Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Organometallic Chemistry 690 (2005) 4784–4793
Journal of Organometallic Chemistry
www.elsevier.com/locate/jorganchem

Synthesis and structure of potential Lewis acid–Lewis base bifunctional catalysts: 2-*N*,*N*-Diisopropylaminophenylboronate derivatives

Samuel W. Coghlan [a], Richard L. Giles [a], Judith A.K. Howard [a], Leonard G.F. Patrick [a], Michael R. Probert [a], Gillian E. Smith [b], Andrew Whiting [a,*]

[a] *Department of Chemistry, Science Laboratories, University of Durham, South Road, Durham DH1 3LE, UK*
[b] *GlaxoSmithKline Research and Development Ltd., Old Powder Mills, Leigh, Nr. Tonbridge, Kent TN11 9AN, UK*

Received 1 April 2005; received in revised form 21 July 2005; accepted 21 July 2005
Available online 12 September 2005

Abstract

Directed *ortho*-metallation is used to introduce a boron function into *N*,*N*-diisopropylbenzamide, resulting in the formation of both borinate and boronate derivatives. *N*,*N*-Diisopropylbenzamide *ortho*-boronate pinacol ester can be reduced with sodium borohydride–TMSCl resulting in *N*,*N*-diisopropylbenzylamino *ortho*-boronic acid. X-ray crystallography and ^{11}B NMR of this compound clearly shows that the hindered isopropylamino groups are sufficient to prevent B–N intramolecular coordination, which contrasts with *N*,*N*-dimethylbenzylamino *ortho*-boronic acid.

Keywords: Metallation; Arylamine; Arylboronate; Boronic acid; Aryldifluoroborane; NMR; X-ray

1. Introduction

In recent years, there has been increased recognition of the advantages of bifunctional catalyst systems [1], which can be applied to a wide range of synthetic processes [2]. Following on from early reports by Letsinger et al. [3] that amino-boronic acid systems could exhibit cooperative catalytic effect on the hydrolysis of chlorohydrins, we undertook a wide-ranging study to examine the scope of catalytic applications to which amino-boronate containing compounds could be applied, and thereby, to develop their potential as bifunctional catalysts [4]. The key factors in these studies have been the development of general methods for the synthesis of amino-boronic acid systems, and gaining an understand ing of the structural properties which contribute to different catalytic activities. To this end, we examined methods for the synthesis of and the resulting structural properties of 1,8-*N*,*N*′-dimethylaminonaphthaleneboronic acid [5], and found that in this system, B–N chelation is present in all the analogues prepared. In this paper, we report our further endeavours into the preparation of bifunctional amino-boronate derivatives based upon *ortho*-benzylamine boronic acid systems. In particular, we explore whether amino-boronate systems could be prepared in which the amine and boronate groups are not permanently coordinated to each other. Our expectation was that adjusting steric requirements around the nitrogen might achieve the desired effect. Herein, we report our results in this direction, some of which are unexpected.

* Corresponding author. Tel.: +0191 374 7491; fax: +0191 384 4737.
E-mail address: andy.whiting@durham.ac.uk (A. Whiting).

0022-328X/$ - see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.jorganchem.2005.07.108

2. Results and discussion

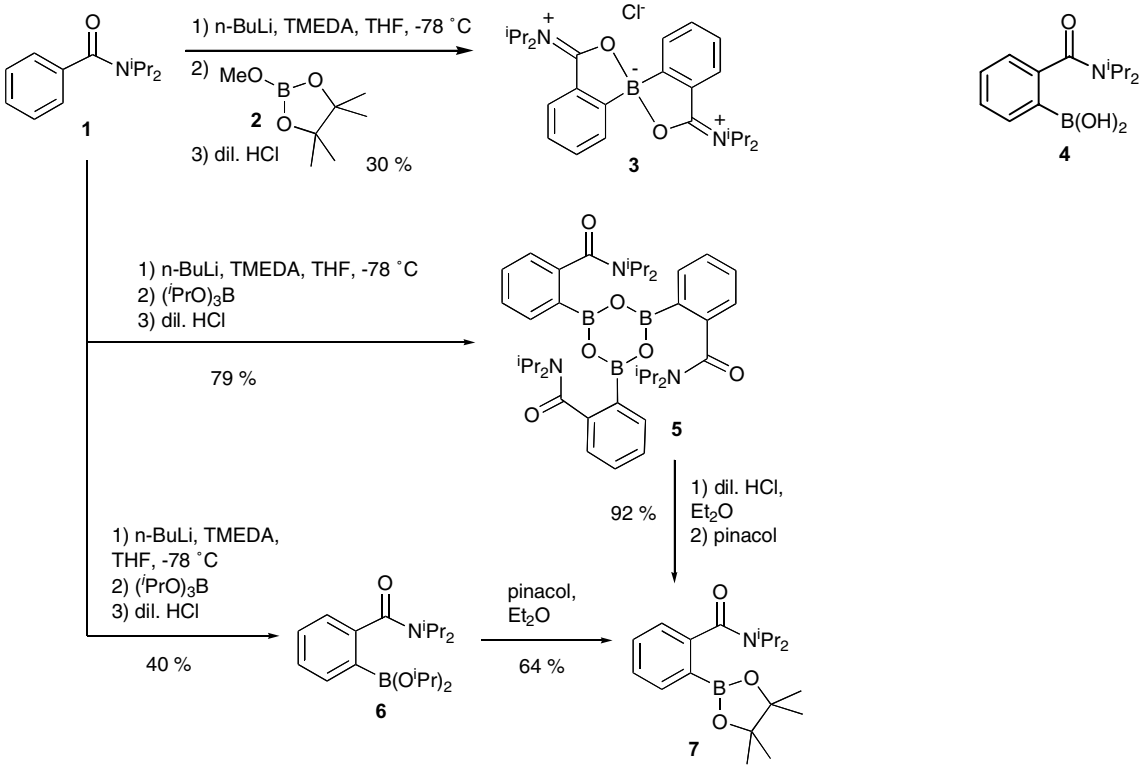
2.1. Directed metallation route to ortho-benzylamine boronates

Since it is known that *ortho*-*N*,*N*-dimethylbenzylamine boronic acid shows strong N–B chelation both in the solution and solid states [6], we decided to prepare the *N*,*N*-diisopropylbenzylamine analogue, using a Snieckus-type directed *ortho*-metallation [7]-boronation route, followed by an amide reduction. Diisopropylamide **1** was therefore treated with *n*-butyllithium–TMEDA (*sec*-butyllithium–TMEDA can also be used for directed metallation, as on the more common diethylamide system [6], though *n*-butyllithium works just as well), followed by addition of a borate electrophile, with the expectation of deriving the required boronate derivative. Initially, we employed the pinacol borate ester **2** as the electrophile, added relatively slowly over 10 min (Eq. (1)), however, from the complex reaction mixture, the only major product isolated by recrystallisation was found to be the borinate derivative **3** (only 30% isolated yield). The unusual "ate"-complex system **3** was confirmed by single crystal X-ray analysis (vide infra).

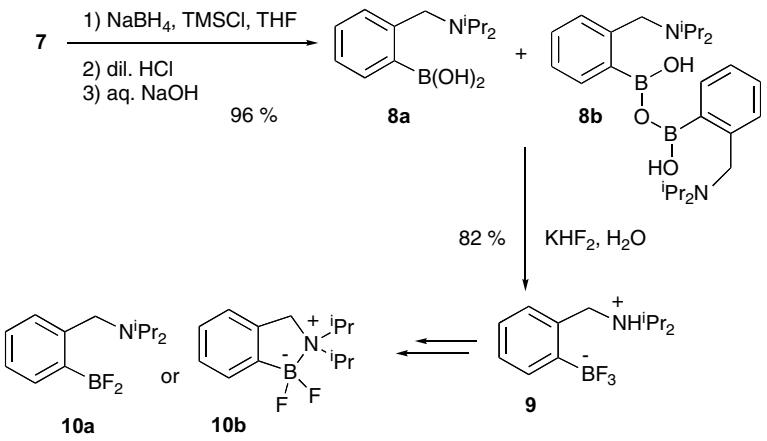
In the light of formation of the unexpected borinate "ate"-complex **3**, we adjusted the reaction conditions in order to try and access the desired boronic acid system **4**. This involved directed metallation with *n*-butyllithium–TMEDA, followed by rapid quenching of the aryl-lithium with triisopropylborate (trimethylborate can also be used, with similar results) and an acidic aqueous work up, followed by crystallisation from aqueous base. However, rather than isolating the expected boronic acid **4**, this reaction produced the stable boroxine **5** cleanly in 79% yield (Scheme 1).

Failure to isolate the boronic acid **4**, therefore led us to try and isolate the diisopropyl ester analogue **6** directly from the directed metallation reaction. Hence, metallation was carried out on amide **1** as before, followed by reaction with triisopropylborate (trimethylborate can also be used, with similar results) and final quenching with one equivalent of hydrochloric acid and direct extraction. This procedure produced the relatively hydrolytically unstable diisopropyl ester **6** in 40% crude yield, which was directly converted to the more stable pinacol ester by transesterification (Scheme 1) in 64% yield. Pinacol ester **7** could also be prepared directly from the corresponding boroxine trimer**5**, by initial acid hydrolysis with hydrochloric acid, followed by esterification with pinacol (Scheme 1) in 92% yield.

Having prepared pinacol ester **7**, the amide reduction was next examined in order to access the corresponding benzylamine **8a**, as outlined in Scheme 2. Smooth reduction of the amide function was readily achieved by in situ generation of borane–THF from sodium borohydride (Scheme 2), with removal of the pinacol ester,



Scheme 1.



Scheme 2.

presumably via the arylborane. No attempt was made to isolate this intermediate, instead, an aqueous work up ensured straightforward isolation of the required benzylamine–boronic acid **8a**. This compound was isolated mainly as the free boronic acid **8a**, however, depending upon how the product was dried, some anhydride **8b** was detected by electrospray mass spectrometry. It is noteworthy that there was no evidence for boroxine formation (vide infra). Slow crystallisation of a sample of boronic acid **8a** produced crystals which were suitable for single crystal X-ray analysis.

Isolation of the boronic acid derivative **8a**, allowed us to then investigate the formation of the corresponding difluoroborane **10**, which we expected would be accessible from the trifluoroborate salt. Hence, reaction with potassium hydrogen difluoride provided the HF salt **9**, rather than the potassium salt [8], or the neutral difluorborane **10**, which can result when there is a basic function proximal to the boron centre [5]. In this case, both the basicity of the amino group and the appearance of a hydrogen bond between a fluorine atom and the N–H (see X-ray structure below), seem to work together to give preference for formation of the HF salt **9**.

It was expected that formation of the difluoroborane **10** would be possible by direct neutralisation of the HF salt. Several attempts to achieve this were made, for example, using sodium carbonate, sodium methoxide, sodium hydride, calcium hydride, *n*-butyllithium and *t*-butyllithium, however, the difluoroborane could not be isolated as a pure, stable compound from any of these attempts. It was possible to gather some evidence for formation of compound **10b** in solution (acetonitrile), especially by ^{11}B NMR, which showed a clear, sharp triplet at δ 3.68 (J 56.3 Hz). This is diagnostic [5] of both the difluoroborane function in **10** and the fact that there is strong B–N chelation according to the low chemical shift suggesting it exists as **10b** rather than **10a**.

Since the borinate derivative **3** had been isolated (vide supra) and shown to exist as the intramolecular "ate"-complex, we also examined transforming this compound into the corresponding fluoroborane by reaction with potassium hydrogen difluoride (Eq. (1)). This resulted in formation of the fluoroborate derivative **11**, in which the Lewis acidic boron stayed complexed to the amide carbonyl as confirmed by X-ray crystallography. The structural differences between compounds **3** and **11** are also reflected in their differing spectroscopic properties, particularly by ^{13}C which shows a single carbonyl resonance for **3** (δ 174.2) vs. two resonances for **11** (δ 173.2

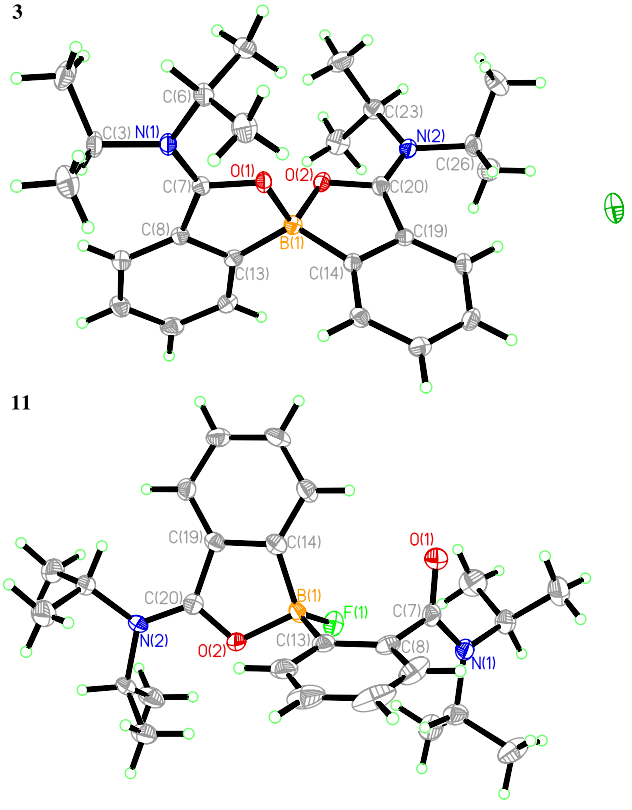
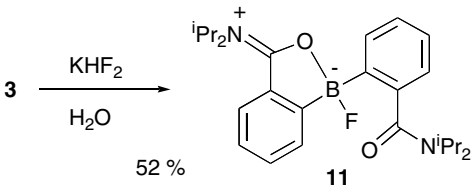


Fig. 1. X-ray structures of borinates **3** and **11**.

and 174.1), showing that solid-state structures (vide infra) persist in solution.



(1)

2.2. X-ray crystallography and structural properties

Confirmation of the solid-state structures for the borinates **3** and **11**, and boronate derivatives **5**, **8a** and **9** was achieved by single crystal X-ray analyses, shown in Figs. 1 and 2, respectively, with a corresponding list of relevant bond lengths and bond angles [Tables 1 and 2, respectively].

The crystal structure of **3** reflects the apparent molecular symmetry which is a non-crystallographic. Inspection of the corresponding bond lengths and angles (Table 1) show this relationship persists in the central core of the molecule. There is an observed shortening of the amide C–N bond, and a concomitant increase in the C=O bond on **3**, when compared to the same uncomplexed amide in **11**. The observed structural changes follow the differences in boron connectivity and charge balances between compounds **3** and **11**.

The crystal structure of compound **11** is also particularly interesting, being derived from spiro-cycle **3** by reaction with fluoride ion. From a chemical perspective, it is odd, especially given the inherent strain in spiro-cycle **3**, that this system does not react with chloride ion to give the boron-chloride analogue of **11**. Instead, the fluoride complex **11** is only derived under acidic (KHF_2) conditions in the presence of fluoride ion. Hence, the formation of the boron "ate"-complex **11** is presumably acid catalysed and the resulting structure shows the effect of the strain imposed by the five-membered ring. This is clearly shown by the lack of normal tetrahedral bond angles, with the five-membered ring exhibiting a 98° bond angle (C14–B1–O2), with the remaining non-cyclic bond angles being 113°, 112° and 106° (see Table 1). This crystal structure of **11**, as with

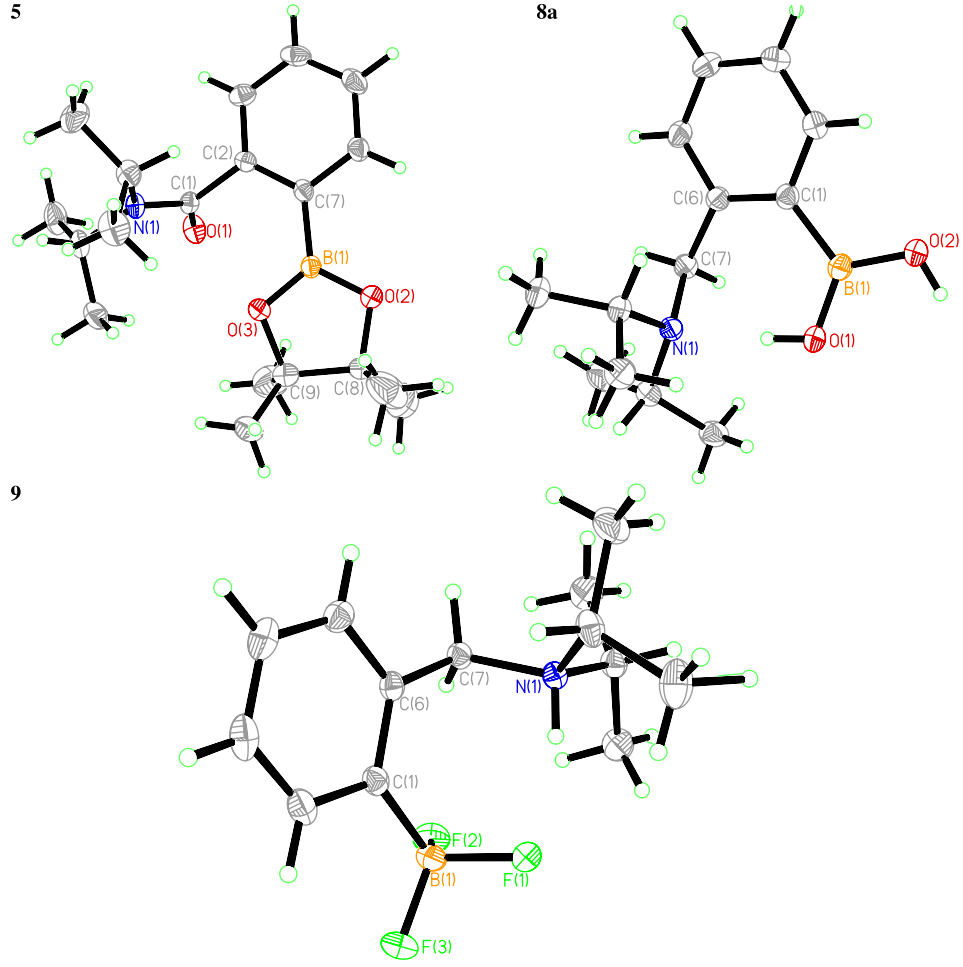


Fig. 2. X-ray structure of pinacol ester **5**, boronic acid **8a** and trifluoroborate salt **9**.

Table 1
Selected bond lengths and bond angles for structures **3** and **11**

*Compound **3***	
Bond lengths	
B–O1	1.525(2)
B1–O2	1.521(2)
B1–C13	1.593(2)
B1–C14	1.590(2)
C7–O1	1.310(17)
C7–N1	1.314(19)
C7–C8	1.497(2)
N1–C3	1.487(19)
N1–C6	1.510(2)
C20–O2	1.315(18)
Bond angles	
O2–B1–O1	105.0(11)
O2–B1–C14	100.4(12)
O1–B1–C14	113.9(13)
O2–B1–C13	115.0(13)
O1–B1–C13	100.2(12)
C14–B1–C13	121.8(13)
C7–O1–B1	112.4(12)
C20–O2–B1	112.2(11)
C12–C13–C8	119.6(14)
C12–C13–B1	131.6(14)
C8–C13–B1	109.0(13)
C15–C14–C19	119.6(13)
C15–C14–B1	131.4(14)
C19–C14–B1	109.0(12)
O1–C7–N1	117.1(13)
O1 C7 C8	111.6(12)
N1 C7 C8	131.3(13)
N2 C20 O2	117.0(13)
N2 C20 C19	131.5(13)
O2 C20 C19	111.5(12)
C7 N1 C3	122.4(13)
C7 N1 C6	120.2(12)
C3 N1 C6	117.3(12)
C20 N2 C26	123.1(12)
C20 N2 C23	120.7(13)
C26 N2 C23	116.1(12)
*Compound **11***	
Bond lengths	
B1–F1	1.407(3)
B1–C13	1.616(3)
B1–O2	1.579(3)
B1–C14	1.605(3)
C7–O1	1.243(3)
C7–N1	1.348(3)
C7–C8	1.508(3)
C8–C13	1.405(3)
C20–C19	1.488(3)
C20–N2	1.324(3)
C20–O2	1.299(2)
Bond angles	
F1–B1–O2	106.5(18)
F1–B1–C14	113.1(18)
O2–B1–C14	98.1(17)
F1–B1–C13	112.7(18)
O2–B1–C13	107.5(17)
F1–B1–O2	106.5(18)
C20–O2–B1	111.5(16)
C12–C13–C8	116.0(2)
C12–C13–B1	122.1(2)
O2–C20–N2	118.8(19)
O2–C20–C19	112.4(18)
N2–C20–C19	128.7(19)
C9–C8–C13	121.3(2)
C9–C8–C7	117.0(2)
C13–C8–C7	121.3(2)
C20–N2–C21	121.6(17)
C20–N2–C24	120.4(18)
C21–N2–C24	118.0(16)
O1–C7–N1	123.0(2)
O1–C7–C8	117.5(2)
N1–C7–C8	119.4(2)
C7–N1–C6	122.7(18)
C7–N1–C3	119.7(19)
C6–N1–C3	117.2(18)

3, shows considerable shortening of the amide C–N bond that forms the cyclic boron carbonyl complex, i.e., 1.324 Å for C20–N2 vs. 1.348 Å for C7-N1, with corresponding lengthening of the C═O bond, i.e., 1.299 Å for C20–O2 vs. 1.243 Å for C7–O1. This is necessary, as with compound **3**, because the amide nitrogen again carries the formal positive charge to balance the negative charge on boron.

Fascinating structural features are also exhibited by the series of crystal structures shown in Fig. 2, for each of the boronate analogues. The boronate pinacol ester **5** provides a useful structure for comparison with each of the structures **8a** and **9**. It shows that the dioxoborolane unit likes to adopt a coplanar orientation with respect to the phenyl ring due to conjugation with the sp^2-hybridised boronate function and that this conjugation is stronger than the alternative amide carbonyl conjugation, which rotates away from the phenyl ring plane.

Reduction of the amide carbonyl and pinacol ester cleavage of **5** derives benzylamine boronic acid **8a**, which retains the boronate to phenyl ring conjugation, as evidenced by the coplanarity of the two functions in the crystal structure of **8a**. However, most striking in the crystal structure of **8a** is the fact that not only is there no evidence for boron–nitrogen complexation in solution (^{11}B NMR δ 29), but there is clearly no complexation in the solid-state either. Indeed, one of the boronic acid functions prefers to form a relatively linear hydrogen-bond to the diisopropylamine nitrogen as part of an seven-membered ring, which is an extremely short H-bond of 2.637 Å (O1–H1–N1), compared to 2.861 Å which is the median value for such bonds according to the Cambridge Structural Database (CSD) [9]. The preference for hydrogen-bonding in both the solid and solution phases for the diisopropylbenzylamine derivative **8a** vs. B–N chelation is in stark contrast to the corresponding dimethylbenzylamine derivative [5] which only exhibits B–N chelation in both solution and solid phases. This result suggests that steric hindrance alone may be sufficient to suppress the intramolecular B–N

Table 2
Selected bond lengths and bond angles for structures **5**, **8a** and **9**

*Compound **5***	
Bond lengths	
B1–O3	1.372(4)
B1–O2	1.378(4)
B1–C7	1.561(4)
O2–C8	1.469(3)
O3–C9	1.463(4)
C8–C9	1.534(5)
C1–O1	1.232(3)
C1–N1	1.353(3)
C1–C2	1.523(4)
C2–C7	1.411(4)
Bond angles	
O3–B1–O2	113.7(2)
O3–B1–C7	124.6(2)
O2–B1–C7	121.7(2)
B1–O2–C8	107.1(2)
B1–O3–C9	106.4(2)
B1–O2–C8	107.1(2)
C1–N1–C24	123.1(2)
C1–N1–C21	119.6(2)
C24–N1–C21	117.2(2)
O1–C1–N1	123.8(2)
O1–C1–C2	118.4(2)
N1–C1–C2	117.7(2)
C3–C2–C7	120.7(2)
C3–C2–C1	118.8(2)
C7–C2–C1	120.2(2)
C6–C7–C2	117.6(2)
C6–C7–B1	119.3(2)
C2–C7–B1	123.1(2)
*Compound **8a***	
Bond lengths	
B1–O2	1.366(15)
B1–O1	1.356(16)
B1–C1	1.588(17)
C6–C1	1.412(16)
C6–C7	1.522(16)
C7–N1	1.480(14)
O1…H1A…N1	2.637(1)
Bond angles	
O1–B1–O2	120.4(11)
O1–B1–C1	123.1(11)
O2–B1–C1	116.5(10)
C2–C1–C6	117.5(11)
C2–C1–B1	116.9(10)
C6–C1–B1	125.6(10)
N1–C7–C6	114.7(9)
C7–N1–C8	112.3(9)
C7–N1–C11	112.1(9)
C8–N1–C11	114.5(9)
N1–H1A–O1	169.7(12)
*Compound **9***	
Bond lengths	
B1–F1	1.460(12)
B1–F2	1.410(12)
B1–F3	1.391(12)
B1–C1	1.618(14)
C7–N1	1.515(11)
C7–C6	1.515(12)
N1…H1N…F1	2.769(1)
Bond angles	
F3–B1–F2	109.6(8)
F3–B1–F1	106.8(8)
F2–B1–F1	105.6(8)
F3–B1–C1	113.4(8)
F2–B1–C1	111.8(8)
F1–B1–C1	109.3(7)
C2–C1–C6	116.9(8)
C2–C1–B1	119.7(8)
C6–C1–B1	123.4(8)
C5–C6–C1	121.0(8)
C5–C6–C7	117.0(8)
C1–C6–C7	121.9(8)
N1–C7–C6	112.8(7)
C7–N1–C8	113.0(7)
C7–N1–C11	113.7(7)
C8–N1–C11	113.9(7)
N1–H1N–F1	165.9(13)

complexation in system **8a**; an observation which may well have important repercussions in bifunctional catalysis [1]. There may also be potential applications in tuning pK_as and exchange kinetics in amino-boronate receptor systems [10], where one would require the proximal arrangement of, for example, Lewis acid and Lewis basic sites, without effective intramolecular deactivation to due to strong self-deactivation.

The crystal structure of trifluoride **9** also shows the presence of hydrogen bonding between one of the boron fluoride functions and the protonated amine, however, in this case giving a seven-membered ring arrangement. The F1–H1–N1 hydrogen bond in **9** is again short compared with a median value of 2.886 Å according to CSD [9]. The steric influence of the diisopropyl substitutents on nitrogen are clearly seen in the crystal structure of **9**, by the fact that the HF salt is preferred over formation of the internally neutral difluoroborane–nitrogen complex, as occurs in systems where intramolecular chelation is not suppressed by steric effects, for example, as in 1-dimethylaminonaphthalene-8-boronates [5].

2.3. Conclusions

Although *ortho*-benzylaminoboronic acid analogues have been known for many years, it has always been assumed that boron–nitrogen chelation will occur [11]. The resulting systems can be utilised, for example, to access unusual boron–nitrogen heterocycles [11], or for preparing novel high affinity receptor systems, for example tartrate [12]. However, the phenomenon that makes these applications useful, i.e., reversible B–N complexation, where the equilibrium lies almost completely in the complexed form, can be seemingly switched off completely. In the present case, simply increasing steric hindrance at the nitrogen in the diisopropylbenzylamine system **8a** is sufficient to prevent

boron–nitrogen complexation in both solid and solution states. Such effects are likely to be important design principles not only for amino-boronic acid receptors, but also for developing bifunctional catalysts based on amino-boronate systems. Further results in the latter area will be reported in due course.

3. Experimental

All ^{1}H NMR spectra were obtained using either a 250 MHz Varian Oxford, or 300 MHz Varian, or 400 MHz Varian Mercury, or 500 MHz Varian spectrometer, using partially deuterated solvent signals as the internal stand ards. ^{13}C NMR spectra were recorded at 100 MHz on a Varian Oxford spectrometer, or 125.5 MHz on a Varian Inova AS500 NMR spectrometer. ^{11}B NMR spectra were recorded at 96 MHz on a Varian Mercury spectrometer or 128.4 MHz on a Bruker 400 spectrometer. ^{19}F NMR were recorded at 188.18 MHz on a Varian 200 spectrometer. Mass spectra and high resolution mass spectra were obtained on a Micromass Autospec spectrometer. Elemental analyses were carried out on an Exeter Analytical CE-440 elemental analyser. Infra red spectra were obtained using a Perkin–Elmer 1615 FTIR operating from a Grams Analyst1600. UV spectra were recorded on an ATI Unicam UV2 UV/Vis spectrometer. Melting points were determined using an Electrothermal melting point apparatus.

All starting materials were obtained commercially from Aldrich or Lancaster and used as received, unless otherwise stated. Solvents were also used as received, unless otherwise stated. Tetrahydrofuran and ether were distilled from sodium benzophenone ketyl. Dichloromethane and toluene were distilled from calcium hydride. TMEDA was distilled from calcium hydride. Alkyl lithiums were acquired from Aldrich and were titrated immediately prior to each use [14]. Air and moisture sensitive reactions were performed under argon and all glassware for use in sensitive reactions was heated for at least 12 h at 160 °C, or flame dried immediately prior to use. Air and moisture sensitive reagents were stored under argon and introduced by syringe or cannula through rubber septa. Evaporations were carried out at 20 mm Hg using a Buchi rotary evaporator and water bath, followed by evaporation to dryness (<2 mm Hg). All reactions using KHF_2 were carried out in Teflon reaction vessels.

3.1. Preparation of borinate 3

To a stirred solution of TMEDA (12.13 ml, 80.4 mmol) in dry tetrahydrofuran (500 ml) at −78 °C under argon was added, dropwise, *n*-butyllithium (1.6 M solution in hexanes, 50 ml, 80.0 mmol). After 30 min, a solution of *N*,*N*-diisopropylbenzamide **1** (15 g, 73.0 mmol) dissolved in dry tetrahydrofuran (60 ml) was added dropwise. After 45 min, the bright yellow solution was treated with pinacol borate ester **2** (14.36 ml, 87.7 mmol), dropwise over 10 min. The mixture was stirred for a further 3 h, during which time the yellow colour faded and the solution became pale green. The reaction mixture was allowed to warm to room temperature, giving a white suspension, which was treated with water (80 ml) and aqueous hydrochloric acid (53.6 ml of a 3 M solution). After partial evaporation of THF, addition of diethyl ether produced a white precipitate which was removed by filtration. The remaining organic layer was separated, dried ($MgSO_4$) and evaporated to give 18.34 g of crude solid, which was recrystallised from hexane to give the borinate derivative **3** (3.14 g, 12%). The remaining mother liquor was re-evaporated, treated with saturated aqueous ammonium chloride (50 ml), to which further hydrochloric acid (15 ml of 1 M solution) was added. The resulting white precipitate was again removed by filtration and dried to give further **3** (4.79 g, 18%). Slow recrystallisation from hexane gave crystals suitable for single crystal X-ray analysis: m.p. 268–269 °C; IR (film) (inter alia) 3332, 2954, 2925, 2854, 1617 (s, CO.N), 1591, 1461 cm^{-1}; UV (CH_3CN) 192 (ε 141,298), 208 (ε 55,283), 256 (ε 47,100) nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45 (d, *J* 7.0 Hz, 6H), 1.52 (d, *J* 7.0 Hz, 6H), 1.63 (t, *J* 7.0 Hz, 12H), 4.07 (sept, *J* 7.0 Hz, 2H), 5.29 (sept, *J* 7.0 Hz, 2H), 7.38–7.36 (m, 2H), 7.62–7.59 (m, 4H), 8.06 (d, *J* 7.5 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.48, 20.51, 20.57, 20.74, 51.69, 53.01, 127.56, 129.90, 130.58, 132.67, 134.80, 174.16; ^{11}B NMR (160 MHz, $CDCl_3$) δ 11.7 (br); MS (ES+) *m*/*z* 419 (100%, M^+); Acc. MS calc. for $C_{26}H_{36}BN_2O_2$ *m*/*z* 419.2861; found 419.2863.

3.2. Preparation of boroxine 5

To a stirred solution of TMEDA (14.7 ml, 97.4 mmol) under argon in dry tetrahydrofuran (350 ml) at −78 °C was added *tert*-butyllithium (65 ml of a 1.63 M solution in pentane). After 30 min, a solution of *N*,*N*-diisopropylbenzamide **1** (20 g, 97.4 mmol) dissolved in dry tetrahydrofuran (50 ml) was added over 5 min. After a further 25 min, the solution was treated with triisopropylborate (22.5 ml, 97.4 mmol) over 2 min. The solution was stirred at −78 °C for a further 10 min, allowed to warm to room temperature and quenched with water (10 ml) after 10 h. The mixture was poured into aqueous saturated ammonium chloride (100 ml), followed by addition of aqueous hydrochloric acid (100 ml of a 3 M solution), and the solvent was partially evaporated. Diethyl ether (300 ml) was added, the aqueous layer (pH 7) was acidified with aqueous hydrochloric acid (50 ml of a 1 M solution) to pH 1, after which, solid sodium carbonate was added slowly until

the aqueous layer reached pH 10. The organic layer was separated, dried ($MgSO_4$), and evaporated to afford 23.63 g of crude product, which was suspended in hot hexane, filtered and dried to afford **5** (17.75 g, 79%): m.p. 238–240 °C; IR (nujol) (inter alia) 3067, 2976, 2933, 1632 (s, CO.N), 1608, 1564 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.07 (d, *J* 6.5 Hz, 6H), 1.27 (d, *J* 6.5 Hz, 6H), 3.39 (sept, *J* 6.5 Hz, 1H), 4.10 (sept, *J* 6.5 Hz, 1H), 7.24 (d, *J* 7.5 Hz, 1H), 7.33–7.42 (m, 2H), 8.04 (d, *J* 7.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.46, 20.54, 47.10, 50.90, 125.00, 129.11, 129.43, 134.93, 140.5 (br s, Ar*C*-B), 141.64, 172.52, 141.61; ^{11}B NMR (96 MHz, $CDCl_3$) δ 21 (br); MS (EI+) *m*/*z* 693 (7%, M^+), 105 (51), 57 (100); Anal. calc. for $C_{39}H_{54}B_3N_3O_6$ requires C, 67.56; H, 7.85; N, 6.06; found: C, 67.38; H, 7.98; N, 5.96%.

3.3. Preparation of pinacol ester 7 via diisopropylester 6

TMEDA (7.50 ml, 49.6 mmol) and *n*-butyllithium (35.9 ml of a 1.38 M solution in hexanes) were stirred in dry tetrahydrofuran (500 ml) at −78 °C under argon. *N*,*N*-diisopropylbenzamide (15.0 g, 45.0 mmol) was added in dry tetrahydrofuran (100 ml) dropwise over 10 min. After 45 min, triisopropylborate (10.4 ml, 45.0 mmol) was added in dry tetrahydrofuran (100 ml) over 15 min. After a further 2 h the mixture was allowed to warm to room temperature and the solvent was removed by evaporation to give a sticky solid, which was then re-dissolved in diethyl ether (500 ml). The ethereal solution was washed with dilute aqueous hydrochloric acid (49.6 ml of a 1 M solution), and water (100 ml). After separation, the aqueous was re-extracted with diethyl ether (2×), the combined organic extracts were dried ($MgSO_4$), and evaporated to afford crude diisopropylester **7** (9.79 g, 40%) which was used without purification. The crude ester **6** (6.29 g, 18.9 mmol) was dissolved in Et_2O (60 ml) and treated with water (40 ml), followed by pinacol (3.55 g, 18.9 mmol) and dilute aqueous hydrochloric acid (9.0 ml of a 1 M solution). After 72 h, the reaction pH was adjusted 9 (aqueous saturated sodium carbonate), separated, and the aqueous layer was re-extracted (3×) with diethyl ether. The combined organic extracts were dried ($MgSO_4$) and evaporated to afford pinacol ester **7** (5.63 g, 90%) as a light brown sticky solid, which slowly crystallised on stand ing. Pure crystals of **7** were isolated by suspension in hexane to afford 4.01 g (64% yield) as white crystals. Further slow re-crystallisation (hexane/Et_2O diffusion) provided crystals suitable for single crystal X-ray analysis: m.p. 108–110 °C; IR (film) (inter alia) 3061, 2977, 2930, 1635 (s, CO.N), 1612, 1596, 1563, 1448, 1432 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 1.12 (d, *J* 6.5 Hz, 6H), 1.32 (s, 12H), 1.58 (d, *J* 7 Hz, 6H), 3.51 (sep, *J* 6.5 Hz, 1H), 3.75 (sep, *J* 6.5 Hz, 1H), 7.16 (d, *J* 7.5 Hz, 1H), 7.32 (1H, m), 7.34–7.44 (1H, m), 7.81 (1H, d, *J* 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 20.45, 20.66, 25.10, 45.94, 51.11, 83.99, 124.81, 127.58, 130.80, 135.76, 145.24, 171.49; δ_B ($CDCl_3$, 96 MHz) 29.98; MS (EI+) *m*/*z* 330 (61%, $M^+ - H$), 273 (30), 188 (67), 130 (49), 83 (100); Acc. MS calc. for $C_{19}H_{30}BNO_3$ *m*/*z* 331.2319; found 331.2324.

3.4. Conversion boroxine 3 into ester 7

A mixture of boroxine **3** (0.55 g, 2.40 mmol), pinacol (0.28 g, 2.4 mmol), dilute aqueous hydrochloric acid (2.40 ml of a 1 M solution), diethyl ether (50 ml) and water (5 ml) was stirred for 48 h, followed by adjustment of the pH to 9 (aqueous saturated sodium carbonate). After separation, the aqueous layer was re-extracted with diethyl ether (3×), the combined organic extracts were dried ($MgSO_4$) and evaporated to afford pinacol ester **7** (0.73 g, 92%) which was spectroscopically and analytically identical to that prepared in the previous experiment.

3.5. Reduction of diisopropylamide 7 to give benzylamine 8

To a stirred suspension of sodium borohydride (12.14 g, 320 mmol) in dry tetrahydrofuran (350 ml) under argon was added chlorotrimethylsilane (81.23 ml, 636 mmol) and the mixture heated at reflux for 2 h. After cooling to RT, the pinacol ester **7** (16.58 g, 23.9 mmol) was added as a suspension in tetrahydrofuran (30 ml) and the mixture heated at reflux for 64 h. After cooling to room temperature, the reaction mixture was quenched carefully with methanol (480 ml) over 30 min (*Caution*. evolves H_2.), followed by water (50 ml). The solvent was partially evaporated, saturated aqueous ammonium chloride (40 ml) was added, followed by aqueous hydrochloric acid (80 ml of a 3 M solution), taking the aqueous layer to pH 1. Dichloromethane (250 ml) was added, followed by solid sodium carbonate with vigorous stirring until the aqueous layer reached pH 9. The organic layer was separated, the aqueous layer was re-extracted with dichloromethane (2 × 100 ml), the combined organic extracts were dried ($MgSO_4$) and evaporated to afford benzylamine **8** (15.88 g, 96%) as a mixture of boronic acid and anhydride. Slow crystallisation from water provided crystals of boronic acid **8a** which were suitable for single crystal X-ray analysis: m.p. 152.0–152.9 °C; IR (nujol) (inter alia) 970, 2352, 2333, 1376, 752 cm^{-1}; UV (CH_3CN) 196 (ε 46,085), 220 (ε 8512) nm; ^1H NMR (400 MHz, $CDCl_3$) δ 1.14 (d, *J* 6.8, 12H), 3.15 (septet, *J*6.8, 2H), 3.86 (s, 2H), 7.26–7.22 (m, 1H), 7.38–7.29 (m, 2H), 7.99–7.96 (m, 1H), 9.58 (br, 2H) (addition of D_2O caused the peak at δ 9.58 to disappear); ^{13}C NMR (101 MHz, $CDCl_3$) δ 19.74, 47.52, 51.89, 127.01, 130.10, 130.70, 136.72, 142.30; ^{11}B NMR (128 MHz,

$CDCl_3$) δ 29.09 (br); MS (ES+) m/z 453 (14%, **8b** $M^+ + H$), 236 (55%, **8a** $M^+ + H$); Acc. MS calc. for $C_{13}H_{23}BNO_2$ m/z 236.1822; found 236.1807.

3.6. Preparation of trifluoroborate complex 9

To a stirred solution of boronic acid **8** (14 g, 61 mmol) in methanol (120 ml) was added potassium hydrogen fluoride (20.15 g, 257.9 mmol) dissolved in a minimal amount of water. After 40 min, the precipitated product was removed by filtration, washed with cold methanol and dried. The resulting solid was recrystallised from acetonitrile to give the HF salt **9** as a white solid (12.95 g, 82%). Slow recrystallisation from acetonitrile gave crystals which were suitable for single crystal X-ray analysis: m.p. 194–196 °C; IR (nujol) (inter alia) 3111, 2938, 2924, 2852, 1462, 1456 cm^{-1}; UV (CH_3CN) 192 (ε 62,950), 272 (ε 1367) nm; ^1H NMR (400 MHz, CD_3CN) δ 1.33 (d, J 6.8 Hz, 6H), 1.37 (d, J 6.8 Hz, 6H), 3.60 (sept, J 6.8 Hz, 2H), 4.37 (d, J 6.4 Hz, 2H), 7.34–7.20 (m, 3H), 7.67 (d, J 7.2 Hz, 1H), 7.60–8.10 (br s, 1H); ^{13}C NMR (100 MHz, CD_3CN) δ 17.42, 18.05, 51.67 (CH_2), 52.65, 127.25, 128.65, 131.51, 132.95, 133.28 (q, J 3.8 Hz); ^{11}B NMR (96 MHz, CD_3CN) δ 1.90 (q, J 58.7 Hz); ^{19}F NMR (376 MHz, CD_3CN) δ −136.36 (br q, J 58.7 Hz); MS (ES+) m/z 258 ($M^+ - 1$, 75%); Anal. calc. for $C_{13}H_{21}BF_3N$ requires C, 60.26; H, 8.17; N, 5.41; F, 22.00; found: C, 60.25; H, 8.24; N, 5.44%.

3.7. Preparation of fluoroborinate 11

To a stirred solution of borinate **3** (1.0 g, 4.01 mmol) in methanol (40 ml) was added potassium hydrogen fluoride (1.25 g, 16.0 mmol) dissolved in a minimal amount of water. After 40 min, the precipitated product was removed by filtration, washed with cold methanol and dried. The resulting solid was recrystallised from acetonitrile to give the fluoride salt **11** as a white solid (0.501 g, 52%). These crystals were suitable for single crystal X-ray analysis: m.p. 197–199 °C; IR (film) (inter alia) 3057, 2953, 2925, 2854, 1628 (s, CO.N), 1602, 1585, 1566, 1478; UV (CH_3CN) 196 (ε 79,342), 248 (ε 17,550) nm; ^1H NMR (400 MHz, CD_3CN) δ 1.01 (d, J 6.8 Hz, 3H), 1.05 (d, J 6.8 Hz, 3H), 1.25 (d, J 6.8 Hz, 3H), 1.45 (d, J 6.8 Hz, 3H), 1.46–1.54 (m, 12H), 3.39 (sept, J 6.8 Hz, 1H), 3.70 (sept, J 6.8 Hz, 1H), 4.01 (sept, J 6.8 Hz, 1H), 5.15 (sept, J 6.8 Hz, 1H), 7.00–7.04 (m, 1H), 7.12–7.18 (m, 2H), 7.66-7.29 (m, 1H), 7.30–7.36 (m, 1H), 7.48 (t, J 7.2 Hz, 1H), 7.83 (d, J 7.2 Hz, 1H), 7.86 (d, J 8.0 Hz, 1H); ^{13}C NMR (101 MHz, CD_3CN) δ 19.29, 19.44, 19.56, 19.92, 19.97, 20.04, 20.12, 20.18, 20.33, 44.82, 50.10, 50.68, 52.22, 124.79, 126.14, 126.65, 127.39, 131.13, 132.44, 132.51, 133.00, 133.14, 143.29, 173.21, 174.08; ^{11}B NMR (128 MHz, $CDCl_3$) δ 10 (br); ^{19}F NMR (188 MHz, CD_3CN) δ −148 (br); MS (ES+) m/z 439 (24%, $M^+ + H$), 419 (100), 144 (32); Anal. calc. for $C_{26}H_{36}BFN_2O_2$: C, 71.23; H, 8.28; N, 6.39; F, 4.33; found: C, 70.32; H, 8.19; N, 6.34%.

Table 3
Crystal and structure refinement data for compounds **3**, **11**, **5**, **8a** and **9**

Molecular compound	**3**	**11**	**5**	**8a**	**9**
(a) Crystal data					
Chemical formula	$C_{26}H_{36}BClN_2O_2$	$C_{26}H_{36}BFN_2O_2$	$C_{19}H_{30}BNO_3$	$C_{13}H_{22}BNO_2$	$C_{13}H_{21}BF_3N$
F_w	454.83	438.38	331.25	235.13	259.12
Crystal system	Monoclinic	Monoclinic	Orthorhombic	Monoclinic	Monoclinic
Space group	$P2_1$	$C2/c$	$P2_12_12_1$	$P2_1/c$	$P2_1/c$
a (Å)	10.7057(2)	13.6546(6)	10.304(2)	13.6197(3)	7.6697(2)
b (Å)	9.3890(2)	14.7501(6)	12.996(2)	7.6578(2)	13.8627(3)
c (Å)	13.4072(3)	25.3101(11)	14.595(3)	13.4864(3)	12.9921(3)
β (°)	106.3620(10)	94.733(2)		109.6060(10)	101.0230(10)
V (Å^3)	1293.06(5)	5080.2(4)	1954.4(6)	1325.04(5)	1355.87(6)
D_{calc} (g cm^{-3})	1.168	1.146	1.126	1.179	1.269
Z	2	8	4	4	4
μ (mm^{-1}) (Mo Kα)	0.172	0.076	0.074	0.077	0.101
(b) Data collection, processing and refinement					
2θ max (°)	60.92	59.82	56.66	55.00	60.06
Data collected	(−14, −13, −18)	(−19, −19, −35)	(−13, −17, −18)	(−17, −9, −17)	(−9, −19, −17)
(h, k, l)	(14, 12, 18)	(18, 20, 33)	(13, 11, 19)	(5, 9, 17)	(10, 17, 18)
Total reflections	13680	20533	12985	9766	12343
Unique reflections [R_{int}] (%)	6720 (4.20)	7088 (11.87)	4844 (3.52)	3041 (3.20)	3959 (1.61)
Observed reflections [$I > 4\sigma(I)$]	5763	3189	4045	2439	3355
Absorption corrections	None	None	None	None	Multi scan
Transmission factors					0.973–0.982
Number of parameters	290	289	217	154	167
R	0.0371	0.0689	0.0744	0.0409	0.0391
R_w	0.0880	0.1065	0.2014	0.1138	0.1106

3.8. X-ray crystallography

All crystals were mounted using hair fibres onto either a Bruker SMART 1 K or SMART 6 K diffractometer and data were recorded at 120 K using Mo K(α) ($\lambda = 0.71073$ Å) X-radiation by use of omega-phi scans. Hydrogen atoms placed geometrically were not refined. The maximum and minimum peaks in the final difference Fourier map were: 0.270 and -0.207 e Å^{-3} and 0.215 and -0.220 e Å^{-3}, respectively, for compounds **3** and **11**, and 1.213 and -0.441 e Å^{-3}, 0.335 and -0.171 e Å^{-3} and 0.477 and -0.203 e Å^{-3}, respectively, for compounds **5**, **8a** and **9**. Calculations were performed using the crystallographic packages SMART [13], SAINT [14] and SHELXTL [15], absorption correction was applied by the use of SADABS [14]. The neutral atom scattering factors were taken from: The International Tables for Crystallography [16] (see Table 3).

4. Supplementary material

Crystallographic data for the structure determinations of compounds **3**, **5**, **8a**, **9** and **11** have been deposited with the Cambridge Crystallographic Data Centre, CCDC nos. 253855, 253857, 253856, 253858 and 253859, respectively. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

Acknowledgements

We thank the EPSRC for a research Grant (GR/R24722/01), a DTA studentship (for RG) and a Senior Research Fellowship (for JAKH), GlaxoSmithKline for CASE funding, S.M. Lynn (GSK, Tonbridge) for information retrieval, and Dr. A.M. Kenwright (Durham) for helpful discussions regarding multinuclear NMR.

References

[1] G.J. Rowlands, Tetrahedron 57 (2001) 1865.
[2] (a) N. Yoshikawa, M. Shibasaki, Tetrahedron 57 (2001) 2569;
(b) M. Kanai, Y. Hamashima, M. Shibasaki, Tetrahedron Lett. 41 (2002) 2405;
(c) Y. Hamashima, M. Shibasaki, Tetrahedron Lett. 42 (2001) 691;
(d) Y. Hamashima, D. Sawada, H. Nogami, M. Kanai, M. Shibasaki, Tetrahedron 57 (2001) 805;
(e) H. Nogami, S. Matsunaga, M. Kanai, M. Shibasaki, Tetrahedron Lett. 42 (2001) 279;
(f) R. Hamasaki, Y. Chounan, H. Horino, Y. Yamamoto, Tetrahedron Lett. 41 (2000) 9883.
[3] (a) R.L. Letsinger, S.H. Dand egaonker, J. Am. Chem. Soc. 81 (1959) 498;
(b) R.L. Letsinger, D.B. MacLean, J. Am. Chem. Soc. 85 (1963) 2230.
[4] Bifunctional catalysts, A. Whiting, Appl. No. 0314220.5. International patent application number PCT/GB2004/002664, 2003 (submitted).
[5] R.L. Giles, J.A.K. Howard, L.G.F. Patrick, M.R. Probert, G.E. Smith, A. Whiting, J. Organomet. Chem. 680 (2003) 257.
[6] S. Toyota, T. Futawaka, M. Asakura, H. Ikeda, M. Oki, Organomet. 17 (1998) 4155.
[7] (a) P. Beak, R.A. Brown, J. Org. Chem. 47 (1982) 34;
(b) A. Giannis, K. Sand hoff, Angew. Chem., Int. Edn. Engl. 38 (1989) 218;
(c) J.-M. Fu, B.-P. Zhao, M.J. Sharp, V. Snieckus, Can. J. Chem. 72 (1994) 227.
[8] (a) E. Vedejs, S.C. Fields, M.R. Schrimpf, J. Am. Chem. Soc. 115 (1993) 11612;
(b) E. Vedejs, R.W. Chapman, S.C. Fields, M.R. Schrimpf, J. Org. Chem. 60 (1995) 3020;
(c) M.F. de la Torre, C. Caballero, A. Whiting, Tetrahedron 55 (1999) 8547.
[9] Cambridge Structural Database, January 2005 ed., Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. Available from: http://www.ccdc.cam.ac.uk/.
[10] S.L. Wiskur, J.J. Lavigne, H. Ait-Haddou, V. Lynch, Y.H. Chiu, J.W. Canary, E.V. Anslyn, Org. Lett. 3 (2001) 1311.
[11] See R.T. Hawkins, H.R. Snyder, J. Am. Chem. Soc. 82 (1960) 3863, and references therein.
[12] C.W. Gray, T.A. Houston, J. Org. Chem. 67 (2002) 5426.
[13] Bruker SMART-V5.625. Data Collection Software. Siemens Analytical X-ray Instruments Inc., Madison, WI, USA.
[14] Bruker SAINT-V6.28A. Data Reduction Software. Siemens Analytical X-ray Instruments Inc., Madison, WI, USA.
[15] Bruker SHELXTL-V6.1. Siemens Analytical X-ray Instruments Inc., Madison, WI, USA.
[16] The International Tables for Crystallography, vol. IV, Kynoch Press, Birmingham, England, 1974, pp. 99–101, 149–150.