = 19.7$ ppm)[7e] by the addition of three equivalents of sodium hydroxide, which gives an identical $^{11}$B NMR spectrum with no signal corresponding to uncomplexed boronic acid ($\delta =$ 32.8 ppm).[7e] The in situ generation of **2b** can be directly used to produce identical catalytic effects. Therefore, several reactions were carried out (Table 1, entries 11–16) to address the origin of the catalytic effect of complex **2b**.

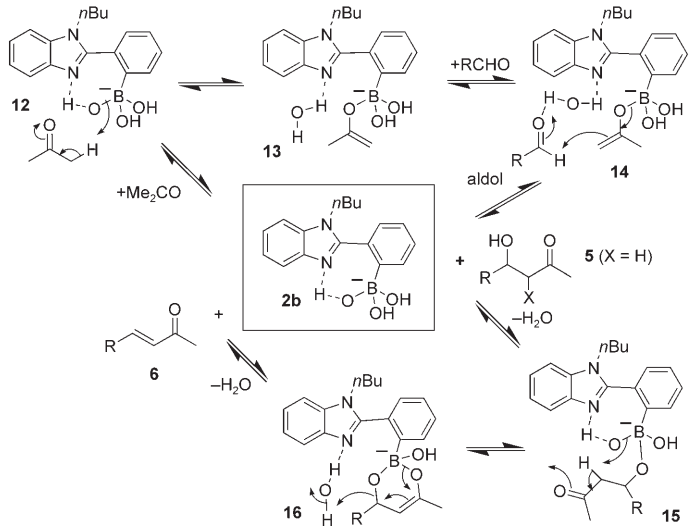
The discrete catalytic effect of **2b** in the aldol reactions was supported by the following observations 1) using 20% NaOH alone (Table 1, entries 11 and 16) produced similar results to using complex **2b**; 2) both phenylboronic acid (entry 13) and its hydroxide ate complex (entry 14) were ineffective catalysts; 3) a mixture of phenylboronic acid hydroxide ate complex and phenyl benzimidazole **7** was also ineffective (entry 15). Indeed, exactly the same results were obtained when using acetone and benzaldehyde (entries 13–15). Hence, the reactivity of catalyst **2b** results from the intramolecular interaction between the benzimidazole and boronate function, which activates the ate complex. To confirm if this activity resulted from hydroxide release, kinetic studies were carried out which showed that the catalytically active species in the aldol reactions was indeed the boronate complex **2b**, that is, that the complex does not simply act as a source of hydroxide ions. The reactions of benzaldehyde with either acetone or hydroxyacetone could be followed by HPLC over time in the presence of either hydroxide ions or catalyst **2b**. Subsequent data analysis[8] showed different kinetic effects between the two catalysts. The observed rate constants for the formation of aldol **5** from the reaction of benzaldehyde with hydroxyacetone catalyzed by hydroxide ions and by complex **2b** were $(4.41 \pm 1.18) \times 10^{-4}\ s^{-1}$ and $(1.54 \pm 0.27) \times 10^{-4}\ s^{-1}$, respectively, whereas those for the reaction of benzaldehyde with acetone were $(2.81 \pm 0.16) \times 10^{-4}\ s^{-1}$ and $(5.54 \pm 0.53) \times 10^{-5}\ s^{-1}$, respectively (all first order kinetics; see the Supporting Information). These preliminary results show that catalyst **2b** not only behaves as a true catalyst, but acts through the cooperative effect of both the boronate-hydroxide complex and benzimidazole group, thus producing an effect that is perhaps closest to the type II aldolases,[9] but differing from proline and its relatives[10] because enamine formation is not possible. In this case, boron enolate **9** is a likely intermediate[11] in the aldol addition of hydroxyacetone (**4a**), which is facilitated by transesterification via complex **8** (Scheme 1). The intramolecular imidazole moiety activates the boronate complex triggering deprotonation and formation of enolate **9**. The resulting aldol addition step, that is conversion of **9** into **10**, is *syn*-selective because of hydrogen bond stabilization of the acyclic-like transition state[12] in which the R group of the aldehyde orientates away from the bulk of the aryl boronate complex.

For the acetone-based aldol, direct deprotonation via **12** is proposed (Scheme 2) to give enolate **13** which then follows a similar mechanism to that of hydroxyacetone to give aldol **5** (X = H). Chalcone formation is proposed to occur via transesterification of catalyst **2b**, deprotonation (**15**), and elimination via intermediate **16**. Hence, the use of boronate complex **2b** potentially obviates the need for preactivation of an enolate precursor[3,4] to generate a boron enolate. The intramolecular benzimidazole activation in complex **2b** is




***Scheme 1.*** Proposed mechanism of action for catalyst **2b** in the aldol addition of hydroxyacetone to an aldehyde.

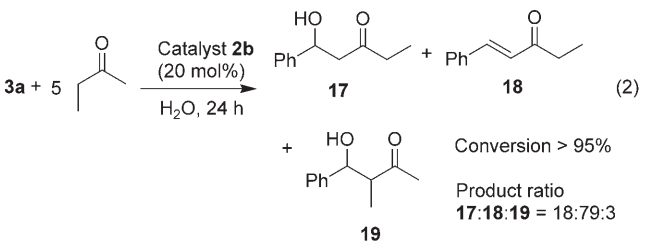
  




***Scheme 2.*** Proposed mechanism of action for catalyst **2b** in the aldol addition of acetone to an aldehyde.

crucial for activity because the phenylboronic acid hydroxide complex alone is inactive as a catalyst, with or without an added external benzimidazole.

Finally, the use of methyl ethyl ketone (MEK) in place of acetone [Table 1; entry 7; Eq. (2)] resulted in a 4:1 ratio of




chalcone **18**/aldol **17**, with only a small amount (3%) of product **19** being evident at >95% conversion. Hence, this corresponds to 97% regiocontrol for deprotonation of MEK, showing the preference for kinetic deprotonation similar to during transformation of **12** to **13** (Scheme 2).

Further studies on the design and application of catalysts based on boron ate complexes are underway and will be reported in due course.

Received: September 17, 2007
Revised: October 10, 2007
Published online: December 4, 2007

**Keywords:** aldol reaction · bifunctional catalysts · boron · homogeneous catalysis · selectivity

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