ACCOUNTS
of chemical research

Synthesis of Aminoboronic Acids and Their Applications in Bifunctional Catalysis

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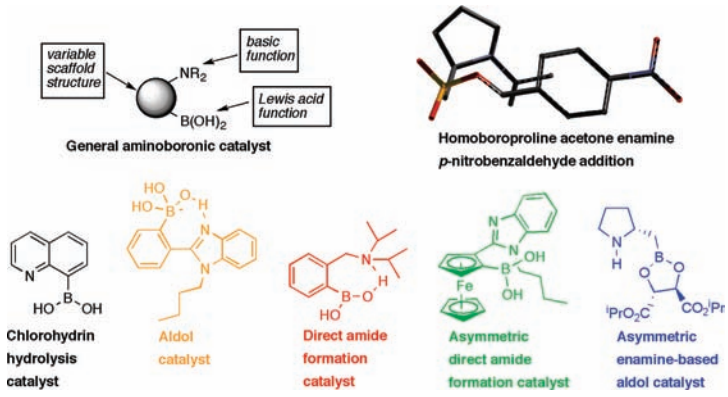
RECEIVED ON NOVEMBER 28, 2008

CONSPECTUS



Amino acids have been known to catalyze organic reactions for many years, but their boronic acid counterparts are much less well-studied. Although there are a number of useful general approaches to the synthesis of protected aminoboronic acids, many practical challenges remain in the isolation and purification of free aminoboronic acids. Despite these issues, now several different chiral and achiral aminoboronic acids show promise as bifunctional organic catalysts. In this Account, we describe both advances in the synthesis of these aminoboronic acids and some of their underdeveloped potential in catalysis. The first aminoboronic acids that demonstrated catalytic properties, such as 8-quinoline boronic acid, enabled the hydrolysis and etherification of chlorohydrins. More recently, aminoboronic acids have effectively catalyzed direct amide formation. In addition, these catalysts can enable the kinetic resolution of racemic amines during the acylation process. Aminoboronic acids can also function as aldol catalysts, acting through *in situ* boronate enolate formation in water, and have facilitated tunable asymmetric aldol reactions, acting through the formation of an enamine. On the basis of these examples, we expect that these molecules can catalyze an even wider range of reactions. We anticipate many further discoveries in this area.

1. Introduction

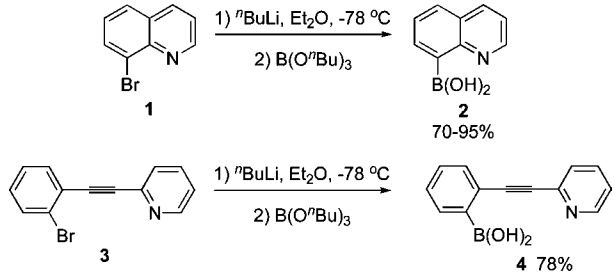
Boronic acids and their derivatives have been a research topic for 150 years, and their synthesis and applications in organic chemistry have been recently reviewed.[1] Herein, is an Account of the synthesis of aminoboronic acids and their applications in bifunctional catalysis.

2. Synthesis of Aminoboronic Acids: Lithium−Halogen Exchange or Direct Lithiation

The synthesis of aminoboronic acids via lithium−halogen exchange or direct lithiation is the method of choice for many bifunctional systems. It has been successfully applied for the preparation of aromatic, ferrocene, and nonaromatic ami-

Published on the Web 04/16/2009 www.pubs.acs.org/acr
10.1021/ar800262v CCC: $71.50

SCHEME 1. Lithium−Halogen Exchange in the Synthesis of Aminoboronic Acids **2** and **4**



noboronic acids, and it is still the most used method for accessing new molecules.

2.1. Synthesis of Aromatic Aminoboronic Acids. The directed lithiation or lithium−halogen exchange in the synthesis of aminoboronic acids started in 1957, when Soddy attempted to prepare a series of quinoline boronic acids by reacting lithiated quinolines with tributyl borate.[2] Later, Letsinger et al. reported the synthesis of 8-quinolineboronic acid **2** in 70−95% yield (Scheme 1),[3] and this was extended to the synthesis of pyridylacetylenephenyboronic acid **4**.[4]

More recently, the lithium−halogen exchange strategy has been used in the synthesis of bifunctional systems **6** (Scheme 2).[5]

To obtain the free boronic acid **6**, careful neutralization of the reaction medium was required (pH 7, Scheme 2), otherwise boronate complexes **7** resulted. The boronic acids **6** also tended to exist in equilibrium with the boroxines **8** (Scheme 2),[5] making purification difficult. The boroxines could, however, be isolated analytically pure, and their novel structure probed by X-ray crystallography.

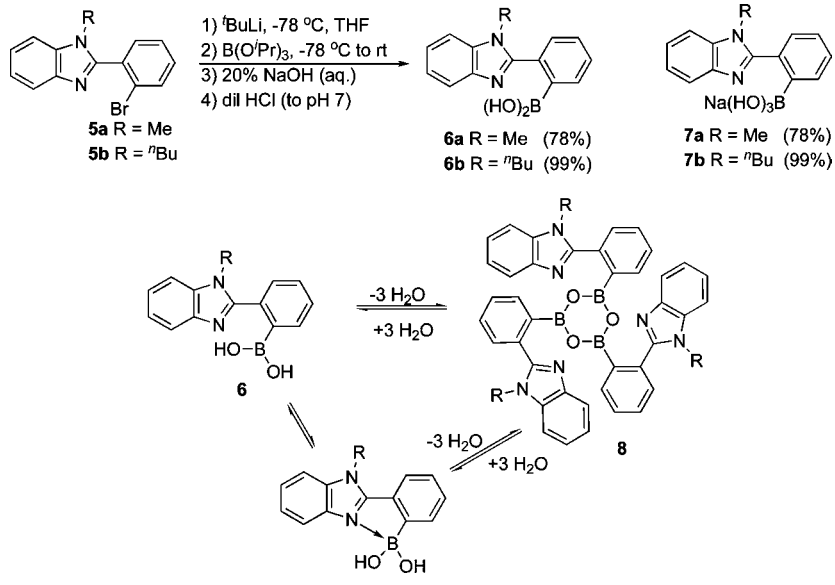
The drawback of lithium−halogen exchange is that the halogen compounds are not always readily available. This can be avoided by using direct *ortho*-lithiation.[6] Indeed, it has shown that a number of aminoboronic acids can be prepared in this way (Scheme 3 and entries 1−9 in Table 1). This methodology was used toward the synthesis of **19** and **20** (entries 10−11 in Table 1).[7−9]

With the exception of compound **15**, all aminoboronic acids could be isolated in good to moderate yields. In the case of **15**, the poor yield was explained in terms of steric congestion at the most activated position. Indeed, other isomeric products were identified, which arose from the attack of butyllithium on the two less sterically congested positions. Poor yields for the synthesis of **18** were improved by prolonging the reaction times and isolating the boroxine **19** rather than boronic acid **18**.

2.2. Synthesis of Ferrocene Aminoboronic Acids. The procedure for the synthesis of aminoboronic acids is similar to the protocol published by Marr et al. (Scheme 4),[10] which relies on directed *ortho*-metalation.[11]

The *ortho*-metalation of ferrocenes was further developed by Ugi in 1970 for the diastereoselective synthesis of 1,2-disubstituted ferrocenes using a chiral-directing metalation group.[12] Since then, the field has received wide attention;[13] however, it was not until after Snieckus et al. reported the use of (−)-sparteine in directed *ortho*-metalations[14] that the synthesis of the first chiral ferrocene aminoboronic acid was achieved (Scheme 5). Following the original procedure,[14] *ortho*-deprotonation of *N*,*N*-diisopropyl ferrocenecarboxamide **24** was achieved with 2.2 equiv of ^{n}BuLi and (−)-sparteine

SCHEME 2. Synthesis of Bifunctional Catalysts **6a** and **6b** and the Equilibrium between Boronic Acid and Boroxine Forms, **6** and **8**



SCHEME 3. Synthesis of Aminoboronic Acids **10**−**20** by *ortho*-Lithiation

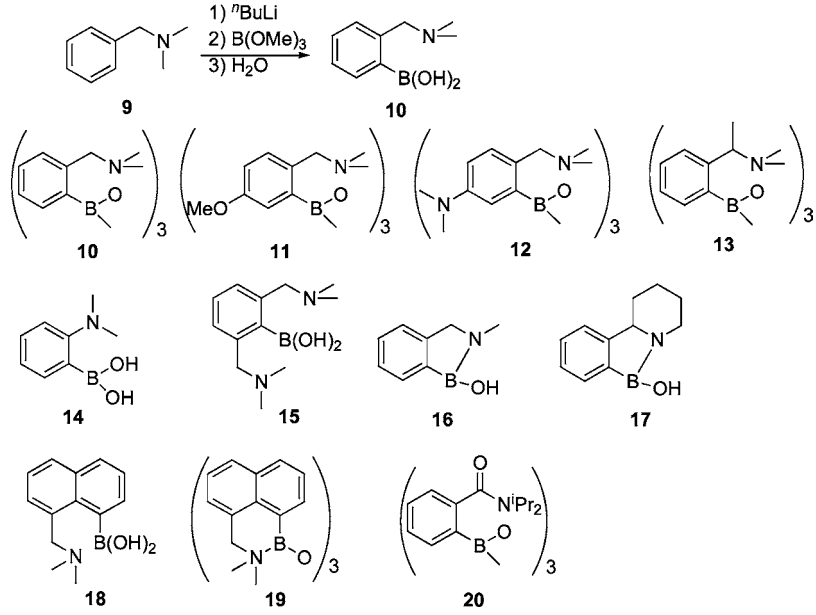
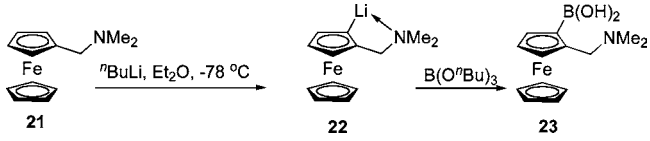


TABLE 1. Synthesis of Aminoboronic Acids **10**−**20** by *ortho*-Lithiation[a]

entry	product	lithiation conditions	yield (%)	reference
1	**10**	TMEDA, Et_2O, 8 h, room temperature	60−65	7
2	**11**	Et_2O, 18 h, room temperature	40	7
3	**12**	Et_2O, 18 h, room temperature	37	7
4	**13**	TMEDA, Et_2O, 7 h, reflux	40−46	7
5	**14**	TMEDA, Et_2O, 7 h, reflux	45	7
6	**15**	TMEDA, Et_2O, 8 h, room temperature	5−10	7
7	**16**	2 equiv of ^{n}BuLi, TMEDA, Et_2O, 4 h, reflux	52	7
8	**17**	2 equiv of ^{n}BuLi, TMEDA, Et_2O, 8 h, room temperature	27	7
9	**18**	TMEDA, Et_2O, 6 h, room temperature	20	7
10	**19**	Et_2O, 5 days, room temperature	69	8
11	**20**	TMEDA, THF, −78 °C, 25 min	79	9

[a] A total of 1 equiv of ^{n}BuLi was used unless stated otherwise. Each product required different isolation and purification procedures.

SCHEME 4. *ortho*-Metalation of *N*,*N*-Dimethylaminomethylferrocene **22** and Reaction with a Borate Ester To Give Aminoboronic Acid **23**



at −78 °C. Quenching with $B(OMe)_3$ provided amideboronic acid **25** in 60%. A reduction of **25** using excess borane provided aminoboronic acid **26**.[15]

Because the enantiopurity of **25** or **26** could not be measured by high-performance liquid chromatography (HPLC) methods, an alternative route was examined (Scheme 6).[15]

Similarly, (−)-sparteine-mediated metalation of **24** was followed by quenching with dibromotetrachloroethane to give *ortho*-bromide **27** in excellent enantioselectivity. 2-Bromoferrocenecarboxamide **27** was then reduced with borane to give amine **28**, which was subjected to lithium−halogen exchange and quenched with trimethyl borate to give the desired aminoboronic acid **26** in high enantiomeric excess (ee) (96% based on the ee of **27**).

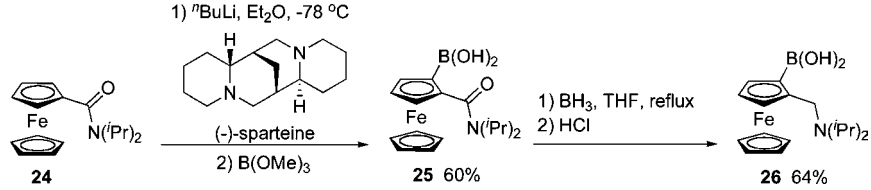
The preparation of aminoboronic acid **29** using directed asymmetric metalation of **30** was also attempted; however, this was unsuccessful. Instead, **31** was isolated following the previously developed lithiation procedure[13b] and then coupled to diamine **32** to give bromoferrocenylbenzimidazole **33** in 89% yield and 99% ee (Scheme 7). Finally, lithium−halogen exchange followed by a reaction with trimethyl borate and hydrolysis resulted in the desired enantiopure product **29** in 60% yield.[16]

More recently, a method for the *ortho*-metalation of *N*,*N*-dimethylaminoferrocene **34** was also developed (Scheme 8).[17]

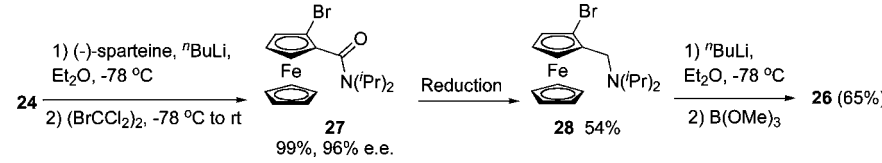
This method relies on activation of *N*,*N*-dimethylaminoferrocene **34** BF_3, which also acts as an *ortho*-directing metalation group. Once again, quenching with triethyl borate provided the aminoboronate, which was transesterified to give boronate ester **36** in (84%). The asymmetric version of this method is yet to be optimized to give synthetically useful ee's; the current procedure provides maximum ee's of 22%.[17]

2.3. Synthesis of Nonaromatic Aminoboronic Acids. The synthesis of nonaromatic aminoboronic acids has tended to rely on the methodology developed by Matteson, using α-chloroboronate esters reacting with amide nucleophiles.[18] Subsequent hydrolysis can then provide free aminoboronates.[19] This approach and its applications has been reviewed eslewhere.[20]

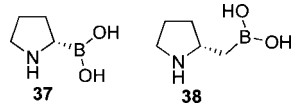
SCHEME 5. Synthesis of Aminoboronic Acid **26**



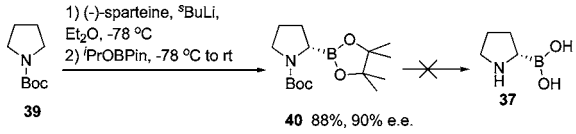
SCHEME 6. Alternative Synthes of Aminoboronic Acid **26**



Recently, new routes to pyrrolidineboronic acids have been developed using lithiation of *N*-Boc-pyrrolidine[21] to derive aminoboronic acids **37**[22] and **38**.[23]



Initial attempts involved the lithiation of *N*-Boc-pyrrolidine **39** in the presence of (−)-sparteine and quenching with a borate ester. Pinacol ester **40** was isolated in 88% yield and 90% ee (eq 1). However, deprotection of **40** and isolation of the free aminoboronic acid **37** proved difficult.

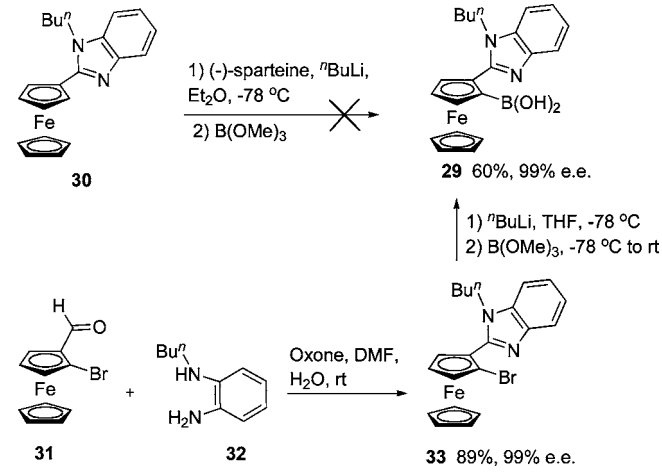


(1)

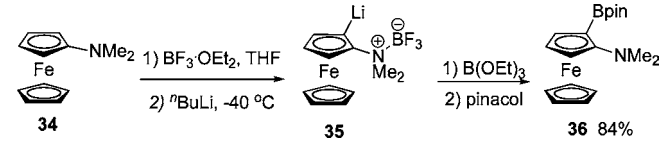
An alternative approach to boroproline **37** was, therefore, examined (Scheme 9). Racemic boronate **41** was prepared using a tetramethylethylenediamine (TMEDA)-mediated lithiation of *N*-Boc-pyrrolidine. Esterification with (−)-pinanediol gave a 1:1 mixture of diastereoisomers **43a** and **43b** (97%). The enantioselective synthesis of boronic acid **41** was achieved using a (−)-sparteine-mediated lithiation to yield (*S*)-**41**. Subsequent formation of the (−)-pinanediol ester gave diastereosiomer **43b** with 90% diastereomeric excess (de) according to HPLC, which confirmed the high asymmetric induction and absolute stereochemistry control in the lithiation−boronation, providing boronic acid (*S*)-**41**.

The absolute stereochemistry of (*S*)-**41** was determined by the formation of the (1*S*,2*S*)-hydrobenzoin ester **45** (Scheme 9), which provided crystals suitable for X-ray analysis, confirming the (*S*)-absolute configuration at C2 in **45** and, therefore, in the parent (*S*)-**41**. Finally, deprotection of (*S*)-**41** using

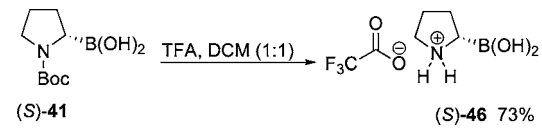
SCHEME 7. Synthesis of Aminoboronic Acid **29**



SCHEME 8. Lithiation of Aminoferrocene **34** by BF_3 Activation

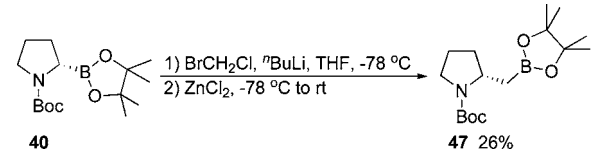


trifluoroacetic acid (TFA) resulted in the isolation of the trifluoroacetate ammonium salt of (*S*)-**46** (73% yield) (eq 2).



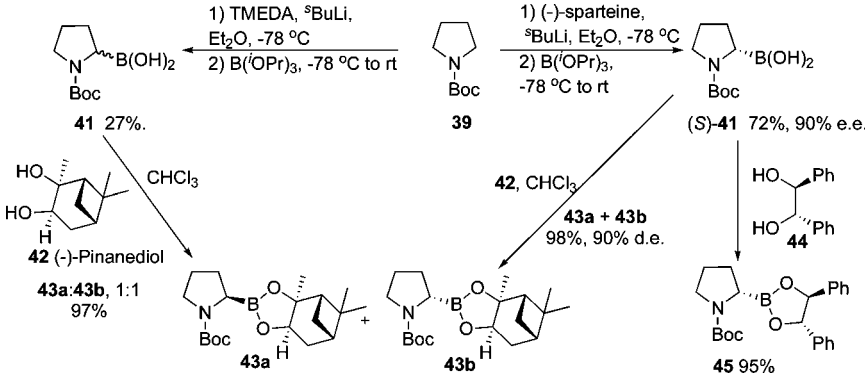
(2)

Having accessed **46** in good yield and high enantiopurity, attention was turned to the synthesis of **38**, which was initially carried out via homologation of boronate ester **40** (eq 3).

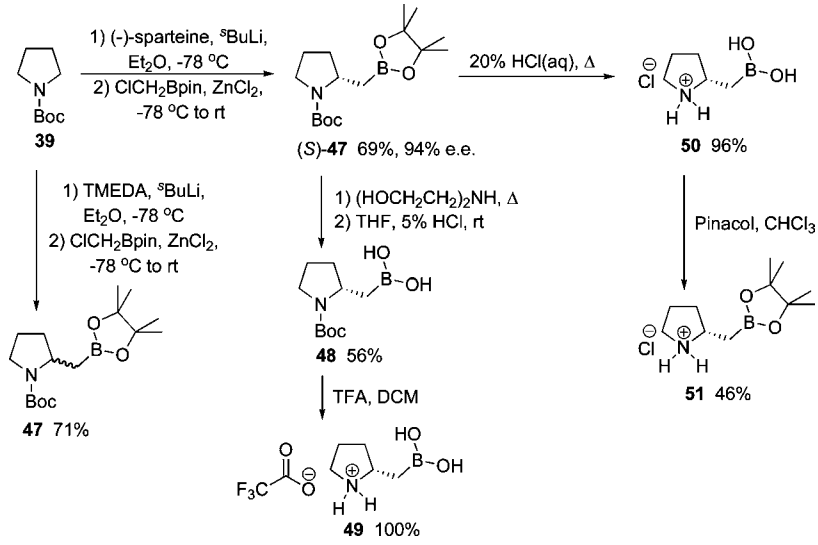


(3)

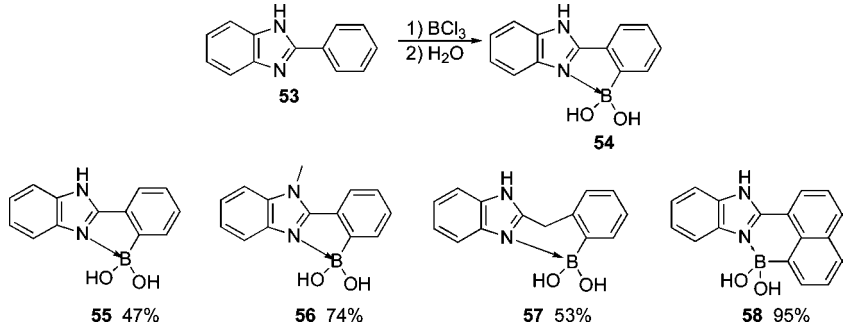
SCHEME 9. Synthesis of *N*-Boc-Pyrrolidine Boronic Acid **41** and Analogues



SCHEME 10. Synthesis of Homoboroproline Analogues via (−)-Sparteine-Mediated Lithiation



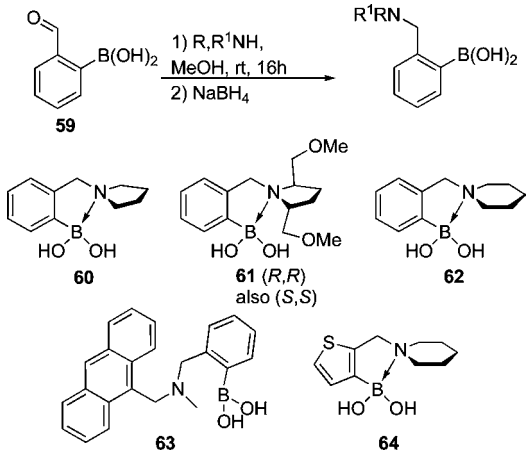
SCHEME 11. Synthesis of Aminoboronic Acids **54**−**58**



As expected, the reaction proceeded with retention of the (*S*) configuration, albeit in poor yield. Further optimization was not achieved; hence, the (−)-sparteine-mediated lithiation was examined (Scheme 10).

Reaction of **39** with (−)-sparteine-^{s}BuLi followed by the addition of chloromethylboronate ester provided **47** in low yield (12%). To improve the yield, anhydrous zinc(II) chloride was added. This facilitated the collapse of the intermediate "ate" complex,[24] resulting in an increased yield of **47** (69%, 94% ee). For the development of a chiral gas chromatography (GC) resolution method, racemic **47** was prepared using TMEDA-mediated lithiation (Scheme 10). Deprotection of **47** was achieved by transesterification with diethanolamine (Scheme 10), followed by acid hydrolysis, to give **48** (56%).[25] The boronic acid **48** produced crystals suitable for X-ray analysis to provide structural confirmation. *N*-Boc-Deprotection of **48** was accomplished with TFA to give homoboroproline TFA salt **49**. Alternatively, simultaneous deprotection of both the

SCHEME 12. Synthesis of Aminoboronic Acids **60**−**64** via Reductive Amination



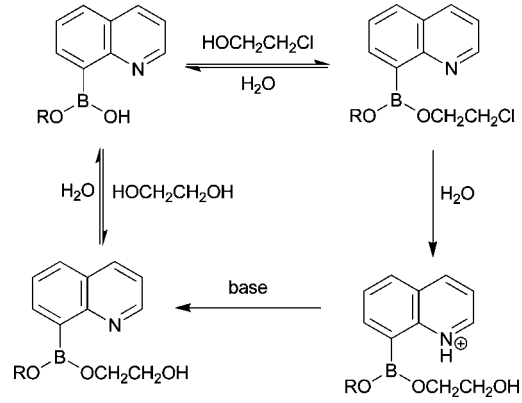
N-Boc and pinacol ester groups was achieved using HCl; however, attempts at purification of **50** proved unsuccessful. However, azeotroping with toluene gave the salt **50**, again confirmed by X-ray analysis after re-esterification with pinacol to give **51**. Finally, confirmation of the absolute stereochemistry of **47** was achieved by oxidation of **47** (H_2O_2−NaOH) to give prolinol **52**.

A comparison of its optical rotation of **52** with the literature[26] confirmed the (*R*)-absolute stereochemistry, hence, the (*S*)-absolute stereochemistry of **47**.

3. Alternative Syntheses of Aminoboronic Acids

There are two other methods for the synthesis of aminoboronic acids that do not involve lithium−halogen exchange or direct lithiation. The first is the direct insertion of boron into a C−H bond, and the second is reductive amination of boronic-acid-containing aldehyde.

SCHEME 14. Proposed Mechanism for the Formation of Glycols Involving the QBA Catalyst



3.1. Direct Insertion of Boron in a C−H Bond. While accessing aminoboronic acids, Letsinger observed that some substrates did not lithiate; in some cases, the starting material was isolated at the end of the reaction as the only product. To access imidazole-based boronic acids (e.g., **54**), an alternative method using direct insertion of boron in a C−H bond was developed (Scheme 11).[27]

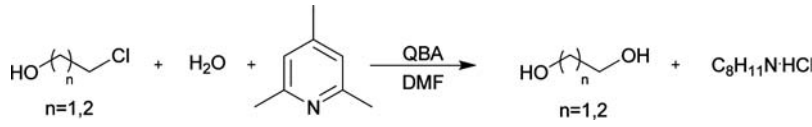
The desired products **54**−**58** could be obtained by passing a stream of boron trichloride through the liquid starting materials at 300 °C followed by hydrolysis. Upon cooling, a brown solid formed, which was ground and extracted with acid. After several neutralizations and extractions, products **54**−**58** were obtained in good yields.

TABLE 2. Hydrolysis of Chloroalcohols with Different Boronic Acid Catalysts

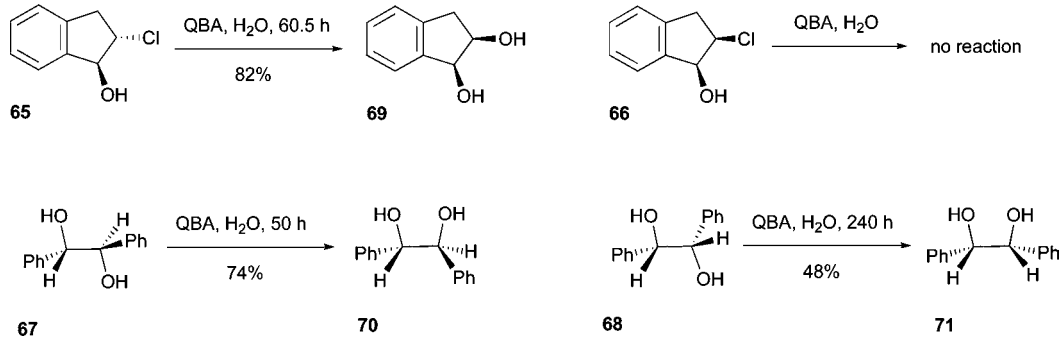
Entry	HO(CH2)nCl	Additive	Conversion (%)
1	n = 1	…	4.0
2	n = 1	C_9H_7N[a]	4.3
3	n = 1	C_9H_7N[a], $C_6H_7O_2B$[b]	3.4
4	n = 1	QBA[c]	44.3
5	n = 2	…	2.9
6	n = 2	C_9H_7N	3.6
7	n = 2	QBA	44.5
8	n = 4	…	3.6
9	n = 4	C_9H_7N	2.2
10	n = 4	QBA, n-BuOH	3.5

[a] Quinoline. [b] Benzeneboronic acid. [c] 8-Quinolineboronic acid **2**.

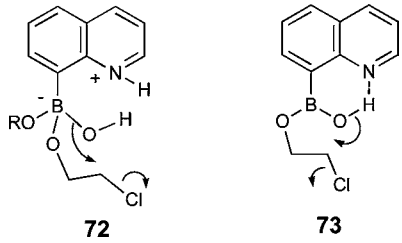
SCHEME 13. Hydrolysis of Chloroalcohols Using Collidine and 8-Quinolineboronic Acid (QBA) **2**



SCHEME 15. Hydrolysis Reaction of the Two Pairs of Isomers



SCHEME 16. Proposed Intermediates in the 8-Quinolineboronic Acid **2** Catalyzed Reactions of Chloroethanol



SCHEME 17. Proposed Intermediate Involved Using the Benzimidazole Catalysts **54** and **57** with Chloroethanol

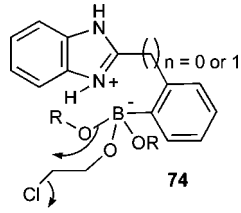


TABLE 3. Rate Constants for the Direct Amide Formation

entry	75	76	77	solvent	catalyst	*K*
1	**a**	**a**	**a**	toluene		$2.91 \pm 0.20 \times 10^{-5}\ s^{-1}$
2	**b**	**a**	**c**	toluene		$2.20 \pm 0.04 \times 10^{-7}$ mol dm^{-3} s^{-1}
3	**a**	**a**	**a**	toluene	**80a**	$4.49 \pm 0.35 \times 10^{-5}\ s^{-1}$
4	**b**	**a**	**c**	toluene	boric acid	$2.16 \pm 0.03 \times 10^{-5}$ mol dm^{-3} s^{-1}
5	**b**	**a**	**c**	fluorobenzene	**80a**	$1.24 \pm 0.11 \times 10^{-5}\ s^{-1}$
6	**b**	**b**	**d**	fluorobenzene	**80a**	$8.26 \pm 0.15 \times 10^{-7}$ mol dm^{-3} s^{-1}
7	**a**	**a**	**a**	fluorobenzene	**80a**	$7.90 \pm 0.48 \times 10^{-5}\ s^{-1}$
8	**a**	**b**	**b**	fluorobenzene	**80a**	$3.97 \pm 0.31 \times 10^{-5}\ s^{-1}$
9	**a**	**a**	**a**	fluorobenzene		$1.04 \pm 0.05 \times 10^{-5}\ s^{-1}$
10	**b**	**a**	**c**	fluorobenzene		0 mol dm^{-3} s^{-1}
11	**a**	**a**	**a**	fluorobenzene	**78**	$2.47 \pm 0.08 \times 10^{-4}\ s^{-1}$
12	**b**	**a**	**c**	fluorobenzene	**80b**	$7.83 \pm 0.17 \times 10^{-7}$ mol dm^{-3} s^{-1}
13	**a**	**b**	**b**	fluorobenzene	**80a**	$3.97 \pm 0.31 \times 10^{-5}\ s^{-1}$
14	**b**	**a**	**c**	fluorobenzene	boric acid	$5.95 \pm 0.07 \times 10^{-7}$ mol dm^{-3} s^{-1}
15	**b**	**a**	**c**	toluene	**79**	$3.02 \pm 0.05 \times 10^{-7}$ mol dm^{-3} s^{-1}
16	**a**	**b**	**a**	toluene	**79**	$5.60 \pm 0.31 \times 10^{-5}\ s^{-1}$
17	**a**	**a**	**a**	fluorobenzene	**79**	$2.47 \pm 0.08 \times 10^{-5}\ s^{-1}$
18	**b**	**a**	**c**	fluorobenzene	**79**	$8.92 \pm 0.11 \times 10^{-7}$ mol dm^{-3} s^{-1}

3.2. Reductive Amination of Boronic Acids. Anslyn et al. have reported the synthesis of several aminoboronic acids **60**−**64** (Scheme 12).[28]

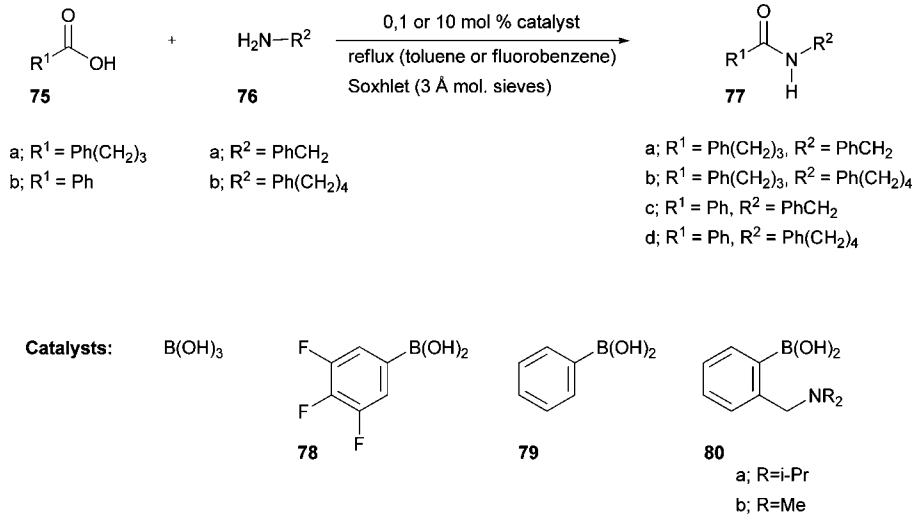
Treatment of 2-formylbenzeneboronic acid **59** with various amines followed by reduction with sodium borohydride gave aminoboronic acids **60**−**64** in good yields. Enantiomerically pure amines could also be used to derive enantiomerically pure aminoboronic acids (e.g., **61**), and this approach could also be used to prepare thiophene-derived aminoboronic acids, such as **64**.

4. Catalytic Applications of Aminoboronic Acids

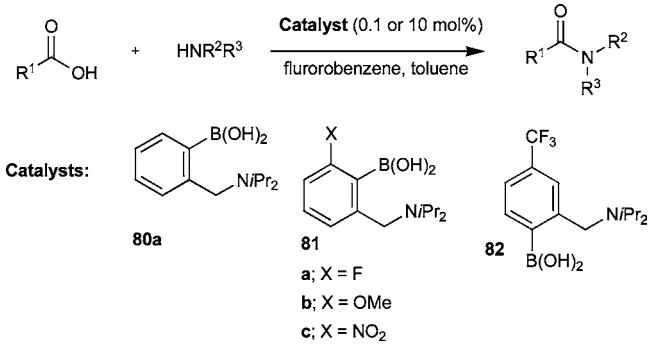
The application of boric and boronic acids in catalytic processes has been studied in several reactions, including imine and ester hydrolysis and the reaction of phenol with formaldehyde.[29] Similarly, catalytic applications of bifunctional aminoboronic acids are relatively undeveloped, although recent results discussed herein show the potential for novel applications, including catalytic asymmetric transformations.

4.1. Chloroalcohol Hydrolysis and Alcoholysis. Letsinger et al. elegantly initiated the use of aminoboronic acids in catalytic (and stoichiometric) reactions of simple chloroalcohol substrates.[3] Preliminary studies with 8-quinolineboronic acid **2** as a catalyst in a range of reactions using a variety of chlorohydrins in *N*,*N*-dimethylformamide (DMF) solution were examined, where the rate of formation of chloride ion indicated of the rate of the reaction. In the presence or absence of quinoline or a mixture of quinoline and benzeneboronic acid, the reactions of all of the chloroalcohols used were slow. In contrast, in the presence of 8-quinolineboronic acid **2**, the rate of liberation of chloride ion was increased and, for example, in chloroethanol, by a factor of 60 (entry 1 versus 4 in Table 2). The mechanism of the reaction was not initially investigated; however, the formation of hydrogen chloride indicated the initial esterification or complexation of the chloroalcohol to boron, with the bifunctional participation of the basic nitrogen-assisting chloride displacement.

SCHEME 18. General Equation for Direct Amide Formation



SCHEME 19. Direct Amide Formation Using Bifunctional Catalysts



Further results from the same group suggested that, rather than the nitrogen atom of the bifunctional catalyst being alkylated, it may be protonated.[30] As a consequence, the same methodology was applied using a stronger base than the catalyst (e.g., collidine) to ensure that the catalyst nitrogen remained unprotonated. This resulted in the rates of the reactions being increased, demonstrating the ability of collidine to aid catalyst turnover (Scheme 13). Moreover, glycols, collidine hydrochloride, and the recovered catalyst were the major products isolated from the reaction. The importance of water was also investigated, with the same reactions being carried out with varying water content, showing that its presence was important at lower concentrations.

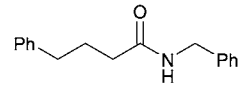
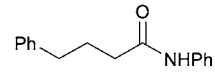
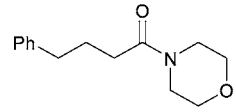
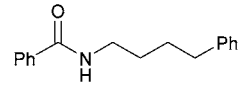
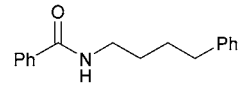
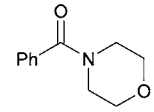
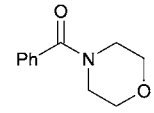
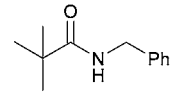
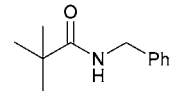
These studies indicated that 8-quinolineboronic acid **2** was esterified by the chloroalcohols. This was followed by displacement of chloride and the protonation of the quinoline nitrogen. Importantly, the glycol was formed, and the aminoboronic catalyst was regenerated by boron ester hydrolysis (Scheme 14).

Further mechanistic studies on the above reaction focused on the important carbon−halogen bond-breaking step.[31] Initially, Letsinger et al. proposed two mechanistic routes: the first involved the displacement of halogen by nitrogen, and the second involved the displacement of halogen by oxygen. Investigation of the potential for retention or inversion of configuration that could take place in Scheme 14 was examined, using the reaction with 8-quinolineboronic acid **2** with two pairs of isomers: *trans*-2-chloro-1-indanol **65** and *cis*-2-chloro-1-indanol **66** and *erythro*-2-chloro-1,2-diphenylethanol **67** and *threo*-2-chloro-1,2-diphenylethanol **68** (Scheme 15).

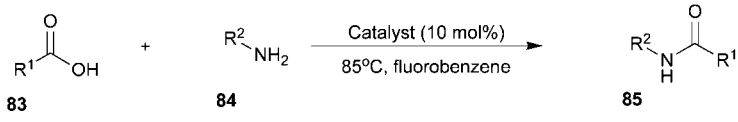
The reaction involving *trans*-2-chloro-1-indanol **65** provided an 82% yield of *cis*-1,2-indandiol **69**, whereas *cis*-2-chloro-1-indanol **66** did not react. Furthermore, in the hydrolysis of the second pair or isomers **67** and **68**, DL-hydrobenzoin **70** was obtained in 74% yield from the *erythro* isomer reaction (run for 50 h), whereas from the *threo* isomer, the *meso*-hydrobenzoin **71** was detected after 240 h but in low yield. The fact that the displacement in the stereoselective hydrolysis occurred with inversion of configuration led to the conclusion that the halogen was displaced by the oxygen. Unfortunately, the exact intermediate in which the oxygen was activated was not determined; however, some possibilities were proposed, including **72** (N.B. this is shown as a hydroxide "ate" complex rather than a water complex being deprotonated by the quinoline nitrogen as originally reported[32]) and **73** (Scheme 16).[32]

The bifunctional nature of another two aminoboronic acids containing an imidazole ring were exploited by the same group, by developing alcoholysis of chloroethanol using 1-butanol.[32] Thus, 2-(2-boronophenyl)-benzimidazole **54** and 2-(2-boronobenzyl)-benzimidazole **57** using differ-

TABLE 4. Direct Amide Formation Using Catalyst **80a**

Entry	Solvent	80a (mol%)	t (h)	Product	Yield (%)
1	PhF	0	24		16
		10			68
2	Toluene	0	22		0
		1			46
3	PhF	0	24		4
		10			67
4	PhF	0	48		0
		10			55
5	Toluene	5	24		71
		10			75
6	PhF	0	24		0
		10			11
7	Toluene	0	24		0
		5	24		16
		10	30		21
8	PhF	0	24		0
		10			15
9	Toluene	0	30		7
		5			42
		10			59

SCHEME 20. Kinetic Resolution of a Racemic Amine by Direct Amide Formation Using **29**



83

a; R^1 = Ph
b; R^1 = (CH_3)Ph

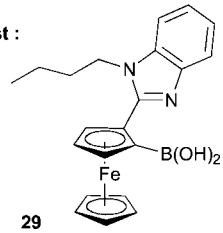
84

a; R^2 = CH(Me)Ph
b; R^2 = CH(Me)Np
c; R^2 = CH(Et)Ph

85

a; R^1 = Ph, R^2 = CH(Me)Ph
b; R^1 = $(CH_2)_3$Ph, R^2 = CH(Me)Ph
c; R^1 = $(CH_2)_3$Ph, R^2 = CH(Me)Np
d; R^1 = $(CH_2)_3$Ph, R^2 = CH(Et)Ph

Catalyst :



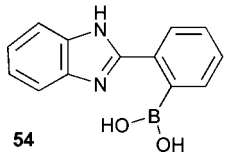
29

ent bases were used to catalyze this reaction, providing the rapid formation of 2-butoxyethanol as the major product, with catalyst recovery. The main reason for the reactivity of catalysts **54** and **57** was proposed to be the same as that for 8-quinolineboronic acid **2**, i.e., that the boronic acid undegoes reversible esterification, resulting in increasing nucleophilicity of the oxygen because of the nitrogen proximity in a manner analogous to that outlined in Scheme 16. However, given the observed formation of 2-butoxyethanol with these catalysts, one might reconsider Letsinger's

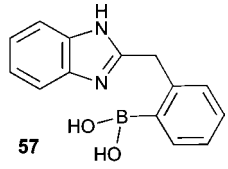
TABLE 5. Direct Amide Formation as Outlined in Scheme 20

entry	catalyst	solvent	**83**	**84** (equiv)	**85**	conversion (%)	ee (%)
1		PhF	**a**	**a**(1)	**a**	0	na
2	**29**	PhF	**a**	**a**(1)	**a**	21	41 (S)
3	**29**	PhF	**a**	**a**(2)	**a**	13	18 (S)
4		PhF	**b**	**a**(1)	**b**	11	na
5	**29**	PhF	**b**	**a**(1)	**b**	34	29 (S)
6	**29**	PhF	**b**	**a**(2)	**b**	67	15 (S)
7		PhF	**b**	**b**(1)	**c**	13	na
8	**29**	PhF	**b**	**b**(1)	**c**	85	9 (S)
9	**29**	PhF	**b**	**b**(2)	**c**	64	6 (S)
10		PhF	**b**	**c**(1)	**d**	12	na
11	**29**	PhF	**b**	**c**(1)	**d**	65	7 (S)
12	**29**	PhF	**b**	**c**(2)	**d**	63	8 (S)
13		iPr$_2$O	**b**	**a**(1)	**b**	<1	na
14	**29**	iPr$_2$O	**b**	**a**(1)	**b**	21	16 (S)

original mechanistic proposals by discounting **73**, updating the process depicted by **72**, and proposing that species such as **74** are likely to be involved (Scheme 17).



54



57

4.2. Direct Amide Formation. Over the last 2 years, the direct formation of amides from carboxylic acids and amines involving aminoboronic acid catalysts has been demonstrated. Initially, Whiting et al. reported the first comparative kinetic studies of the uncatalyzed (thermal) and boric acid, boronic acids **78** and **79**, and amino-boronic acid **80** catalyzed reactions in refluxing toluene and later at a lower temperature in refluxing fluorobenzene.[33] In this solvent, it was shown that proto-deboronation of arylboronic acids did not take place and that catalytic effects assisted the reactions considerably above background uncatalyzed reactions. One of the most attractive features of this study was the demonstrated utility of the bifunctional catalyst **80a** for less reactive substrate combinations, such as aryl carboxylic acids and less electron-rich amines. Moreover, applying soft ionization electrospray mass spectrometric techniques provided information on the possible acylating species involved in the amidation reaction. Knowing that the carboxylate activation and not the amine acylation was the rate-determining step, the formation of either monoacyloxyboronic acid or diacyloxyboronate was thought to be of the most likely species involved in the acylation. The latter would be more reactive and, hence, proposed to be the most likely species involved in amide formation (Table 3).

In addition, it was proposed that a combination of a more basic and hindered bifunctional system, such as **80a**, together with an electron-withdrawing group to further activate the boronic acid, resulted in a more useful bifunctional catalyst. Consequently, the catalytic activity of the *ortho*-*N*,*N*-di-*iso*-propylbenzylaminoboronic acid derivatives **81** and **82** was examined.[34] The use of an electron-donating group, such as methoxy **81b**, decreased the reactivity of the catalyst compared to **80a** (Scheme 18). In contrast, the addition of a *para*-trifluoromethyl group **82** increased the rate of direct amide formation, especially under the lower temperature fluorobenzene conditions.

Taking into consideration that catalyst loading, concentration, and time were the important optimization factors from DoE studies, the reaction (Scheme 19) was extended to the use of phenyl-substituted carboxylic acids and various amines using catalyst **80a**. The reaction was found to be effective for the formation of amides from more reactive substrates when fluorobenzene was used (entries 1, 3, and 4 in Table 4). In contrast, toluene was necessary for less reactive substrates (entries 2, 4, and 9 in Table 4). One of the most important aspects of these direct amide formation reactions is the ability to recover the solvent and molecular sieves used; hence, the only byproduct is water, which makes this type of process potentially the most clean and green approach to amide formation.

The use of bifunctional aminoboronic acids for direct amide formation was extended by the first report of an enantioselective synthesis of amides **85** using a planar chiral ferrocene-derived catalyst **29** to achieve kinetic resolution (Scheme 20).[16] Catalyst **29** provided the amide **85a** in 41% ee (entry 2 in Table 5) using benzoic acid **83a**; however, when the more reactive carboxylic acid **83b** was used, the asymmetric induction was reduced (entries 4−12 in Table 5). In addition, proto-deboronation of the catalyst **29** led to competitive side reactions from boric acid. Proto-deboronation was reduced when a lower boiling point solvent was used (entries 13 and 14 in Table 5). It was proposed[16] that the nitrogen−boron distance had a major impact on the enantioselectivity of the final product, because the reaction may involve the benzimidazole function hydrogen bonding to the incoming ammonium salt to react with a diacylboronate intermediate.[33] Hence, kinetic resolution might occur at the ammonium group hydrogen-bonding stage.

4.3. Aldol Reaction. Recently, in an attempt to show for the first time that boron enolates could be generated *in situ* from ketone compounds, it has been shown that the "ate" complex of benzimidazolylphenylboronic acid **7b** could catalyze direct aldol reactions in water (Scheme 21).[35] Initially, hydroxyacetone was reacted with various aldehydes **86**, providing the aldol adducts **88** (entries 1−6 in Table 6), with high

SCHEME 21. Catalytic Aldol Reaction Using Catalyst **7b**

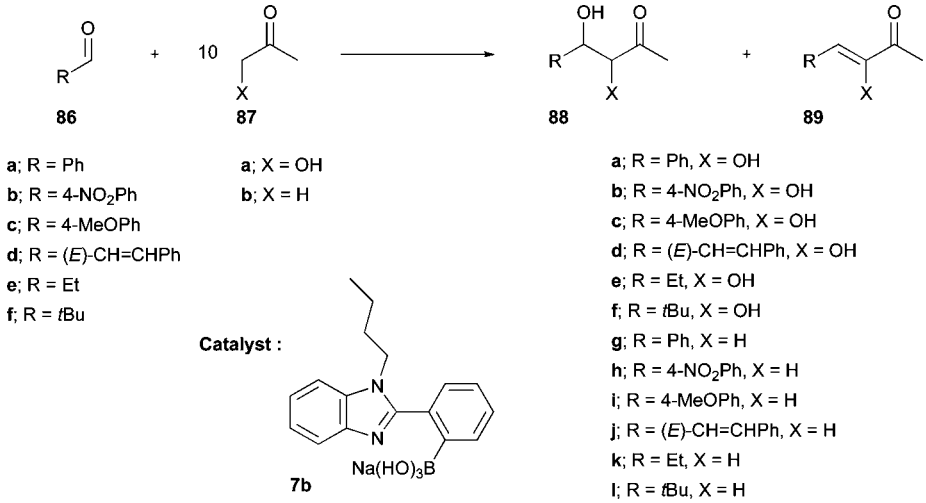


TABLE 6. Product Ratios and Yields of the Aldol Reaction in Scheme 20

entry	**86**	**87**	*t* (h)	conversion (%)	yield **88** (%) (*syn*/*anti*)	yield **89** (%)
1	**a**	**a**	7	>99	97 (2.75:1)	0
2	**b**	**a**	7	>99	76 (5.5:1)	0
3	**c**	**a**	9	ca. 70	46 (2.2:1)	0
4	**d**	**a**	7	>99	64 (1.3:1)	0
5	**e**	**a**	7	>99	68 (2:1)	0
6	**f**	**a**	7	>99	62 (1:0)	0
7	**a**	**b**	7	>99	19	77
8	**b**	**b**	7	>99	0	64
9	**c**	**b**	9	>93	10	81
10	**d**	**b**	7	>85	10	75

syn selectivity. In contrast, the reaction of acetone with the aldehydes **86** formed primarily condensation products **89**, whereas with some aldehydes, a complex mixture was observed (entries 7−10 in Table 6). The reactivity and stereoselectivity of the "ate" catalyst **7b** was proposed to be dependent upon intramolecular cooperation between the benzimidazole and boronate groups;[35] i.e., the formation of the boron enolate "ate" complex occurred because of the intramolecular nitrogen increasing the effective basicity of a boronte−hydroxy group. The resulting boron-bound enolate was then proposed to be strategic for the *syn* selectivity observed in the aldol addition of hydroxyacetone. Furthermore, in the aldol addition of acetone, an analogous mechanism was proposed, following deprotonation of the ketone, and elimination occurs because of the higher reactivity of the boronate-bound intermediate aldol adduct.

The novel report of the *in situ* formation of boron enolates in water was followed for the first demonstration of the utility and catalytic compatibility of an enamine and intramolecular boronic acid. Hence, an asymmetric aldol reaction of acetone with *p*-nitrobenzaldehyde was developed, catalyzed by homoboroproline **38** and its ester derivatives, producing mainly the β-hydroxycarbonyl compound (aldol adducts) with moderate to high enantioselectivity.[23] Catalyst **38** was difficult to prepare as a neutral compound and was, therefore, produced *in situ* by neutralization of its HX salts using either Et_3N or iPr_2NEt (entries 1−8 in Table 6). The neutral homoboroproline **38** provided the aldol adduct **90** as the major enantiomer in up to 43% ee, whereas its shorter homologue boroproline (derived from **46**) was a sluggish catalyst and provided no asymmetric induction. The contrast between boroproline and homoboroproline **38** supported the idea that catalyst **38** worked by *in situ* formation, followed by aldehyde activation by the boronic acid function, as outlined in Scheme 22 (R′ = H). This analysis was further supported by *in situ* esterification of the boronic acid function of **38** with chiral and achiral

SCHEME 22. Catalyzed Reaction of *p*-Nitrobenzaldehyde with Acetone Using the Catalyst Salt **38**

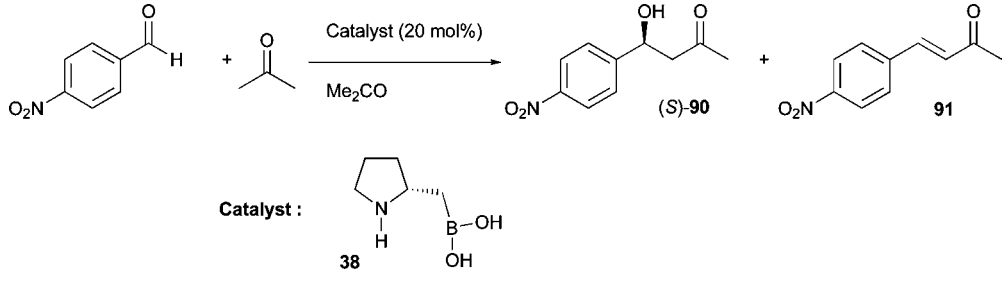
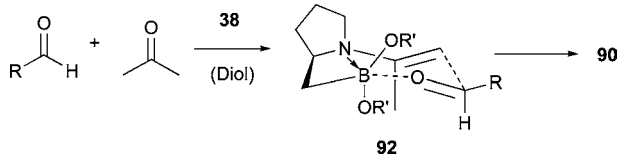


TABLE 7. Yields of the Aldol Reaction Outlined in Scheme 22

entry	conditions	additive(s)	*t* (h)	conversion (%)	yield **90** (%)	ee (%)	yield **91** (%)
1	(*S*)-**38**·TFA	Et_3N	6	>99	92	40	7
2	(*S*)-**38**·TFA	iPr_2NEt	6	92	71	43	21
3	(*S*)-**38**·HCl	Et_3N	6	>99	90	38	10
4	(*S*)-**38**·HCl	iPr_2NEt	6	95	92	40	3
5	(*S*)-**38**·HBr	Et_3N	24	97	93	43	4
6	(*S*)-**38**·HBr	iPr_2NEt	24	97	92	43	5
7	(*S*)-**38**·HI	Et_3N	40	86	81	38	5
8	(*S*)-**38**·HI	iPr_2NEt	24	63	61	37	2
9	(*S*)-**38**·HCl, (*R*,*R*)-diisopropyl tartrate	Et_3N, 4 Å M.S.	20	65	58	90	7
10	(*S*)-**38**·HCl, (*S*,*S*)-diisopropyl tartrate	Et_3N, 4 Å M.S.	20	76	63	90	13
11	(*S*)-**38**·HCl, (*R*,*R*)-diethyl tartrate	Et_3N, 4 Å M.S.	20	87	78	90	9
12	(*S*)-**38**·HCl, catechol	Et_3N, 4 Å M.S.	20	14	11	70	3
13	(*S*)-**38**·HCl, (*R*,*R*)-diisopropyl tartrate	Et_3N	20	98	94	82	4

SCHEME 23. Proposed Enamine Transition State Involving Catalyst **38** and Its Ester Derivatives as an Aldol Catalyst



diols (entries 9−13 in Table 7), which allowed probing of the proposed transition state **92** (Scheme 23). Tartrate esters increased boronate Lewis acidity, tightening the transition state **92** and increasing the asymmetric induction to 90% (from a 94% ee catalyst), independent of the absolute stereochemistry of sterics or stereochemistry of the tartrate (entries 9−11 in Table 7). Catechol could also be used to increase the effective Lewis acidity of catalyst **38**; however, its additional hydrolytic susceptibility led to compromised results, i.e., 80% ee (entry 12 in Table 7). In addition, the importance of drying the reaction mixture to favor boronate ester formation was demonstrated by entry 13 in Table 7, where the ee dropped from 90 to 82% in the absence of molecular sieves because of competition between the boronic acid **38** versus its corresponding tartrate ester mediating the reaction. However, although the ee increased by drying of the reaction mixture, the rate of reaction dropped, showing the importance of catalyst turnover because of imminium ion hydrolysis and, hence, catalyst regeneration.

5. Conclusion and Future Prospects

The synthesis of aminoboronic acids can be accomplished readily to derive a diverse range of potential catalytic systems. The resulting application of these bifunctional catalysts is under development; however, those reactions that have been examined clearly demonstrate that there are major opportunities for catalyzing a wide range of reactions. In addition, the potential for achieving catalytic asymmetric processes using these types of systems increases the attraction of further studies in this area.

BIOGRAPHICAL INFORMATION

Irene Georgiou graduated from the University of Cyprus with a B.S. in chemistry. She is currently a graduate student in the Whiting group at Durham University, studying the synthesis and application of bifunctional aminoboronic acids as organocatalysts.

Gennadiy Ilyashenko received his B.Sc. degree from Queen Mary and Westfield College University of London and stayed on to complete his Ph.D. in the area of oxidative asymmetric catalysis under the supervision of Dr. M. Watkinson. He then took a postdoctoral position at Durham University, working with Dr. A. Whiting, followed by further postdoctoral studies at University of East with Dr. C. Richards, where he is currently.

Andy Whiting carried out Ph.D. studies with Professor R. J. Stoodley at Newcastle University, working on β-lactam chemistry, before moving on to postdoctoral research at Boston College, with Professor T. Ross Kelly, working on natural product synthesis and the development of chiral Diels−Alder Lewis-acid catalysts. After a short period in industry, Ciba-Geigy Central Research, he moved to his first academic position as Lecturer in Chemistry at the University of Manchester Institute of Science and Technology (UMIST) and, in 2001, moved to a Readership at Durham University.

FOOTNOTES

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