The first example of enamine–Lewis acid cooperative bifunctional catalysis: application to the asymmetric Aldol reaction†

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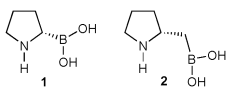
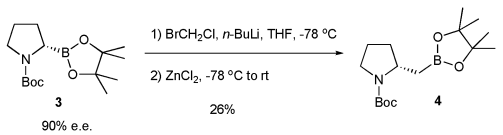
(−)-Sparteine directed lithiation of *N*-Boc-pyrrolidine, alkylation with chloromethylboronate pinacol ester and acid-based deprotection provides homoboroproline HX salt in 94% ee, which is then an efficient enamine-type pyrrolidine catalyst in an asymmetric aldol reaction when neutralised and especially when esterified *in situ* with a tartrate ester, for example, providing 90% ee of the aldol adduct derived from acetone and *p*-nitrobenzaldehyde.

Bifunctional aminoboronic acids[1] are showing promise as green, non-transition-based catalysts in direct amide formation[2] and aldol reactions.[3] A key element in their catalytic reactivity is the cooperative relationship between the Lewis acidic boronic acid and basic or nucleophilic nature of the amino group, without intramolecular deactivation through B–N chelation.[1,2] A further development for potential asymmetric catalytic applications of these systems could be a cooperative catalytic interaction between an enamine and a boronate, assuming that the boronate could be prevented from enamine activation and hydrolysis, and that the enamine would not coordinate the Lewis acid. Since the report[4] of a proline-catalysed asymmetric aldol reaction,[5] and other related systems,[6] a pyrrolidine-substituted boronic acid seemed to be worthy of initial investigations. It is widely accepted that proline and related compounds act similarly to aldolases, *i.e.* through enamine/iminium ion catalysis and the carboxylic acid acts as Brønsted co-catalyst.[7] The substitution of the carboxylic acid in proline by functions with lower pK_a's is known to give new organocatalysts with improved solubility without loss of asymmetric induction,[8] however, there is no example featuring a Lewis acid as the complimentary functionality to the amine, and hence, enamine. In this communication, we report preliminary investigations into the synthesis and application of pyrrolidine-boronic acid-based bifunctional asymmetric catalysts.



1 **2**

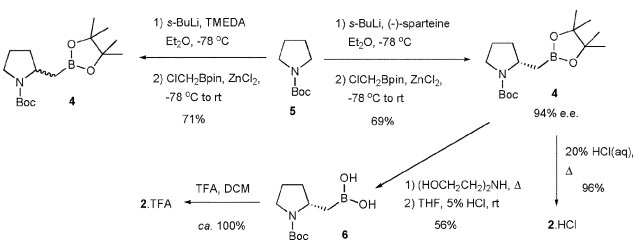
Following our recent asymmetric synthesis of boroproline **1** as its TFA salt using a sparteine-directed metallation,[9] the synthesis of the homoboroproline analogue **2** was initiated *via* homologation of **3**[9] (eqn (1)).



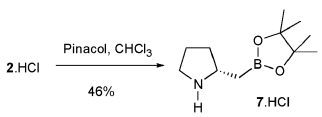
(1)

Reaction of **3** with $ClCH_2Li$[10] gave homologated product **4** in low yield,[11] however, with the expected retention of the (*S*)-configuration. Optimisation could not be achieved, hence, a (−)-sparteine-directed lithiation[12,13] of **5** using chloromethylboronate pinacol ester[14] was attempted (Scheme 1). Initial reaction of **5** with (−)-sparteine-*s*-BuLi followed by the addition of chloromethylboronate ester provided **4** in low yield (12%). To assist the collapse of the intermediate "ate"-complex, anhydrous zinc(II) chloride[10a] was added, resulting in an improved 69% yield (94% ee) of **4**. To develop a chiral GC resolution method,‡ racemic **4** was also prepared using TMEDA–s-BuLi (Scheme 1). Deprotection of **4** was achieved by removal the pinacol ester with diethanolamine (Scheme 1), followed by acid hydrolysis to give **6** (56%).[15]

Boronic acid **6** was isolated as a crystalline solid and recrystallisation from THF gave crystals suitable for X-ray analysis and structural confirmation (see ESI,† Fig. S1). *N*-Boc-deprotection of **6** was accomplished with TFA to give homoboroproline TFA salt of (*S*)-**2**. Alternatively, simultaneous deprotection of both *N*-Boc and pinacol ester groups was achieved using aq. HCl. Attempts at purification of (*S*)-**2**·HCl using Dowex 50WX8-200 resin[16] proved unsuccessful, however, azeotroping with toluene gave **2**·HCl, the identity of which was confirmed by re-esterification with pinacol to give **7** (eqn (2)).



Scheme 1 Synthesis of (*S*)-homoboroproline **2** as TFA and HCl salts.



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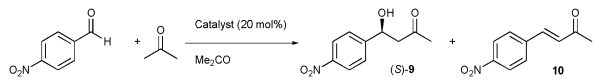
† Electronic supplementary information (ESI) available: Experimental procedures, characterisations of new compounds, analytical methods, ^1H, ^{13}C and ^{11}B NMR spectra. CCDC 666984 and 666985. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b806779a

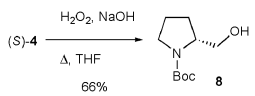
Table 1 Aminoboronic acid-catalysed aldol reaction of *p*-nitrobenzaldehyde and acetone



Entry	Conditions	*t*/h	Yield **9** (%)	ee[a] (%)	Yield **10** (%)
1	(*S*)-**2**·HCl	24	0	—	0
2	KO^{t}Bu	24	43	0	11
3	(*S*)-**2**·HCl + KO^{t}Bu	24	62	8	11
4	Et_3N	24	0	—	0
5	(*S*)-**2**·HCl + Et_3N	24	90	38	10
6	(S)-**1**·TFA	24	0	—	0
7	(*S*)-**1**·TFA + Et_3N	24	14	0	0

[a] Determined by chiral HPLC and major enantiomer was (*S*).§

Recrystallisation from acetone provided crystals of **7** suitable for X-ray analysis (See ESI,† Fig. S2). Confirmation of the absolute stereochemistry of **2** was achieved by oxidation of **4** (H_2O_2–NaOH) to give prolinol **8** (eqn (3)). Comparison of its optical rotation with the literature[17] confirmed the (*R*)-absolute stereochemistry of **8**.



(3)

With both (*S*)-**1** and (*S*)-**2** in hand as salts, their preliminary catalytic activity could be determined on an aldol reaction (eqn (3)) with the results shown in Table 1. Because it was not possible to isolate neutral boroproline **1** or its homologue **2**, formation of both was achieved *in situ* by neutralisation with base (Table 1). None of the salts **1** or **2** were soluble in acetone, however, upon addition of Et_3N, solvation occurred along with the aldol reaction between acetone and *p*-nitrobenzaldehyde. Importantly, the salts of both **1** and **2** are inactive as aldol catalysts, as is Et_3N. The use of a stronger base (KO^{t}Bu) highlights the potential for background base-mediated reactions (Table 1, entry 2); the low asymmetric induction recorded in Table 1, entry 3 represents the competition between the general base-catalysed aldol and enamine catalysis. In contrast, Et_3N prevents the background reaction (Table 1, entry 4) and under these conditions, the aminoboronic acids **1** and **2** showed catalytic activity (Table 1, entries 5 and 7). Boroproline **1** was a poor catalyst (Table 1, entry 7, no asymmetric induction) whereas homoboroproline **2** showed good catalytic activity (Table 1, entry 5, 90% conversion and 38% ee)

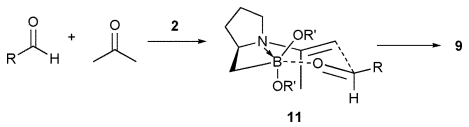
In order to try and probe the mode of action of **2** further, it was necessary to determine if changing either the base, counterion, boronate Lewis acidity or sterics might have any effect on either the rate of the aldol reaction or ee The HBr and HI salts of **2** (prepared as the HCl salt, see ESI†) were compared using both Et_3N and Hünig's base. Also, **2** was examined in the presence of diols which were expected to both increase boron Lewis acidity and stereochemistry around the boronate group through *in situ* esterification of the boronic acid. Steric effects were probed by examination of pinacol ester **7**. The results are summarised in Table 2.

Entries 1, 5 and 7 (Table 2) demonstrate that there is no effect from either the ammonium salt or the counterion. Trifluoroacetate, bromide and iodide anions compare similarly to chloride (Table 2, entry 3), hence, anion association or exchange is negligible. Ammonium counterions also have no influence (see Table 2, entries 2, 4, 6 and 8) (Note: Hünig's base has a very minor influence on the aldol reaction, entry 9. Table 2). Most importantly, it is possible to confirm that the enamine-based reactions are assisted by the intramolecular boronic moiety in homoboroproline **2**, and the relative placement of the boronic acid to the secondary amine is key to reactivity. This is shown by the observation that boroproline **1** is a poor catalyst (entry 7, Table 1)

Table 2 Aminoboronic acid-catalysed aldol reaction of *p*-nitrobenzaldehyde and acetone

Entry	Conditions	Base/ additive	*t*/ h	Conversion (%)	Yield **9** (%)	ee[a] (%)	Yield **10** (%)
1	(*S*)-**2**·TFA	Et_3N	6	>99	92	40	7
2	(*S*)-**2**·TFA	iPr_2NEt	6	92	71	43	21
3	(*S*)-**2**·HCl	Et_3N	6	>99	90	38	10
4	(*S*)-**2**·HCl	iPr_2NEt	6	95	92	40	3
5	(*S*)-**2**·HBr	Et_3N	24	97	93	43	4
6	(*S*)-**2**·HBr	iPr_2NEt	24	97	92	43	5
7	(*S*)-**2**·HI	Et_3N[b]	40	86	81	38	5
8	(S)-**2**·HI	iPr_2NEt[b]	24	63	61	37	2
9	—	iPr_2NEt	24	6	6	N/A	<1
10	Pyrrolidine		6	>99	>99	N/A	<1
11	$PhB(OH)_2$		6	N/A	N/A	N/A	N/A
12	Pyrrolidine + $PhB(OH)_2$	—	6	49	49	N/A	<1
13	(*S*)-**2**·HCl, (*R,R*)-diisopropyl tartrate	Et_3N, 4 Å M.S.	20	65	58	90	7
14	(*S*)-**2**·HCl, (*S,S*)-diisopropyl tartrate	Et_3N, 4 Å M.S.	20	76	63	90	13
15	(*S*)-**2**·HCl, (*R,R*)-Diethyl tartrate	Et_3N, 4 Å M.S.	20	87	78	90	9
16	(*S*)-**2**·HCl, catechol	Et_3N, 4 Å M.S.	20	14	11	70	3
17	(*S*)-**2**·HCl, (*R,R*)-diisopropyl tartrate	Et_3N	20	98	94	82	4
18	(*S*)-**7**·HCl	Et_3N	6	82	46	30	36
19	(*S*)-**1**.TFA, (*R,R*)-diisopropyl tartrate	Et_3N	20	<2	<2	—	<1

[a] Determined by chiral HPLC, major enantiomer (*S*) in all cases.§ [b] Two equivalents.



Scheme 2 Proposed mechanism of action of catalyst **2** and its diol ester derivatives.

and that pyrrolidine reactivity (entry 10, Table 2) is reduced by the presence of a boronic acid (entry 12, Table 2) (which is also unreactive, (entry 11, Table 2). In order to answer the question as to whether the boronate function has a major impact upon the stereochemistry-controlling step, match/mismatch stereochemical effects[18] were investigated by *in situ* boronate esterification (entries 13–17, Table 2). When catalyst **2** was esterified (assisted by molecular sieves) with either enantiomer of diisopropyl tartrate, essentially identical results were obtained (entries 13 and 14, Table 2), and the ee was amplified to 90 from 38%. The lack of matching or mismatching effects demonstrates that the absolute stereoselection of homoboroproline **2** is controlled by the substituted-pyrrolidine and not the boronate. Indeed, steric effects around the tartrate have no influence (entry 15, Table 2) since diethyl tartrate provides an identical ee to the diisopropyl tartrate (entry 13, Table 2). This less hindered diethyl ester is more reactive (87% conversion in 20 h, *vs.* 65% for the more hindered ester) which reinforces the finding that the major effect is neither stereochemical nor steric, but entirely electronic. Hence, the overall effect of the boronate group is to assist aldehyde activation and aldol transition state is predicted to be tightened by a more Lewis acidic boron (*i.e. via* Scheme 2). This is confirmed by *in situ* formation of the catechol ester (entry 16, Table 2); the ee is roughly double that of the free boronic acid (70%). This is a slow reaction which may result from competitive "ate"-complex formation with hydroxide or catechol anion. The balance between increasing boronate Lewis acidity through tartrate ester formation *vs.*the need for water to be present for catalyst turnover is exemplified in entries 13 and 17 (Table 2). Better catalyst turnover (98% conversion, 20 h) is assisted by not drying the reaction (no molecular sieves, entry 17); a slower reaction results from drying. Steric effects at boron were confirmed by use of pinacol ester **7** since no improvement in ee was observed (Table 2, entry 18 *vs.* entry 3). Indeed, (*S*)-**7** merely causes increased dehydration to derive the chalcone (36%). Finally, there is reinforcement of the importance of a transition state such as **11**[7] (Scheme 2) in these reactions involving **2**, since esterification of **1** with a tartrate fails to switch on catalyst reactivity (entry 19, Table 2) and results in almost complete catalyst deactivation.

Proline and its derivatives are general catalysts for a wide range of asymmetric C–C bond forming reactions. The systems reported herein which are readily accessible catalysts based on homoboroproline are tunable *in situ* and they provide the enantiomeric aldol products to those derived from L-proline, and in high ee (90% for a 94% ee catalyst). Furthermore, there is considerable scope for the development of systems related to **2** which rely on the cooperative enamine–Lewis acid catalysis.

Notes and references

‡ *GC conditions*: CP-Chiralsil-Dex-CB column (35 m × 0.25 mm × 0.25 μm), 128 °C, FID, t_R (*S*) = 124 min; t_R (*R*) = 127 min.

§ Chiral HPLC conditions: Chiracel OJ-H, hexane–IPA (90 : 10), 1 mL min^{-1}, λ = 254 nm; t_R [(*R*)-**9**] = 36.3 min, t_R [(*S*)-**9**] = 41.9 min.

1 (*a*) R. L. Giles, J. A. K. Howard, L. G. F. Patrick, M. R. Probert, G. E. Smith and A. Whiting, *J. Organomet. Chem.*, 2003, **680**, 257–262; (*b*) S. W. Coghlan, R. L. Giles, J. A. K. Howard, L. G. F. Patrick, M. R. Probert, C. E. Smith and A. Whiting, *J. Organomet. Chem.*, 2005, **690**, 4784–4793; (*c*) D. Hérault, K. Aelvoet, A. J. Blatch, A. Al-Majid, C. A. Smethurst and A. Whiting, *J. Org. Chem.*, 2007, **72**, 71–75; (*d*) A. S. Batsanov, D. Herault, J. A. K. Howard, L. G. F. Patrick, M. R. Probert and A. Whiting, *Organometallics*, 2007, **26**, 2414–2419.

2 (*a*) K. Arnold, B. Davies, R. L. Giles, C. Grosjean, G. E. Smith and A. Whiting, *Adv. Synth. Catal.*, 2006, **348**, 813–820; (*b*) K. Arnold, A. S. Batsanov, B. Davies and A. Whiting, *Green Chem.*, 2008, **10**, 124–134; (*c*) K. Arnold, B. Davies, D. Hérault and A. Whiting, *Angew. Chem., Int. Ed.*, 2008, **47**, 2673–2676.

3 K. Aelvoet, A. S. Batsanov, A. J. Blatch, C. Grosjean, L. G. F. Patrick, C. A. Smethurst and A. Whiting, *Angew. Chem., Int. Ed.*, 2008, **47**, 768–770.

4 B. List, R. A. Lerner and C. F. Barbas III, *J. Am. Chem. Soc.*, 2000, **122**, 2395–2396.

5 (*a*) Z. G. Hajos and D. R. Parrish, *J. Org. Chem.*, 1974, **39**, 1615–1621; (*b*) U. Eder, G. Sauer and R. Wiechert, *Angew. Chem., Int. Ed. Engl.*, 1971, **10**, 496–497.

6 (*a*) B. List, *Synlett*, 2001, **11**, 1675–1686; (*b*) H. Gröger and J. Wilken, *Angew. Chem., Int. Ed.*, 2001, **40**, 529–532; (*c*) B. List, *Acc. Chem. Res.*, 2004, **37**, 548–557; (*d*) B. List, *Tetrahedron*, 2002, **58**, 5573–5590; (*e*) W. Notz, F. Tanaka and C. F. Barbas III, *Acc. Chem. Res.*, 2004, **37**, 580–591; (*f*) J. Seayad and B. List, *Org. Biomol. Chem.*, 2005, **3**, 719–724; (*g*) B. List, *Chem. Commun.*, 2006, 819–824.

7 (*a*) H. Iwamura, D. H. Wells, Jr, S. P. Mathew, M. Klussmann, A. Armstrong and D. G. Blackmond, *J. Am. Chem. Soc.*, 2006, **126**, 16312–16313; (*b*) B. List, L. Hoang and H. J. Martin, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5839–5842; (*c*) S. Bahmanyar, K. N. Houk, H. J. Martin and B. List, *J. Am. Chem. Soc.*, 2003, **125**, 2475–2479; (*d*) L. Hoang, S. Bahmanyar, K. N. Houk and B. List, *J. Am. Chem. Soc.*, 2003, **125**, 16–17; (*e*) K. N. Rankin, J. W. Gauld and R. J. Boyd, *J. Phys. Chem. A*, 2002, **106**, 5155–5159; (*f*) S. Bahmanyar and K. N. Houk, *J. Am. Chem. Soc.*, 2001, **123**, 11273–11283, and references herein.

8 (*a*) Z. Tang, F. Jiang, X. Cui, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang and Y.-D. Wu, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5755–5760; (*b*) Z. Tang, F. Jiang, L.-T. Yu, X. Cui, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang and Y.-D. Wu, *J. Am. Chem. Soc.*, 2003, **125**, 5262–5263; (*c*) S. Sathapornvajana and T. Vilaivan, *Tetrahedron*, 2007, **63**, 10253–10259.

9 A. S. Batsanov, C. Grosjean, T. Schütz and A. Whiting, *J. Org. Chem.*, 2007, **72**, 6276–6279.

10 (*a*) D. Matteson and K. M. Sadhu, *J. Am. Chem. Soc.*, 1983, **105**, 2077–2078; (*b*) H. C. Brown, S. M. Singh and M. V. Rangaishenvi, *J. Org. Chem.*, 1986, **51**, 3150–3155.

11 D. Font, C. Jimeno and M. A. Pericàs, *Org. Lett.*, 2006, **8**, 4653–4655.

12 (*a*) S. T. Kerrick and P. Beak, *J. Am. Chem. Soc.*, 1991, **113**, 9708–9710; (*b*) P. Beak, S. T. Kerrick, S. Wu and J. Chu, *J. Am. Chem. Soc.*, 1994, **116**, 3231–3239; (*c*) K. M. Bertini Gross and P. Beak, *J. Am. Chem. Soc.*, 2001, **123**, 315–321; (*d*) M. C. Whistler, S. MacNeil, V. Snieckus and P. Beak, *Angew. Chem., Int. Ed.*, 2004, **43**, 2206–2225.

13 M. J. McGrath, J. L. Bilke and P. O'Brien, *Chem. Commun.*, 2006, 2607–2609.

14 R. J. Mears and A. Whiting, *Tetrahedron*, 1993, **49**, 177–186.

15 M. E. Jung and T. I. Lazarova, *J. Org. Chem.*, 1999, **64**, 2976–2977.

16 S. Mitsumori, H. Zhang, P. Ha-Yeon Cheong, K. N. Houk, F. Tanaka and C. F. Barbas, *J. Am. Chem. Soc.*, 2006, **128**, 1040–1041.

17 (*a*) D. Braghiroli, R. Avallone and M. Di Bella, *Tetrahedron: Asymmetry*, 1997, **8**, 2209–2213; (*b*) G. Cardillo, L. Gentilucci, A. Qasem, F. Sgarzi and S. Spampinato, *J. Med. Chem.*, 2002, **45**, 2571–2578; (*c*) M. Kurokawa, T. Shindo, M. Suzuki, N. Nakajima, K. Ishihara and T. Sugai, *Tetrahedron: Asymmetry*, 2003, **14**, 1323–1334.

18 S. Masamune, B. M. Kim, J. S. Petersen, T. Sato and S. J. Veenstra, *J. Am. Chem. Soc.*, 1985, **107**, 4549–4551.