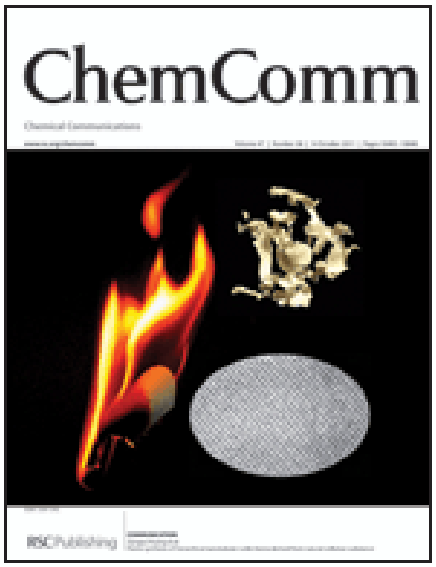

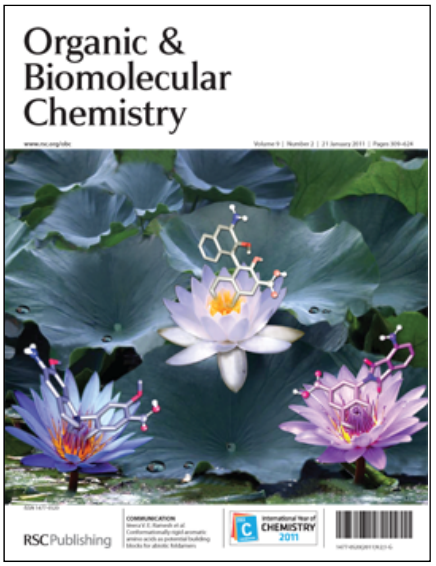

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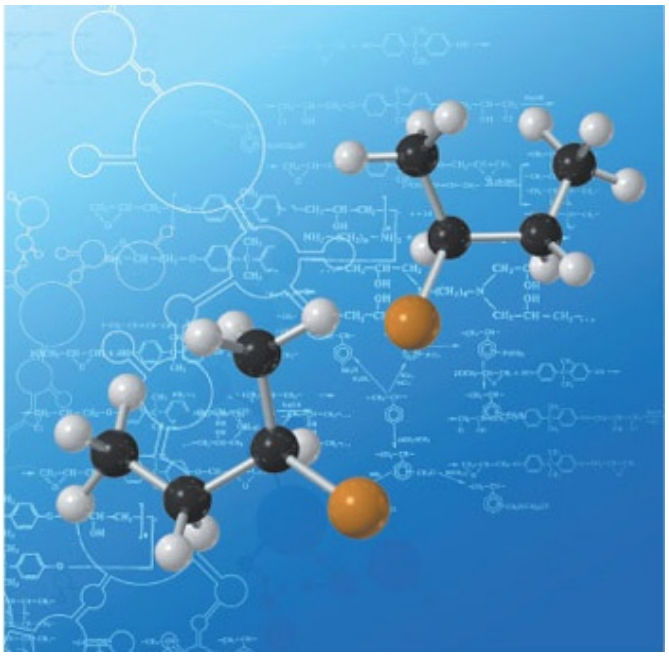

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PAPER

Mechanism and optimisation of the homoboroproline bifunctional catalytic asymmetric aldol reaction: Lewis acid tuning through *in situ* esterification†‡

Irene Georgiou and Andrew Whiting*

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The use of homoboroproline as a bifunctional catalyst in the asymmetric aldol reaction has been investigated mechanistically, particularly with respect to tuning the Lewis acidity of boron by *in situ* esterification with mildly sigma-electron withdrawing diols such as hydrobenzoin and tartrate esters. The stability of simple cyclohexyl and cyclopentyl boronate diol esters shows that the 5-ring boronate esters are more stable, which sheds light on the mode of action of esterified homoboroproline catalyst in the enamine-mediated aldol reaction, which is also studied by NMR. The result is reaction optimisation to provide an efficient aldol reaction and a proposed mechanistic proposal.

Introduction

The rapidly growing interest in the area of asymmetric organocatalysis is not only due to the versatile character of small organic molecules to function as efficient and selective catalysts but is also attributed to their important role in the construction of complex and enantiopure molecular skeletons. Since the report by Barbas and List[1] of the first proline-catalysed asymmetric intermolecular aldol reaction, the synthesis and application of organocatalysts based on enamine-iminium ion activation has received considerable attention.[2] Most organocatalysts used currently are functionally synergic systems which have two distinct functionalities within the same molecule.[3] Complementary to the great variety of bifunctional catalysts available, a privileged yet still under developed class of Lewis acidic organocatalysts are aminoboronic acids.[4]

Even though their use was pioneered by Letsinger,[5] the wider application of aminoboronic acids as catalysts has not extended until recent years.[4] In an attempt to illustrate and assess the potential of such molecules in synthesis, a variety of aminoboronic acids have been synthesised by our group and their catalytic activity has been mainly examined in the areas of direct amide formation and aldol reactions.[6,7] Recently, and inspired by the high catalytic activity and enantioselectivity observed in proline-catalysed reactions, the synthesis of proline-based aminoboronic acids such as homoboroproline **1** was developed and published by our group.[7] The cooperative action of the nucleophilic secondary amine functionality and the Lewis acidic boronic acid catalysed the formation of aldol products with asymmetric induction similar to L-proline, and usefully, with the opposite absolute stereochemistry.[1a] The goal of this paper is to report the full details of this work and to enlarge upon the aldol catalysis possible using aminoboronic acid **1**.

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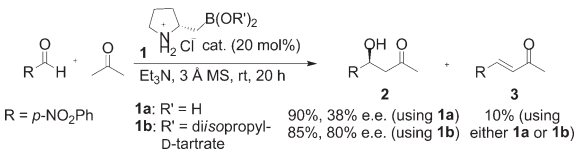
Results and discussion

Initial catalytic experiments focused on the benchmark aldol reaction between *p*-nitrobenzaldehyde and acetone, producing mainly β-hydroxycarbonyl aldol adduct **2** (eqn (1)). Catalyst **1** was difficult to prepare as a neutral compound, and was therefore produced *in situ* by neutralisation of its HCl salt using Et_3N. The neutral homoboroproline accomplished the formation of the aldol adduct **2** as the major enantiomer in 38% enantiomeric excess (e.e.). Surprisingly, although neutralised **1a** turned out to be a moderate catalyst, the *in situ* esterification of the boronic acid function with moderately electron deficient diols, improved the e.e. of the aldol product. Hence, the *in situ* formation of ester **1b** after neutralization increased the boronate Lewis acidity, presumably tightening the transition state, and therefore, enhanced the e.e. to 80%.[7]

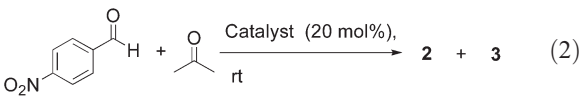


(1)

Importance of bifunctionality

In order to prove the necessity of the cooperative bifunctional reactivity of the pyrrolidine ring nitrogen and the boronate function of catalyst **1**, further studies on the 'benchmark' aldol

reaction were carried out (eqn (2)). Firstly, it was necessary to determine that for the cooperative catalysis to take place, the two reactive groups needed to be intramolecular. Hence, using both diisopropyl D-tartrate **4** and (*R*,*R*)-hydrobenzoin **5** esters of benzeneboronic acid were prepared by reacting phenylboronic acid with the respective diols in toluene using Dean–Stark conditions (Scheme 1).

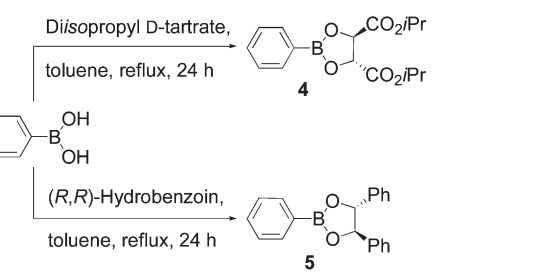


(2)

Pyrrolidine was catalytically active by itself (entry 1, Table 1), as expected,[7,8] however, benzeneboronic acid was unreactive (entry 2, Table 1) and therefore, both benzeneboronate esters **4** and **5** were similarly unreactive by themselves and unable to provide any aldol product (entries 3 and 4, Table 1). Importantly, the pyrrolidine reactivity was substantially reduced by the addition of a boronate ester, such as **4** (entry 5, Table 1) and no asymmetric induction was observed. This clearly demonstrates the importance of the intramolecular bifunctional cooperative effects needed between the secondary amine and the boronate function of the catalytic species derived from catalyst **1**.

Lewis-acid tuning and ^{11}B NMR analysis

Before optimising the reaction conditions for the aldol reaction, the esterification of cyclohexyl- and cyclopentyl-boronic acids with different diols was examined in order to determine how easily the different esters formed, assess their relative stabilities and determine if they could be isolated.[9] The reactions were carried out in refluxing toluene using azeotropic water removal (as with esters **4** and **5**), however, in all cases, the desired boronate esters were easily hydrolysed during the purification process. Hence, in order to prove their formation, a new approach in which the purification of the final product could be avoided was necessary. As a result the boronate esters were formed *in situ* by reacting the relevant boronic acid and diol. The boronic acids **6** were each reacted with either diisopropyl D-tartrate **7a**, (*R*,*R*)-hydrobenzoin **7b** or catechol **7c** under dehydrating conditions in refluxing $CDCl_3$, as outlined in eqn (3). After filtration, ^{11}B NMR analysis was carried out directly for each boronate ester formed[10] and the results are shown in Figs. 1 and 2.

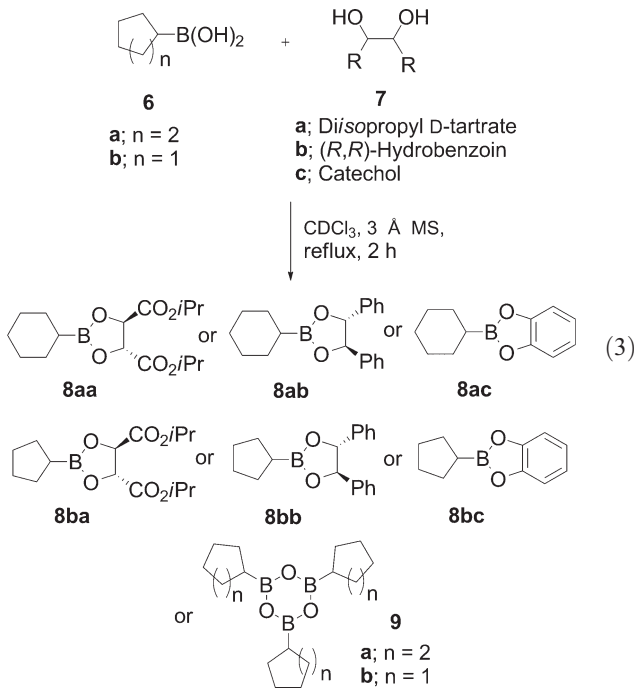


Scheme 1 Phenylboronic acid esterification to give esters **4** and **5**.

Table 1 Catalysed aldol reaction of *p*-nitrobenzaldehyde and acetone

Entry	Catalyst	Conversion[a] [%]	Yield of **2**[b] [%]	Yield of **3**[b] [%]
1	Pyrrolidine	>99	>99	<1
2	$PhB(OH)_2$	n.r.	–	–
3	**4**	n.r.	–	–
4	**5**	n.r.	–	–
5	Pyrrolidine + **4**	38	36	>2

[a] Reaction time was 24 h. [b] Isolated yield after SiO_2 column chromatography.



(3)

Starting with cyclohexylboronic acid **6a**, the attempts to generate the corresponding esters **8aa**, **8ab** and **8ac** resulted in the ^{11}B NMR spectra shown in Fig. 1. Interestingly, attempts to form both the tartrate **8aa** and hydrobenzoin **8ab** esters of cyclohexylboronic acid **6a** resulted in two ^{11}B NMR peaks (δ 36 and 23, and 35 and 23 respectively) in each case, in contrast with the catechol boronate ester **8ac**, where only a single peak at δ 23 was observed. This chemical shift is diagnostic of boroxine formation (presumably with water or some other nucleophile still present to create partial tetrahedral geometry[10,11]) perhaps due to hydrolytic susceptibility of the catechol ester,[12] *i.e.* forming **9a**. Hence, reaction of the cyclohexylboronic acid **6a** with catechol does not result in esterification, rather it assists boronic acid dehydration alone. This observation contrasts with the esterification of **6a** with both diisopropyl D-tartrate **7a** and (*R*,*R*)-hydrobenzoin **7b**, since in these cases (Fig. 1, spectra b and c) esterification does occur (to give **8aa** and **8ab** respectively), however, the larger peaks also correspond unexpectedly to boroxine **9a** formation. Hence, even these boronate esters are also unstable, though not to the same extent as the catechol ester.

Examining the esterification of cyclopentylboronic acid **6b** with diisopropyl D-tartrate **7a**, (*R*,*R*)-hydrobenzoin **7b** and catechol **7c** showed quite subtly different results. Although, boroxine **9b** formation still occurred in the presence of catechol (δ 23, Fig. 2, spectrum d), boroxine formation was minimal using the other two diols. Hence, the major peak at δ 34 peak in spectrum b (Fig. 2) showed that the cyclopentylboronate tartrate ester **8ba** was considerably more stable than its cyclohexyl counterpart

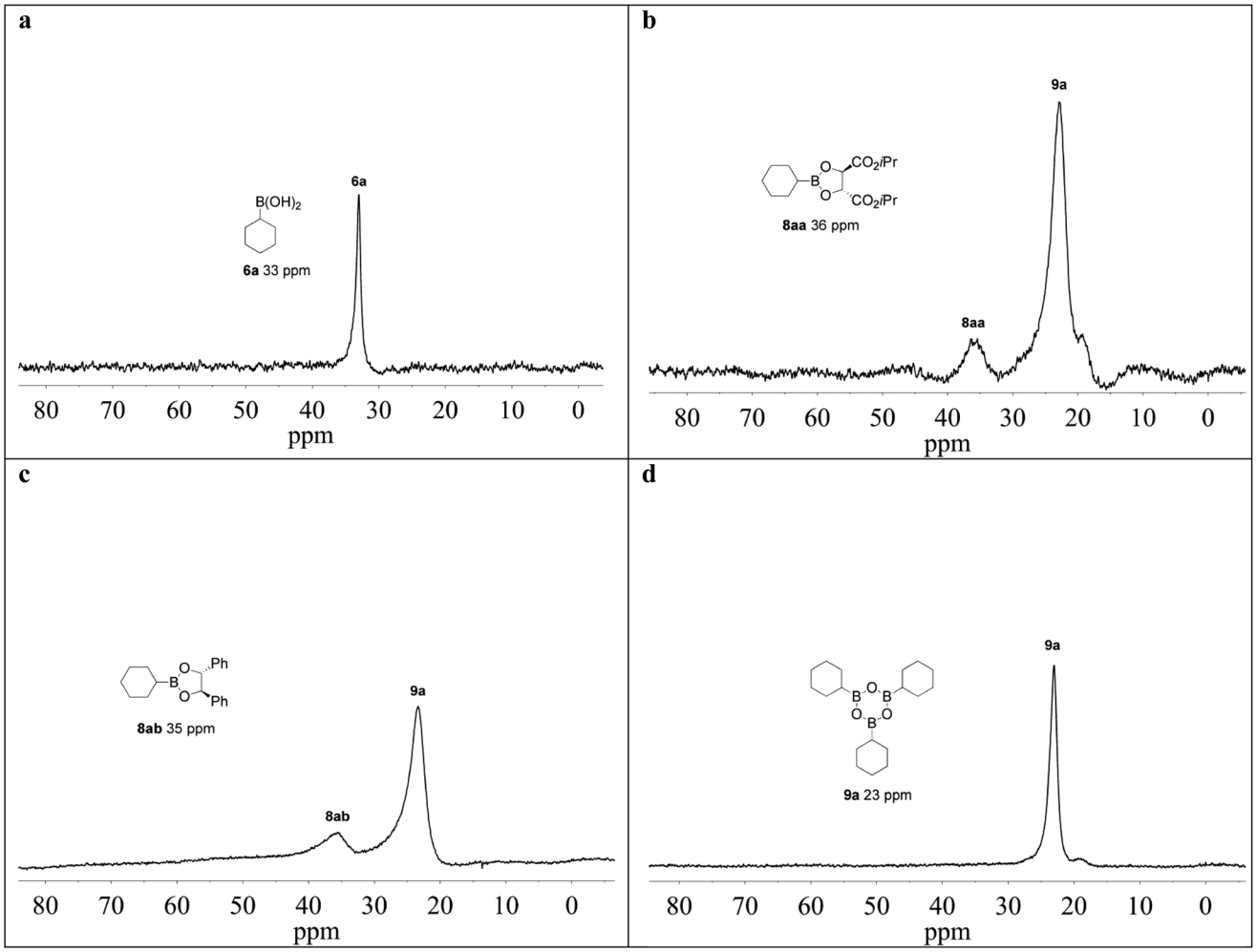
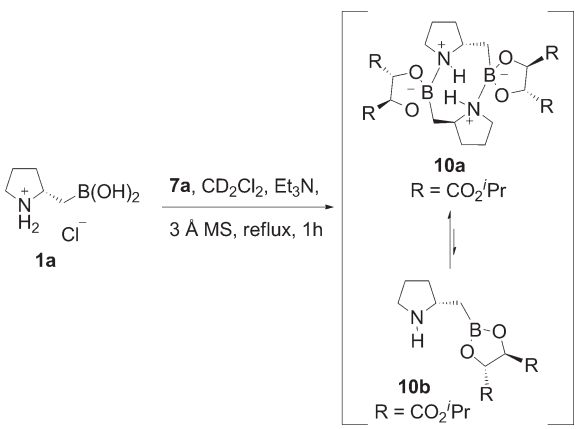


Fig. 1 ^{11}B NMR spectra of cyclohexylboronic acid **6a** (a) esterified with diisopropyl-D-tartrate (b), (*R*,*R*)-hydrobenzoin (c) and catechol (d).

8aa. Interestingly, the corresponding hydrobenzoin ester **8bb** appeared to be even more stable (see Fig. 2, spectrum c), with a major δ 36 ^{11}B NMR peak and only a small boroxine peak at δ 23. These observations suggest two important conclusions: 1) Cyclopentylboronic acid diol esters appear to be more stable than their six-ring analogues, the origin of which is not clear as yet; 2) Hydrobenzoin **7b** esters are the most stable examined here, and therefore, they might be expected to be most useful for improving the asymmetric induction in the aldol reaction if ester stability is a key factor, as we hypothesised. It is also important to note that if this ^{11}B NMR analysis is carried out over longer reaction times, the relative peak intensities and positions do not change, hence, this type of *in situ* esterification process for boronate Lewis-acidity tuning should be suitable for longer reaction times.

Having studied the esterification of simple cycloalkylboronic acids **6**, an attempt to synthesise and characterize the homoboroproline-derived catalyst **1** was undertaken *in situ*. Hence, homoboroproline HCl salt **1a** was dissolved in CD_2Cl_2 followed by the addition of diisopropyl-D-tartrate and triethylamine (eqn (4)). After 2 h at 30 °C, Et_3NHCl could be removed by filtration upon cooling and the resulting reaction mixture monitored by NMR. The ^{11}B NMR spectrum showed a single major peak at δ 10, compared with the starting material which appeared at δ 30 (Fig. 3). The former does not correspond to either a boroxine (*vide supra*) or a free boronic acid, since there was no free diol present in the ^{1}H NMR spectrum. As a result, we propose that the peak at δ 10 corresponds to the dimer **10a** (eqn (4)). Hence, although the dimer was observed in the absence of substrate, we assume that dimer **10a** exists in equilibrium with its monomer form **10b** in order to act as a catalyst in the aldol reaction, *i.e.* as in eqn (1).



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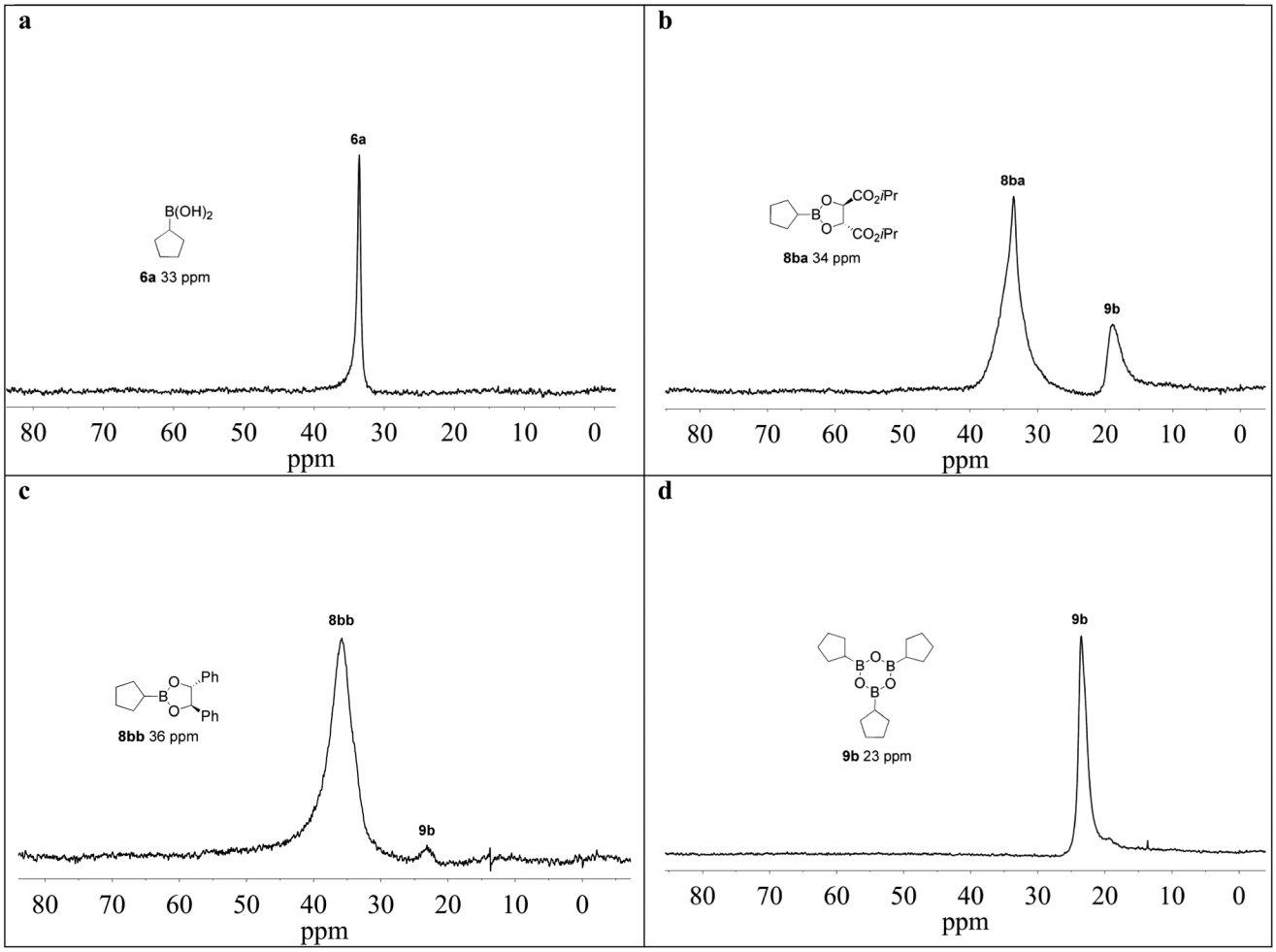
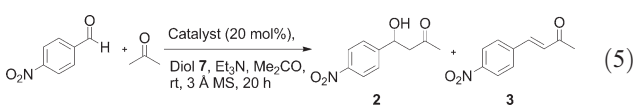


Fig. 2 ^{11}B NMR spectra of cyclopentylboronic acid **6b** (a) esterified with diisopropyl-D-tartrate (b), (*R*,*R*)-hydrobenzoin (c) and catechol (d).

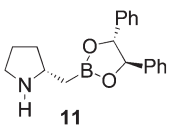
Reaction optimisation

Taking into consideration the results of the ^{11}B NMR analysis, it was necessary to further explore the catalytic activity of the different boronate ester derivatives of the catalyst **1a**. Hence, we examined the aldol reaction between *p*-nitrobenzaldehyde and acetone, however, the homoboroproline catalyst **1a** was allowed to react with the relevant diols **7** for 2 h in the presence of molecular sieves before the addition of the aldehyde substrate to ensure that the esterification reaction had reached equilibrium (eqn (5)). The subsequent aldol reactions were monitored for catalytic activity and asymmetric induction, and the results are shown in Table 2.



(5)

Table 2, entry 1 shows the comparable reaction to that previously reported in which catalyst **10b** effects high asymmetric induction in the aldol adduct **2**, together with some aldol condensation product. In the same time period, the catalyst **11** provides a higher e.e. aldol product (Table 2, entry 2), however, this is accompanied by an increase in the amount of aldol condensation product **3**. Interestingly, use of catechol which was shown to cause substantial boroxine formation (*vide supra*) and results in a slower reaction which fails to go to completion over 20 h, and gives a lower e.e. aldol **2** (Table 2, entry 3). Hence, these results show that the catalytic activity and enantioselectivity are closely related to the stability of the boronate ester formed *in situ*, and hence, the highest asymmetric induction was achieved when the hydrobenzoin boronate ester **11** was the catalytic species.



Having examined the impact of the esterification process, it was necessary to examine the effect of reaction conditions, and particularly solvent polarity upon the reaction. Hence, using *in situ* formation of catalyst **11**, the aldol reaction between acetone and *p*-nitrobenzaldehyde was examined, as outlined in Table 3 and eqn (6).

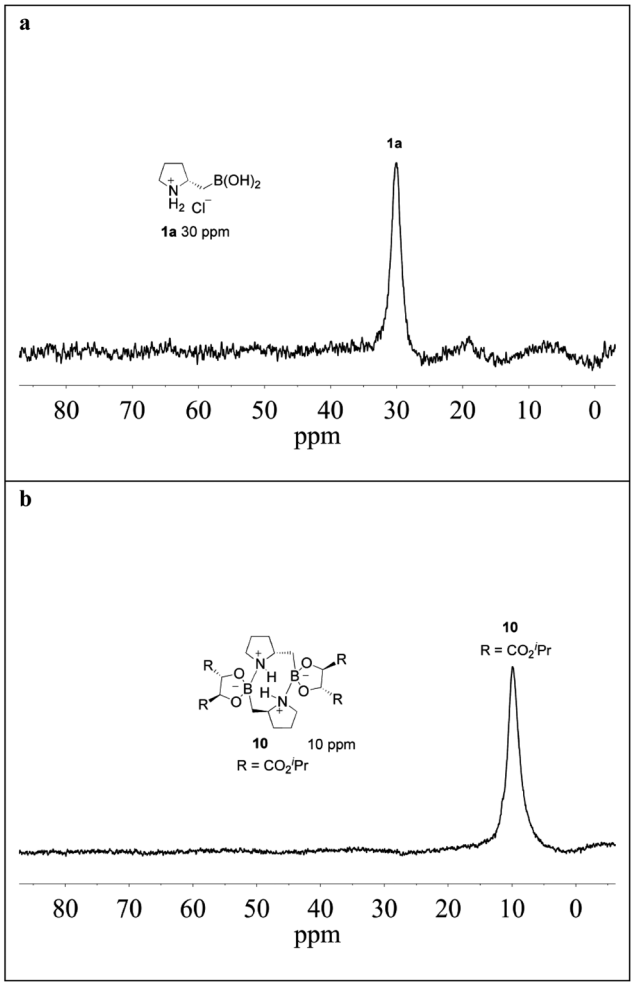
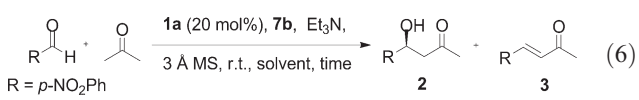


Fig. 3 ^{11}B NMR spectra: (a) pyrrolidine-based boronate ester **1a**; (b) condensation reaction of **1a** with diisopropyl-D-tartrate.

Table 2 Catalytic aldol reaction of *p*-nitrobenzaldehyde in neat acetone

Entry	Catalyst	Yield of **2**[a] [%]	e.e.[b] [%]	Yield of **3**[a] [%]
1	**1a**+ **7a**	85	80	10
2	**1a** + **7b**	63	90	20
3	**1a** + **7c**	11	70	3

[a] Isolated yield after SiO_2 column chromatography. [b] Determined by HPLC analysis.



(6)

Table 3 shows that for the four reactions carried out under identical conditions over 20 h (entries 1–4), the highest e.e.'s were obtained using either acetone (entry 1) or DMF (entry 3). However, the DMF reaction appeared to be the faster of the two reactions, as shown by the greater aldol condensation product **3** formed. Hence, the reaction was followed until complete consumption of the aldehyde (entry 5), which showed that the

Table 3 Solvent screening of the catalytic reaction between *p*-nitrobenzaldehyde and acetone

Entry	Solvent	Time [h]	Yield of **2**[a] [%]	e.e.[b] [%]	Yield of **3**[a] [%]
1	Acetone	20	87	93	10
2	THF	20	45	88	41
3	DMF	20	54	93	34
4	DMSO	20	74	81	18
5	DMF	5	88	95	4

[a] Isolated yield after SiO_2 column chromatography. [b] Determined by HPLC analysis.

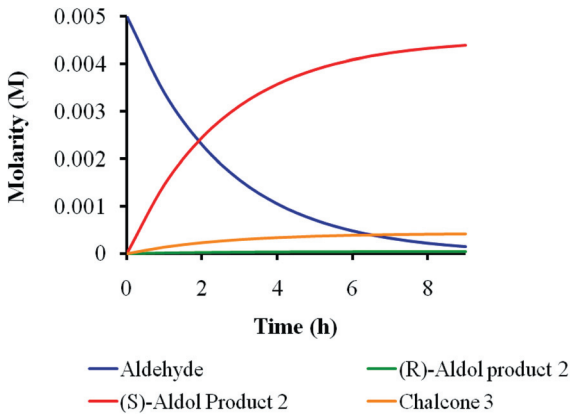


Fig. 4 Molarity of the starting material, (*S*)-aldol product **2**, (*R*)-aldol product **2** and chalcone **3** over time when the reaction was carried out in neat acetone using the di*iso*propyl D-tartrate derived catalyst, *i.e.* **10b**.

reaction was actually complete in 5 h. Under these conditions, the e.e. improved to 95%, with only 4% aldol condensation product **3** being formed. Therefore, in DMF, catalyst **11** appears to be the most active catalyst giving essentially 99% e.e. aldol product, since the homoboroproline **1a** used was only 96% e.e., and the reaction is faster in DMF.

Mechanistic studies

In order to understand the mode of action of the catalysts of type **10b** and **11**, the standard aldol reaction between acetone and *p*-nitrobenzaldehyde was monitored over time using HPLC. Before the addition of the aldehyde, diisopropyl-D-tartrate catalyst **10b** was generated *in situ* by reacting the homoboroproline catalyst **1a** with diol **7a** in the presence of molecular sieves in neat acetone. The catalytic reaction was further monitored every hour for a total period of 9 h. The results are summarised in Fig. 4.

According to Fig. 4, the aldol reaction was complete in 8 h and the by-product **3** remained at a relatively low level throughout. The enantioselectivity of the desired product **2** remained relatively constant over time, showing the absence of any non-linear effects.[13] Consequently, the best yields of aldol adduct **2** and e.e. values can be expected when the reaction is quenched soon after completion, minimising the potential for aldol **2** elimination. Similar results were observed with the (*R*,*R*)-hydrobenzoin analogue of **1a**, *i.e.* **11**, in DMF (Fig. 5). In this case,

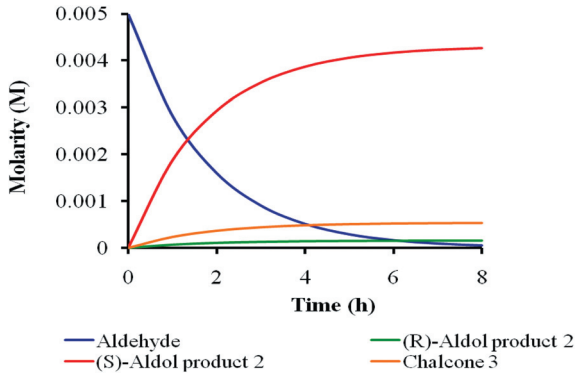


Fig. 5 Molarity of the starting material, (*S*)-aldol product **2**, (*R*)-aldol product **2** and chalcone **3** over time when the reaction was carried out in DMF using the (*R*,*R*)-hydrobenzoin derived catalyst, *i.e.* **11**.

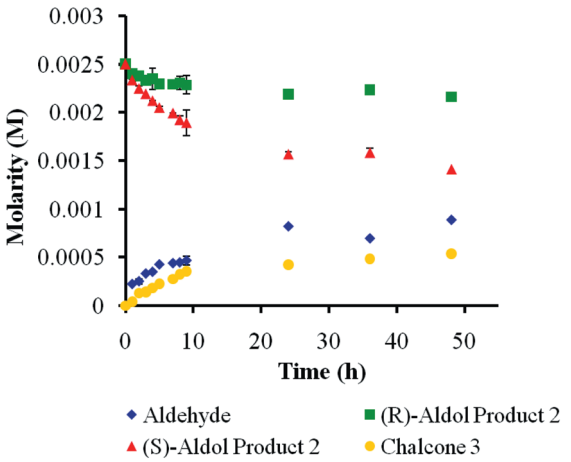


Fig. 6 Molarity of the starting material, racemic aldol **2** and chalcone **3** over time for the reaction outlined in eqn (7).

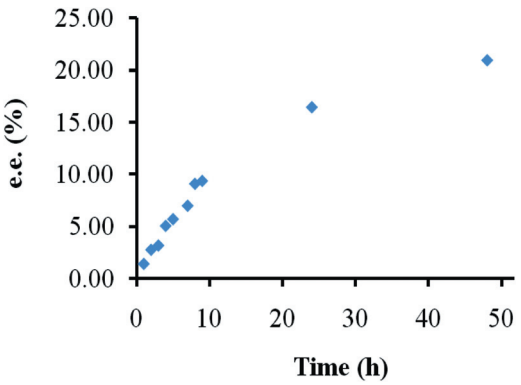
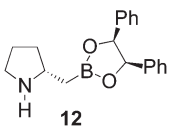


Fig. 7 Enantiomeric excess of (*R*)-aldol product **2** over time when the reaction outlined in eqn (7) was carried out in the absence of acetone.

complete conversion was achieved in a shorter reaction time, as expected, *i.e.* around 5 h, with minimal elimination occurring and again, no sign of non-linear asymmetric induction. Both these results are consistent with the idea that although both the catalysts **10b** and **11** are capable of existing as dimeric species, they react as monomeric entities providing aldol adducts **2** with consistently high asymmetric induction over time.

As well as collecting the data shown in Fig. 4 and 5, at the same time, this reaction was carried out using *meso*-hydrobenzoin as the diol, in order to confirm that the chirality of the diol has no effect on the asymmetric induction of the final aldol product, *i.e.* generating a catalyst *in situ* **12**, rather than **11**. The enantiomeric excess decreased slightly from 95% to 89%. However, we have already reported[7] that the boronate ester stereochemistry does not affect the sense or magnitude of asymmetric induction (*i.e.* no double diastereoselectivity effects[7]) and therefore, this minor decrease is more likely to be due to the *meso*-hydrobenzoin ester boronate ester being less stable.



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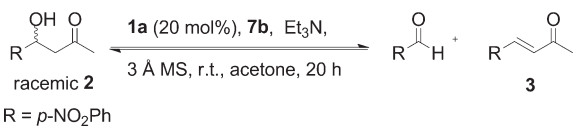
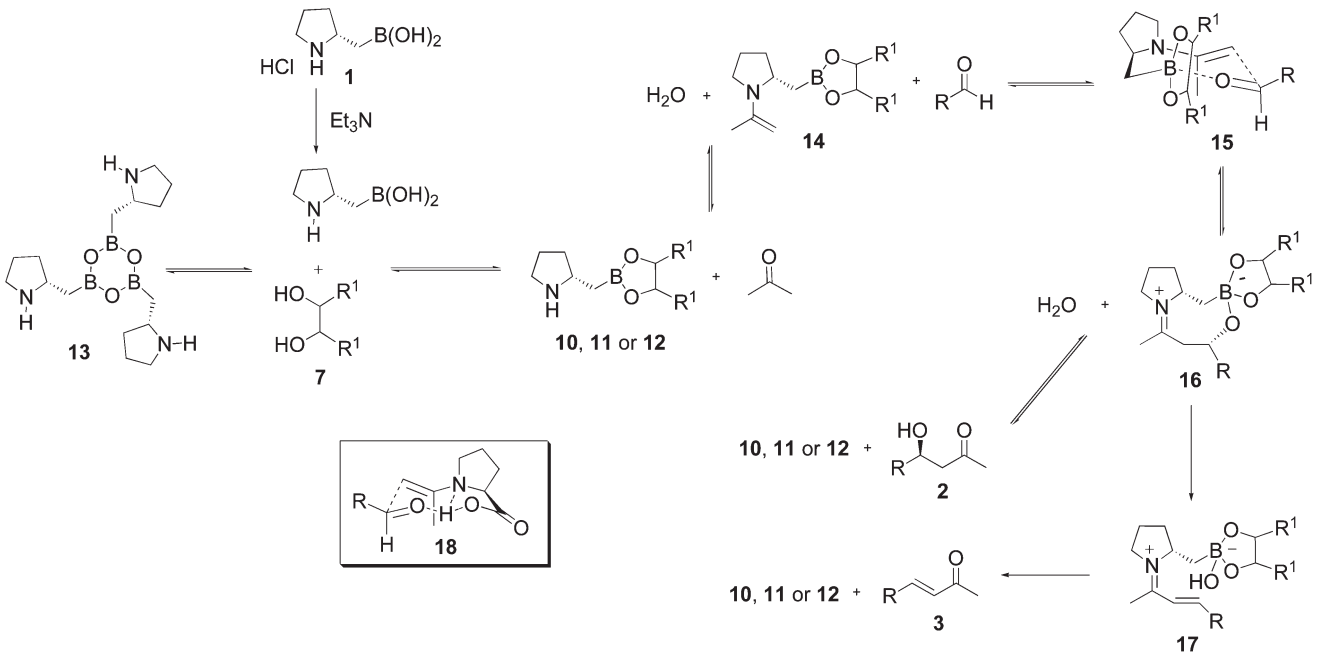
Finally, it seemed to be the case that longer reaction times could result in an increase in the amount of aldol condensation product **3** being formed (see Table 3). The likely explanation being that aldol adduct **2** could be undergoing a slow elimination reaction in the presence of the catalyst (such as **11**) once the starting materials had been consumed. Indeed, examination of Figs. 4 and 5 confirms that the amount of aldol condensation product remains relatively low over the first few hours of the reaction. Therefore, we investigated whether the racemic aldol product **2** could undergo kinetic resolution in the presence of the catalyst **11** to provide the aldol adduct **2** with high e.e. and the aldol condensation **3** as the by-product. Hence, a racemic sample of aldol adduct **2** was reacted with catalyst **11** in both the absence and presence of acetone in DMF, as in eqn (7). The results are shown in Fig. 6 and the corresponding e.e. shown in Fig. 7.



(7)

The fate of the racemic aldol in the presence of the hydrobenzoin ester of **1a** under the conditions outlined in eqn (7) is intriguing, as shown in Figs. 6 and 7. These show that the two enantiomers of the racemic aldol product **2** are consumed at different rates. In addition, the condensation product **3** appears at a roughly similar rate to the starting aldehyde, both of which seem to be levelling off after *ca.* 24 h. Concurrently, there is a greater decrease in the concentration of the (*S*)-aldol product of **2**, and hence, the concentration of the (*R*)-aldol product remains essentially constant which is matched by an increase in the enantiomeric excess of (*R*)-**2** from 0.15% to 21% because of the selective loss of the (*S*)-enantiomer over 48 h, as reinforced in Fig. 7. It is, therefore, clear that a kinetic resolution process is occurring throughout the 48 h period, though the increase in e.e. does level off. What these experiments suggest is that the catalyst derived from enantiomer **1a** (in the absence of acetone – see below) consumes the (*S*)-aldol product **2** highly selectively in two ways: 1) by elimination to the chalcone **3**; and 2) by reversal



Scheme 2 Proposed catalytic cycle for the pyrrolidine-based boronate ester aldol reaction involving homoboroproline **1** derived catalysts acting through proposed transition state **15**, compared with **18** for L-proline.

of the aldol-addition reaction giving the starting materials (as demonstrated by an increase in aldehyde concentration). It is, therefore, the (*S*)-aldol product which is preferably consumed, giving rise to an increase in the e.e. of the (*R*)-aldol product. The slight reduction in the amount of the (*R*)-aldol product can be explained by the fact that catalyst e.e. is only 96%, hence, there is a minor decrease in its concentration (see Fig. 6). Interestingly, when the same reaction (as eqn (7)) is conducted in the presence of acetone (see ESI†), the release of the starting aldehyde was not observed due to the fact that this reacts rapidly with acetone again to re-afford the aldol product **2**; a reaction which favours formation of the (*S*)-enantiomer of **2**. Hence, the asymmetric induction of the kinetic resolution process decreases to 10% after 24 h, which is less than without acetone (*ca.* 21% e.e.). Taking into consideration these results, a catalytic reaction mechanism similar to that of proline is a reasonable model, *i.e.* as in Scheme 2.

Hence, the initial *in situ* esterification with diol **7** of the boronic acid **1** after neutralisation results in the formation of boronate esters **11**–**12**, and to varying extents (with seemingly the exception of hydrobenzoin), the boroxine **13**. This is followed by the secondary amine reacting with acetone to form the corresponding enamine **14**. Lewis acid coordination of the aldehyde by the boronate ester, enables the formation of complex **15** to be formed (compare this with the transition state **18** which is thought to be the most likely species by which L-proline achieves the same type of reaction[1,17]), and hence, the enamine to add the aldehyde through a highly organised transition state, presumably resulting in an iminium ion species in which the boronate forms a tetrahedral aldolate 'ate'-complex, *i.e.* **16**. Hydrolysis of the iminium ion and protonation of the boronate 'ate'-complex of **16** affords aldol product **2** with high enantioselectivity. However, β-elimination of complex **16** could also give rise to the iminium ion analogue of the chalcone **17**, which after hydrolysis delivers the chalcone product **3**. Under normal conditions, the hydrolysis of complex **16** is seemingly faster than the elimination reaction resulting in **17**, presumably as a result of a sufficient concentration of water despite the presence of molecular sieves.

Conclusions

Catalyst **1a** is moderately effective in enamine-mediated aldol reactions,[7] however, when esterified *in situ* with different diols the boron Lewis acidity can be tuned. This is not entirely straightforward, however, because the facility of the diol to tune the boron Lewis acidity depends upon the stability of the boronate ester. Interestingly, cyclohexylboronic acid derived esters appear to be slightly less stable than the corresponding cyclopentylboronate esters, with the hydrobenzoin derivative **8bb** showing good stability compared to the other systems examined. Catechol esterification results in assisting complete formation of the boroxine as opposed to forming a more Lewis acidic boronate function. Hence, applying this knowledge to the esterification of homoboroproline **1a**, using hydrobenzoin as the esterification diol gives the highest boronate ester stability and catalyst **11** is believed to be the active species. Importantly, this ester essentially provides complete asymmetric control in the aldol reaction, *i.e.* 95% e.e. for a 96% e.e. catalyst when run under optimised reaction conditions; *i.e.* running the reactions at room temperature in DMF in the presence of molecular sieves to maintain the boronate ester. Despite the presence of the molecular sieves, water from the enamine formation is not removed because the hydrolysis of the iminium intermediate appears to be facile. A slow hydrolysis would allow time for further chalcone **3** to form, which appears to be the case if the reaction is left for

longer reaction times, once the starting materials have been consumed. Hence, *in situ* Lewis acidity tuning is an important tool for catalyst modification and optimisation and the application of this approach in further asymmetric transformations will be reported in due course.

Experimental

(4*R*,5*R*)-Diisopropyl-2-phenyl-1,3,2-dioxaborolane-4,5-dicarboxylate 4

To a solution of benzeneboronic acid (750 mg, 6.15 mmol) in toluene (100 mL), diisopropyl D-tartrate (1.08 mL, 5.13 mmol) was added. The mixture was heated under reflux for 24 h using a Dean–Stark apparatus. After cooling to room temperature, the solution was dried, filtered and the solvent was removed *in vacuo* to give a crude brown solid. The solid was then recrystallised from hexane to give the boronate ester **4**[9a] as a white solid (1.34 g, 81%). Mp 73–74 °C; ^{1}H NMR (700 MHz; $CDCl_3$) δ_H 1.32 (12H, d, J = 6.3 MHz, CH_3), 4.96 (2H, s, CHOB), 5.16 (2H, sep, J = 6.3 MHz, OCH), 7.40–7.42 (2H, m, CHAr), 7.51–7.54 (1H, m, CHAr), 7.90–7.91 (2H, dd, J_1 = 1 MHz, J_2 = 7 MHz, CHAr); ^{13}C NMR (176 MHz, $CDCl_3$) δ_C 21.8 (CH_3), 70.2 (OCH), 78.3 (CHOB), 128.0 (CAr), 132.3 (CAr), 135.4 (CAr), 135.8 (CAr), 169.1 (COO); ^{11}B (128.4 MHz, $CDCl_3$) δ 33.1; Elemental anal. cal. for $C_{16}H_{21}BO_6$: C, 60.03; H, 6.61. Found C, 59.71; H, 6.48; IR (film) 3287, 3028, 1627 (s), 1490 cm^{-1}; HRMS (ASAP) $C_{16}H_{21}BO_6 + H^+$ requires m/z 321.1504, found m/z 321.1500.

(4*R*,5*R*)-2,4,5-Triphenyl-1,3,2-dioxaborolane 5

To a solution of phenylboronic acid (250 mg, 2.05 mmol) in toluene (40 mL) was added (*R*,*R*)-hydrobezoin (439 mg, 2.05 mmol). The mixture was heated to reflux for 20 h using a Dean–Stark apparatus. After cooling to room temperature, the solution was dried, filtered and the solvent was evaporated to give the crude solid. The solid was then recrystallised from hexane to the boronate **5**[14,15] ester as a white solid (312 mg, 52%). Mp 92–95 °C; ^{1}H NMR (700 MHz; $CDCl_3$) δ_H 5.34 (2H, s, CHOB), 7.35–7.37 (6H, m, CHA_r), 7.40–7.42 (4H, m, CHA_r), 7.44–746 (2H, m, CHA_r) 7.54–7.56 (1H, m, CHA_r), 7.99–8.00 (2H, m, CHA_r); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 87.1 (CHOB), 126.0, 128.1, 128.5, 129.0, 132.0, 135.4, 140.5 (CHA_r). ^{11}B (128.4 MHz, $CDCl_3$) δ 33.5; Elemental anal. cal. for $C_{20}H_{17}BO_2$: C, 80.03; H, 5.71. Found C, 79.98; H, 5.74; IR (film) 3080, 2941, 1602 (s), 1497 cm^{-1}; HRMS (ASAP) $C_{20}H_{17}BO_2 + NH_4^+$ requires m/z 318.1660, found m/z 318.1659.

General procedure for the aldol reaction – Table 1

To a solution of *p*-nitrobenzaldehyde (151 mg, 1 mmol) in acetone (10 mL), 20 mol% of the examined catalyst (0.2 mmol) was added. The reaction mixture was stirred at room temperature for 24 h and then quenched with sat. aq. NH4Cl (10 mL). The aqueous layer was extracted into EtOAc (3 × 10 mL). The combined organic extracts were dried and concentrated *in vacuo*. Silica gel chromatography (petroleum ether : EtOAc, 5 : 4) afforded the aldol product **2** as a yellow oil and the chalcone **3** as a yellow solid. All spectroscopic and analytical properties were identical to those reported in the literature.[16,17]

General procedure for the *in situ* formation of the cyclohexylboronate esters – eqn (4)

To a solution of cyclohexylboronic acid (15 mg, 0.12 mmol) in $CDCl_3$ (2 mL), the relevant diol (0.12 mmol) was added. The reaction mixture was refluxed for 2 h in the presence of 3 Å molecular sieves and then filtrated *in situ*. ^{11}B NMR analysis was carried out on the residue.

General procedure for the *in situ* formation of the cyclopentylboronate esters – eqn (4)

To a solution of cyclopentylboronic acid (15 mg, 0.13 mmol) in $CDCl_3$ (2 mL), the relevant diol (0.13 mmol) was added. The reaction mixture was refluxed for 2 h in the presence of 3 Å molecular sieves and then filtrated *in situ*. ^{11}B NMR analysis was carried out on the residue.

Procedure for the *in situ* formation of the pyrrolidine-based boronate ester 10b – eqn (5)

To a solution of compound **1a**[7] (15 mg, 0.09 mmol) in CD_2Cl_2 (1.5 mL), diisopropyl D-tartrate (19 μL, 0.09 mmol) was added. The reaction mixture was refluxed for 1 h in the presence of 3 Å molecular sieves, then cooled at −78 °C and filtrated *in situ*. ^{11}B analysis was carried out on the residue.

General procedure for the aldol reaction with the *in situ* formation of the catalytic boronate ester – eqn (6)

Compound **1a**[7] (16.5 mg, 0.1 mmol) and the relevant diol (0.1 mmol) were stirred at 25 °C in the presence of 200 mg of 3 Å molecular sieves in acetone (5 mL) for 2 h before *p*-nitrobenzaldehyde (75.6 mg, 0.5 mmol) and triethylamine (13.9 μL, 0.1 mmol) were added. The reaction mixture was stirred at 25 °C for 24 h and then quenched with sat. aq. NH_4Cl (5 mL). The aqueous layer was extracted into EtOAc (3 × 5 mL). The combined organic extracts were dried and concentrated *in vacuo*. Silica gel chromatography (petroleum ether : EtOAc, 5 : 4) afforded the aldol condensation product **2** as a yellow oil and the chalcone **3** as a yellow solid. All spectroscopic and analytical properties were identical to those reported in the literature.[15,16]

General procedure for the aldol reaction with the *in situ* formation of the boronate ester using different solvents – eqn (7)

Compound **1a**[7] (16.5 mg, 0.1 mmol) and (*R*,*R*)-hydrobenzoin (21.4 mg, 0.1 mmol) were stirred in 4 mL of the relevant solvent for 3 h before *p*-nitrobenzaldehyde (75.6 mg, 0.5 mmol) and acetone (0.37 mL, 5 mmol) were added. After stirring at 25 °C for 20 h in the presence of 3 Å molecular sieves, the reaction was quenched with sat. aq. NH_4Cl (5 mL) and extracted into EtOAc (3 × 5 mL). The combined organic extracts were dried and concentrated *in vacuo*. Silica gel chromatography (hexane : EtOAc, 1 : 1) afforded the aldol condensation product **2** as a yellow oil and the chalcone **3** as a yellow solid. All spectroscopic

and analytical properties were identical to those reported in the literature.[15,16]

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