1
Structure, Properties, and Preparation Of Boronic Acid Derivatives. Overview of Their Reactions and Applications

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1.1
Introduction

Structurally, boronic acids are trivalent boron-containing organic compounds that possess one alkyl substituent (i.e., a C–B bond) and two hydroxyl groups to fill the remaining valences on the boron atom (Figure 1.1). With only six valence electrons and a consequent deficiency of two electrons, the sp^2-hybridized boron atom possesses a vacant p orbital. This low-energy orbital is orthogonal to the three substituents, which are oriented in a trigonal planar geometry. Unlike carboxylic acids, their carbon analogues, boronic acids are not found in nature. These abiotic compounds are derived synthetically from primary sources of boron such as boric acid, which is made by the acidification of borax with carbon dioxide. Borate esters, the main precursors for boronic acid derivatives, are made by simple dehydration of boric acid with alcohols. The first preparation and isolation of a boronic acid was reported by Frankland in 1860 [1]. By treating diethylzinc with triethylborate, the highly air-sensitive triethylborane was obtained, and its slow oxidation in ambient air eventually provided ethylboronic acid. Boronic acids are the products of the second oxidation of boranes. Their stability to atmospheric oxidation is considerably superior to that of borinic acids, which result from the first oxidation of boranes. The product of a third oxidation of boranes, boric acid, is a very stable and a relatively benign compound to humans (Section 1.2.2.3).

Their unique properties as mild organic Lewis acids and their mitigated reactivity profile, coupled with their stability and ease of handling, makes boronic acids a particularly attractive class of synthetic intermediates. Moreover, because of their low toxicity and their ultimate degradation into the environmentally friendly boric acid, boronic acids can be regarded as "green" compounds. They are solids that tend to exist as mixtures of oligomeric anhydrides, in particular the cyclic six-membered boroxines (Figure 1.1). For this reason and other considerations outlined below, the corresponding boronic esters are often preferred as synthetic intermediates. Although other classes of organoboron compounds have found tremendous utility in organic

Boronic Acids. Edited by Dennis G. Hall

ISBN 3-527-30991-8

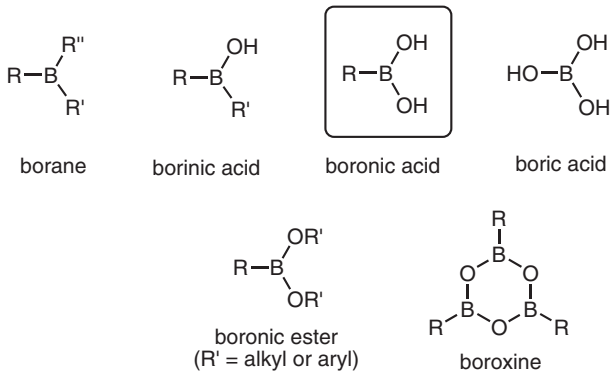


Figure 1.1 Oxygenated organoboron compounds.

synthesis, this book focuses on the most recent applications of the more convenient boronic acid derivatives. For a comprehensive description of the properties and reactivity of other classes of organoboron compounds, interested readers may refer to a selection of excellent monographs and reviews by Brown [2], Matteson [3], and others [4–7]. In the past two decades, the status of boronic acids in chemistry has risen from peculiar and rather neglected compounds to a prime class of synthetic intermediates. Much progress, described in hundreds of publications, has happened since the last review on boronic acid chemistry by Torssell in 1964 [8]. For instance, hopes for boronic acid based therapeutics have finally concretized [9]. The recent approval of the anti-cancer agent Velcade®, the first boronic acid containing drug commercialized (Section 1.6.5), further confirms the new status of boronic acids as an important class of compounds in chemistry and medicine. This chapter describes the structural and physicochemical properties of boronic acids and their many derivatives, as well as their methods of preparation. A brief overview of their synthetic and biological applications is presented, with an emphasis on topics not covered in other chapters.

1.2
Structure and Properties of Boronic Acid Derivatives

1.2.1
General Types and Nomenclature of Boronic Acid Derivatives

The reactivity and properties of boronic acids is highly dependent upon the nature of their single variable substituent; more specifically, by the type of carbon group (R) directly bonded to boron. In the same customary way as for other functional groups, boronic acids are classified conveniently in subtypes such as alkyl-, alkenyl-, alkynyl-, and aryl- boronic acids.

When treated as an independent substituent, the prefix borono is employed to name the boronyl group (e.g., 3-boronoacrolein). For cyclic derivatives such as boronic esters, the IUPAC RB-1-1 rules for small heterocycles (i.e., the Hantzsch–Widman system) are employed along with the prefix "boro". Thus, saturated five- and six-membered cyclic boronic esters are, respectively, named as dioxaborolanes and dioxaborinanes. For example, the formal name of the pinacol ester of phenylboronic acid is 2-phenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. The corresponding nitrogen analogues are called diazaborolidines and diazaborinanes , and the mixed nitrogen–oxygen heterocycles are denoted by the prefix oxaza. Unsaturated heterocycles are named as boroles.

1.2.2 Boronic Acids

1.2.2.1 Structure and Bonding

The X-ray crystal structure of phenylboronic acid (**1**, Figure 1.2) was reported in 1977 by Rettig and Trotter [10]. The crystals are orthorhombic, and each asymmetric unit consists of two distinct molecules, bound through a pair of O–H---O hydrogen bonds (A and B, Figure 1.3). The CBO_2 plane is quite coplanar with the benzene ring, with a respective twist around the C–B bond of 6.6°and 21.4° for the two independent molecules of $PhB(OH)_2$. Each dimeric ensemble is also linked with hydrogen bonds to four other similar units to give an infinite array of layers (C, Figure 1.3). X-ray crystallographic analysis of other arylboronic acids like *p*-methoxyphenyl boronic acid (**2**) [11] and 4-carboxy-2-nitrophenyl boronic acid (**3**, Figure 1.2) [12] are consistent with this pattern. Recently, the structures of two heterocyclic boronic acids, 2-bromo- and 2-chloro- 5-pyridylboronic acids (**4** and **5**), were reported [13].

Whereas the boronic acid group has a trigonal geometry and is fairly coplanar with the benzene ring in structures **1**and **2**, and **4** and **5**, it is almost perpendicular to the ring in **3**. This is likely due to a combination of two factors: minimization of steric strain with the ortho-nitro group, and also because of a possible interaction between one oxygen of the nitro group and the trigonal boron atom. Inspired by the structur-

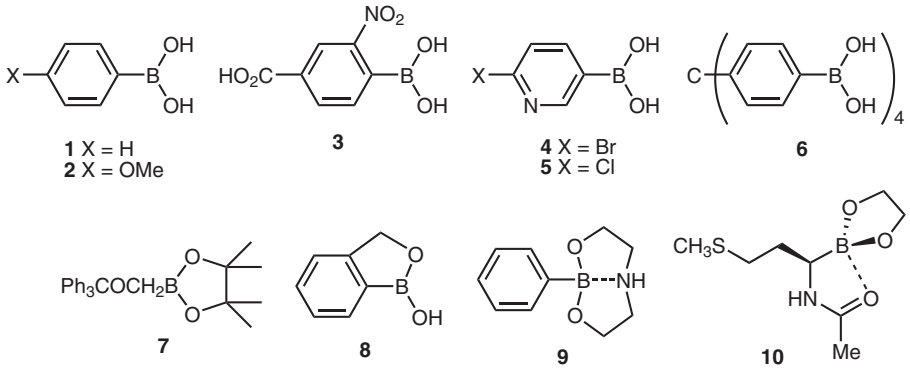


Figure 1.2 Boronic acid derivatives analyzed by X-ray crystallography.

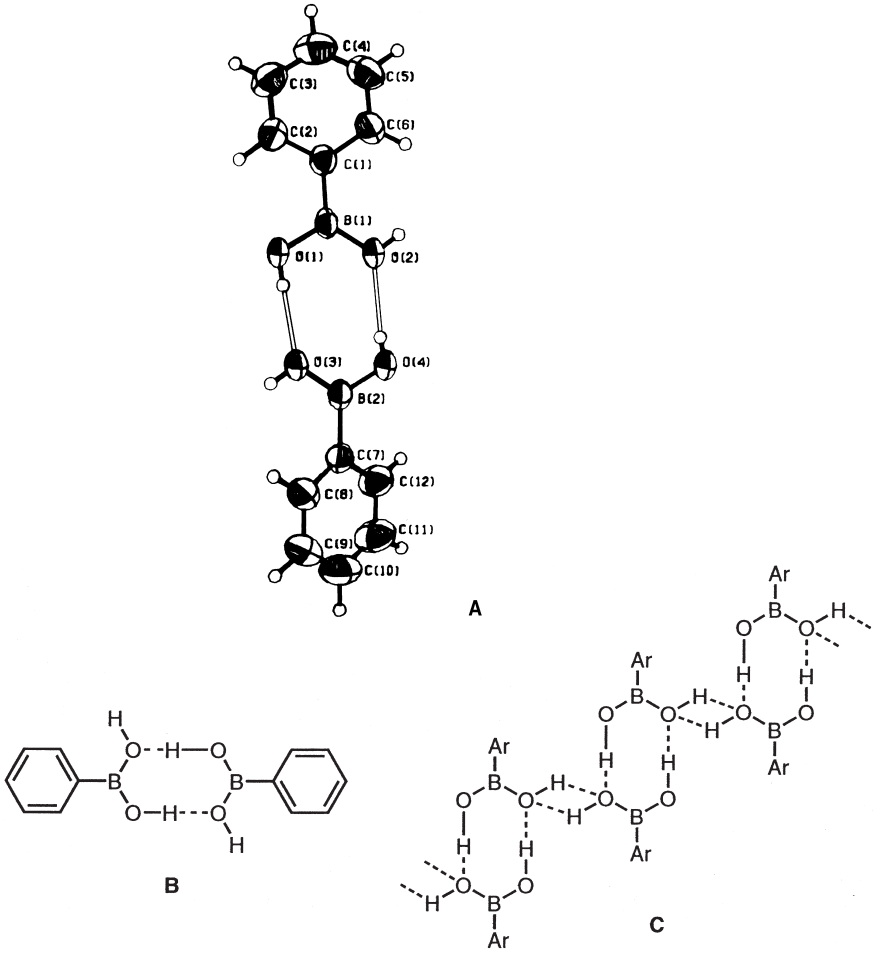


Figure 1.3 Representations of the X-ray crystallographic structure of phenylboronic acid. (A) ORTEP view of a dimeric unit. (B) Dimeric unit showing hydrogen bonds. (C) Extended hydrogen-bonded network.

al behavior of phenylboronic acid and its propensity to form hydrogen-bonded dimers, Wuest and co-workers recently reported the design of new diamond-like porous solids from the crystallization of tetrahedral-shaped tetraboronic acid **6** (Figure 1.2) [14]. Recently, phenyl- and *p*-methoxyphenyl boronic acids were found to co-crystallize with 4,4′-bipyridine into similar supramolecular assemblies involving hydrogen bonds between $B(OH)_2$ groups and the bipyridine nitrogens [15]. With a range of approximately 1.55–1.59 Å, the C–B bond of boronic acids and esters is slightly longer than typical C–C single bonds (Table 1.1). The average C–B bond energy is also slightly less than that of C–C bonds (323 vs. 358 kJ mol^{-1}) [16]. Consistent with strong B–O bonds, the B–O distances of tricoordinate boronic acids such as

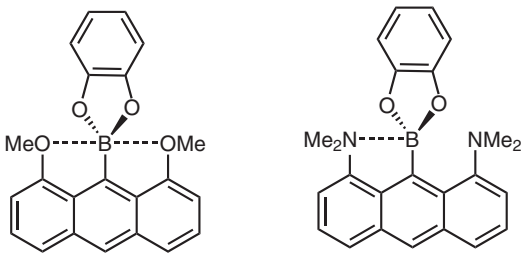
phenylboronic acid are fairly short, and lie in the range 1.35–1.38 Å (Table 1.1). These values are slightly larger than those observed in boronic esters. For example, the B–O bond distances found in the X-ray crystallographic structures of trityloxymethyl pinacolate boronic esters (e.g., **7** in Figure 1.2) are in the range 1.31–1.35 Å (Table 1.1), and the dioxaborolane unit of these derivatives is nearly planar [17]. The X-ray crystallographic structure of cyclic hemiester **8** (Figure 1.2) has been described [18]. Like phenylboronic acid, this compound also crystallizes as a hydrogen-bonded dimer; however, without the extended network because of the absence of a second hydroxyl group. The cyclic nature of this derivative induces a slight deviation from planarity for the tricoordinate boronate unit, as well as a distortion of the bond angles. The endocyclic B–O bond in **8** is slightly longer than the B–OH bond. This is attributed to the geometrical constraints of the ring, which prevents effective lone pair conjugation between the endocyclic oxygen and the vacant orbital of boron.

To complete boron's octet, boronic acids and their esters may also coordinate basic molecules and exist as stable tetracoordinated adducts. For example, the X-ray crystallographic structure of the diethanolamine adduct of phenylboronic acid (**9**, Figure 1.2), which was also reported by Rettig and Trotter [19], confirmed the transannular B–N bridge long suspected from other spectroscopic evidence such as NMR [20, 21]. This dative B–N bond is 1.67 Å long (Table 1.1). This interaction induces a strong $N^{\delta+}$–$B^{\delta-}$ dipole that points away from the plane of the aryl ring – an effect that was elegantly exploited in the design of a diboronate paraquat receptor [22]. When tetracoordinated, such as in structures **9** or **10** [23] (Figure 1.2), the B–O bond of boronic esters increases to about 1.43–1.47 Å, which is as much as 0.10 Å longer than the corresponding bonds in tricoordinate analogues (Table 1.1). These markedly longer B–O bonds are comparable to normal C–O ether linkages (~1.43 Å). These comparisons emphasize the considerable strength of B–O bonds in trigonal boronic acid derivatives. This bond strength originates from conjugation between the lone pairs on the oxygens and boron's vacant orbital, which confers partial double bond character to the B–O linkage. It was estimated that formation of tetrahedral adducts (e.g., with NH_3) may result in a loss of as much as 50 kJ mol^{-1} of B–O bond energy compared to the tricoordinate boronate [24]. Not surprisingly, trigonal B–O bonds are much stronger than the average C–O bonds of ethers (519 vs. 384 kJ mol^{-1}) [16].

Table 1.1 Bond distances from X-ray crystallographic data for selected boronic acid derivatives (Figure 1.2).

Compound	B–C (Å)	B–O^1 (Å)	B–O^2 (Å)	B–X (Å)	Reference
1	1.568	1.378	1.362	–	10
2	1.556	–	–	–	11
3	1.588	1.365	1.346	–	12
4	1.573	1.363	1.357	–	13
5	1.573	1.362	1.352	–	13
7	1.560	1.316	1.314	–	17
8	1.494	1.408	1.372	–	18
9	1.613	1.474	1.460	1.666	19
10	1.613	1.438	1.431	1.641	23

In rare instances where geometrical factors allow it, boronic acid derivatives may become hypervalent. For example, catechol ester **11** (Figure 1.4) was found by X-ray crystallographic analysis to be pentacoordinated in a highly symmetrical fashion as a result of the rigidly held ether groups, which are perfectly positioned to each donate lone pair electrons to both lobes of the vacant p orbital of boron [25]. The boronyl group of this two-electron three-atom center is planar, in a sp^2 hybridization state, and the resulting structure has a slightly distorted trigonal bipyramidal geometry. The corresponding diamine **12**, however, behaved quite differently and demonstrated coordination with only one of the two NMe_2 groups [26].



11 **12**

Figure 1.4 Model compounds for boronate hypercoordination.

Due to electronegativity differences (B = 2.05, C = 2.55) and notwithstanding the electronic deficiency of boron, which is mitigated by the two electron-donating oxygen atoms (vide supra), the inductive effect of a boronate group should be that of a weak electron-donor. The ^{13}C NMR alpha effect of a boronate group is very small [27]. Conversely, the deficient valency of boron and its relatively similar size to carbon has long raised the intriguing question of possible pi-conjugation between carbon and boron in aryl- and alkenylboronic acids and esters [28]. NMR data and other evidence like UV and photoelectron spectroscopy, and LCAO-MO calculations, suggest that B–C conjugation occurs to a modest extent in alkenylboranes [29–31], and is probably minimal for the considerably less acidic boronate derivatives. A thorough comparative study of ^{13}C NMR shift effects, in particular the deshielding of the beta-carbon, concluded to a certain degree of mesomeric pi-bonding for boranes and catecholboronates [27]. For example, compared to analogous aliphatic boronates, the beta-carbons of a dialkyl alkenylboronate and the corresponding catechol ester are deshielded by 8.6 and 18.1 ppm respectively. In all cases, the beta-carbon is more affected by the boronate substituent than the alpha-carbon, which is consistent with some contribution from the B–C π-bonding form (B) to give resonance hybrid C (Figure 1.5). X-Ray crystallography may also provide clues on the extent of B–C π-bonding. The B–C bond distances for arylboronic acids (Table 1.1) differ enough to suggest a small degree of B–C π-bonding. The B–C bond distance (1.588 Å) in the electron-poor boronic acid **3**, which is incapable of π-conjugation because its vacant p orbital is orthogonal to the π-system of the phenyl ring, is expectedly longer than that of phenyl-

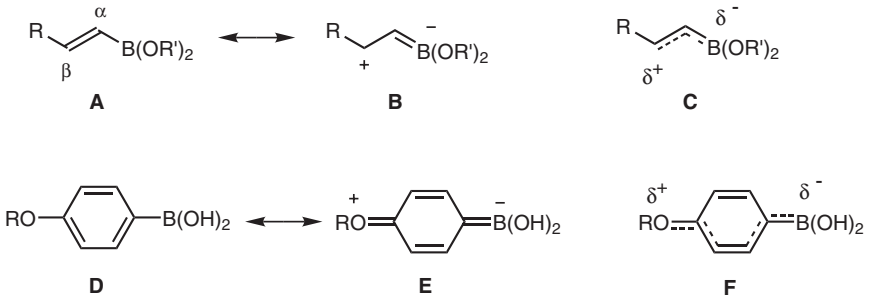


Figure 1.5 Limit mesomeric forms involving B–C π overlap.

boronic acid (1.568 Å). Interestingly, the B–C bond of **2** is 1.556 Å long, suggesting only a minimal contribution from the mesomeric form E (Figure 1.5).

Conversely, the B–C bond (1.613 Å) in the diethanolamine adduct **9** (Table 1.1), where the boron vacant orbital is also incapacitated from B–C overlap, is 0.045 Å longer than that of free phenylboronic acid (**1**). In so far as bond length data correlates with the degree of π-bonding [32], this comparison is consistent with a small B–C π-bonding effect in arylboronic acids and esters (i.e., hybrid form F in Figure 1.5). This view is further supported by chemical properties such as substituent effects on the acidity of arylboronic acids (Section 1.2.2.4.1) and ^{11}B chemical shifts correlations [33]. Likewise, B–C π-bonding in alkenylboronic acids and esters should be significant, but this effect must be weak compared to the electron-withdrawing effect of a carbonyl or a carboxyl group. For instance, alkenylboronic esters do not readily act as Michael acceptors with organometallic reagents in the same way as unsaturated carbonyl compounds [34]. Yet, the formal electron-withdrawing behavior of the boronate group seems undeniable, as shown by the reactivity of dibutylethylene boronate in cycloadditions with ethyldiazoacetate [35] and in Diels–Alder reactions where it provides cycloadducts with dienes like cyclopentadiene [36] and cyclohexadiene, albeit only at elevated temperatures (ca. 130 and 200 °C respectively) [37, 38]. The behavior of ethylene boronates as dienophiles has been rationalized by MO calculations [28], but their reactivity stands far from that of acrylates in the same reaction. In fact, more recent high level calculations suggest that the reactivity of alkenylboronates in Diels-Alder reactions may be due more to a three-atom-two-electron center stabilization of the transition state rather than a true LUMO-lowering electron-withdrawing mesomeric effect from the boronate substituent [39]. Further evidence for the rather weak electron-withdrawing character of boronic esters comes from their modest stabilizing effect in boronyl-substituted carbanions, where their effect has been compared to that of a phenyl group (Section 1.3.8.3).

1.2.2.2 **Physical Properties and Handling**

Most boronic acids exist as white crystalline solids that can be handled in air without special precautions. At ambient temperature, boronic acids are chemically stable and most display shelf-stability for long periods (Section 1.2.2.5). They do not tend to dis-

proportionate into their corresponding borinic acid and boric acid even at high temperatures. To minimize atmospheric oxidation and autoxidation, however, they should be stored under an inert atmosphere. When dehydrated, either with a water-trapping agent or through co-evaporation or high vacuum, boronic acids form cyclic and linear oligomeric anhydrides such as the trimeric boroxines (Figure 1.1). Fortunately, this is often inconsequential when boronic acids are employed as synthetic intermediates. Many of their most useful reactions (Section 1.5), including the Suzuki cross-coupling, proceed regardless of the hydrated state (i.e., free boronic acid or boronic anhydride). Anhydride formation, however, may complicate analysis and characterization efforts (Section 1.4.3). Furthermore, upon exposure to air, dry samples of boronic acids may be prone to decompose rapidly, and boronic anhydrides were proposed as initiators of the autoxidation process [40]. For this reason, it is often better to store boronic acids in a slightly moist state. Incidentally, commercial samples tend to contain a small percentage of water that helps in their long-term preservation. Due to their facile dehydration, boronic acids tend to provide somewhat unreliable melting points (Section 1.4.3.1). This inconvenience, and the other above-mentioned problems associated with anhydride formation, largely explain the popularity of boronic esters as surrogates of boronic acids (Section 1.2.3.2).

The Lewis acidity of boronic acids and the hydrogen bond donating capability of their hydroxyl groups combine to lend a polar character to most of these compounds. Although the polarity of the boronic acid head can be mitigated by a relatively hydrophobic tail as the boron substituent, most small boronic acids are amphiphilic. Phenylboronic acid, for instance, has a benzene–water partition ratio of 6 [41]. The partial solubility of many boronic acids in both neutral water and polar organic solvents often complicates isolation and purification efforts (Section 1.4).

1.2.2.3 **Safety Considerations**

As evidenced by their application in medicine (Chapter 13), most boronic acids present no particular toxicity compared to other organic compounds [42]. Small water-soluble boronic acids demonstrate low toxicity levels, and are excreted largely unchanged by the kidney [43]. Larger fat-soluble boronic acids are moderately toxic [43–45]. Boronic acids present no particular environmental threat, and the ultimate fate of all boronic acids in air and aqueous media is their slow oxidation into boric acid. The latter is a relatively innocuous compound, and may be toxic only under high daily doses [46]. A single acute ingestion of boric acid does not even pose a threatening poisoning effect in humans [47] unless it is accompanied by other health malfunctions such as dehydration [48].

1.2.2.4 **Acidic Character**

By virtue of their deficient valence, boronic acids possess a vacant p orbital. This characteristic confers them unique properties as mild organic Lewis acids that can coordinate basic molecules. By doing so, the resulting tetrahedral adducts acquire a carbon-like configuration. Thus, despite the presence of two hydroxyl groups, the acidic character of most boronic acids is not that of a Brønsted acid (i.e., oxyacid) (Equation 1, Figure 1.6), but usually that of a Lewis acid (Equation 2). When coordinated

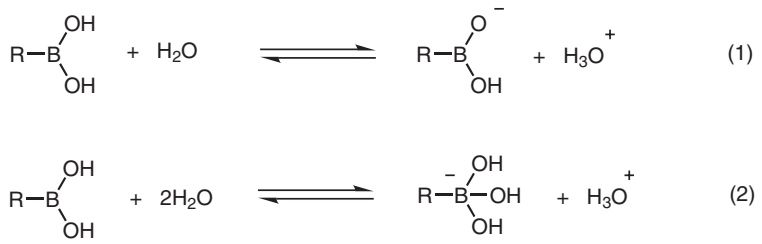


Figure 1.6 Ionization equilibrium of boronic acids in water.

with an anionic ligand, although the resulting negative charge is formally drawn on the boron atom, it is in fact spread out on the three heteroatoms.

1.2.2.4.1 Complexation Equilibrium in Water and Structure of the Boronate Anion

Although the acidic character of boronic acids in water had been known for several decades, the structure of the boronate ion (the conjugate base) was not elucidated until 1959. In their classical paper on polyol complexes of boronic acids [49], Lorand and Edwards demonstrated that the trivalent neutral form, likely hydrated, is in equilibrium with the anionic tetrahedral species (Equation 2, Figure 1.6), and not with the structurally related Brønsted base (i.e., the trivalent ion shown in Equation 1). It is this ability to ionize water and form hydronium ions by "indirect" proton transfer that characterizes the acidity of most boronic acids in water. Hence, the most acidic boronic acids possess the most electrophilic boron atom that can best form and stabilize a hydroxyboronate anion. The acidic character of boronic acids in water had been measured using electrochemical methods as early as the 1930s [50–52]. Phenylboronic acid, with a pK_a of 8.8 in water, is of comparable acidity to a phenol (Table 1.2). It is slightly more acidic than boric acid (pK_a 9.2). The pK_as of Table 1.2 show that the relative order of acidity for different types of boronic acids is aryl > alkyl. Bulky substituents proximal to the boronyl group were suggested to decrease the acid strength due to steric inhibition in the formation of the tetrahedral boronate ion. For example, ortho-tolylboronic acid is less acidic than its para isomer (pK_a 9.7 vs. 9.3, Table 1.2) [8]. This difference was explained in terms of F-strain in the resulting ion (Equation 3, Figure 1.7) [62], and this observation was taken as further evidence for the Lewis acidic behavior of boronic acids. As expected, electron-withdrawing substituents on the aryl group of arylboronic acids increase the acid strength by a fairly significant measure [50, 52, 55, 63]. For example, the highly electron-poor 3-methoxycarbonyl-5-nitrophenyl boronic acid (**13**) was attributed a pK_a of 6.9 [58]. Exceptionally, the ortho-substituted nitrobenzeneboronic acid [57] is much less acidic than its para isomer [55] (pK_a 9.2 vs. 7.1, Table 1.2), presumably due to internal coordination of one of the nitro oxygens [52]. One of the most acidic of known boronic acids, with a pK_a of ca. 4.0, is 3-pyridylboronic acid (**14**), which exists mainly as a zwitterion in water (Equation 4, Figure 1.7) [59]. Similarly, benzeneboronic acids of type **15** (Equation 5), which benefit from anchimeric participation of the ortho-dialkylaminomethyl group, display a relatively low pK_a of about 5.2 [61]. In this case, the actual first pK_a is that of ammo-

Table 1.2 Ionization constant (pK_a) for selected boronic acids.

Boronic acid, $RB(OH)_2$	pK_a	Reference
Boric acid, $B(OH)_3$	9.0	53
Methyl	10.4	53
Phenyl	8.9	54
3,5-Dichlorophenyl	7.4	54
3,5-bis(Trifluoromethyl)phenyl	7.2	54
3-Methoxyphenyl	8.7	54
4-Methoxyphenyl	9.3	55
4-Carboxyphenyl	8.4	56
2-Nitrophenyl	9.2	57
4-Nitrophenyl	7.1	55
4-Bromophenyl	8.6	54
4-Fluorophenyl	9.1	54
2-Methylphenyl	9.7	8
3-Methylphenyl	9.0	8
4-Methylphenyl	9.3	8
3,5-Dimethylphenyl	9.1	54
3-Methoxycarbonyl-5-nitrophenyl (**13**)	6.9	58
3-Pyridyl (**14**)	4.0, 8.2	59
8-Quinolinyl	4.0, 10	60
2-($R^1R^2NCH_2$)phenyl (e.g., **15**)	5.2–5.8	61

nium ion deprotonation and formation of the tetrahedral B–N ate adduct **15**. Application of boronic acids of type **15** in the aqueous recognition of saccharides is discussed in Chapter 12.

Boronic acids display Brønsted acidity (cf. Equation 1, Figure 1.6) only in exceptional cases where the formation of a tetrahedral boronate adduct is highly unfavorable. For example, coordination of hydroxide ion to boron in heterocyclic boronic acid derivative **16**, to form **17B**, would break the partial aromatic character of the central ring (Equation 6, Figure 1.7). Indeed, based on ^{11}B NMR and UV spectroscopic evidence, it was suggested that **16** acts as a Brønsted acid in water and forms conjugate base **17A** through direct proton transfer [64]. A few other boronic acids are suspected of behaving as Brønsted acids for the same reasons [65].

1.2.2.4.2 Bimolecular Lewis Acid–Base Complexation under Non-aqueous Conditions

As evidenced by the high pH required in the formation of boronate anions, boronic acids and most dialkyl esters are weak Lewis acids. This behavior contrasts sharply with trialkylboranes, which form strong adducts with phosphines, amines, and other Lewis bases [66]. Aside from the formation of boronate anions, discussed in the previous section, very few stable intermolecular acid–base adducts of boronic acids (esters) exist. Long ago, aliphatic amines and pyridine were found to form complexes in a 1:3 amine:boronic acid stoichiometry [67]. Combustion analyses of these air-stable solids suggested that two molecules of water are lost in the process, which led the authors to propose structure **18** (Equation 7, Figure 1.8). Subsequently, Snyder

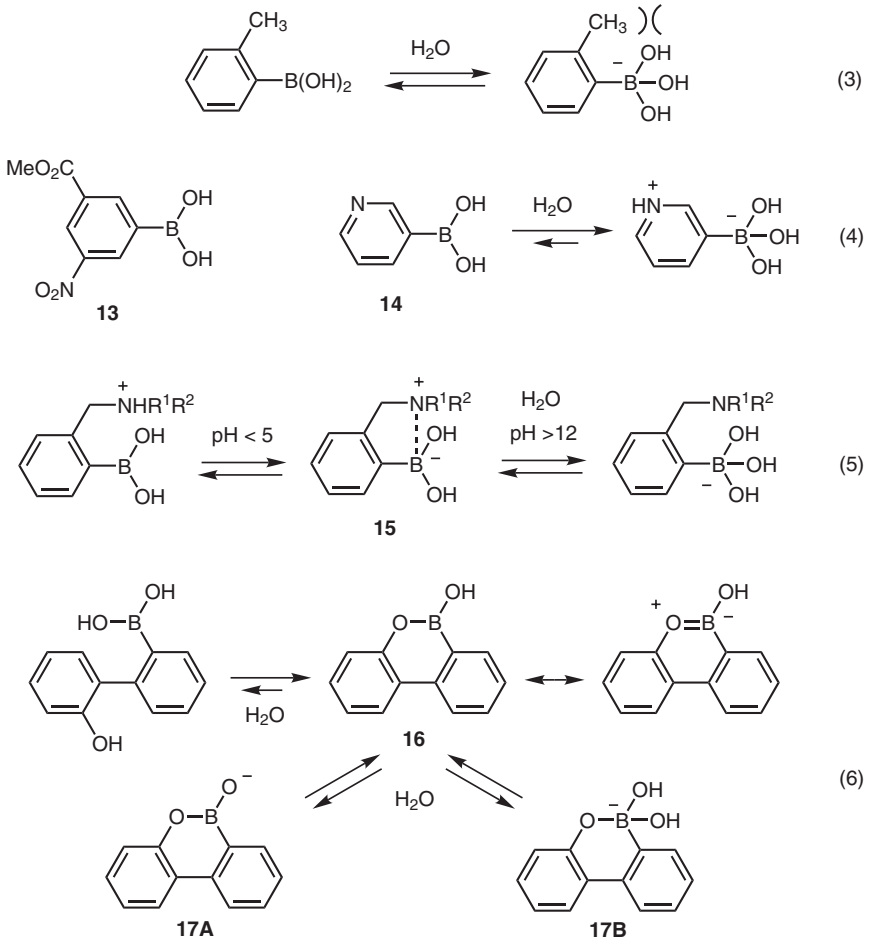
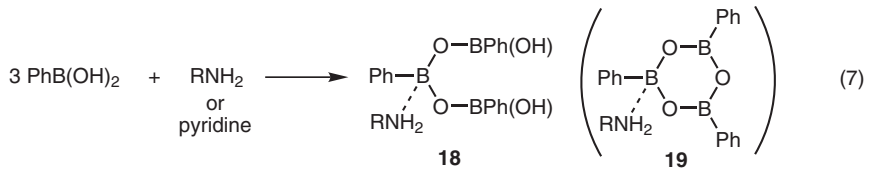


Figure 1.7 Ionization equilibrium for special types of boronic acids.

and co-workers used IR spectroscopy to demonstrate that these 1:3 complexes involved, instead, the fully dehydrated boroxine (**19**) [68]. These complexes are analogous to the diethanolamine boronates discussed in Section 1.2.2.1, although in the latter case the transannular nature of the B–N coordination bond is a highly favorable factor. Catechol boronates are more Lewis acidic and, provided cooperative effects are exploited, bimolecular complexes with fluoride anions and amines have been reported. For example, NMR spectroscopic and X-ray crystallographic studies showed that catechol boronate-containing crown ether **21** forms a stable complex (**22**) with potassium fluoride (Figure 1.8) [69]. The B–F bond strength was thought to be a key factor as other halide salts do not form a similar complex. A synergetic effect from crown ether complexation of potassium also comes into play because the catechol ester of phenylboronic ester did not afford any adduct with KF. Indeed, X-ray structure analysis of complex **22** confirmed this assumption by showing that the potassium



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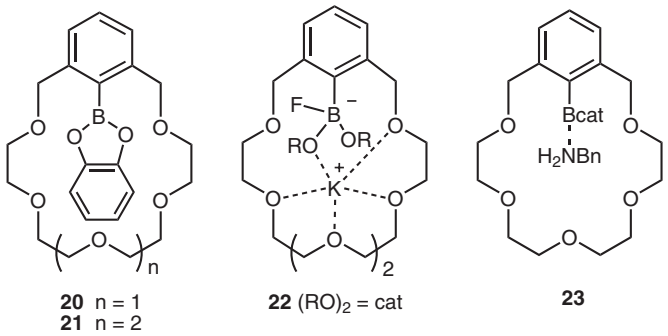
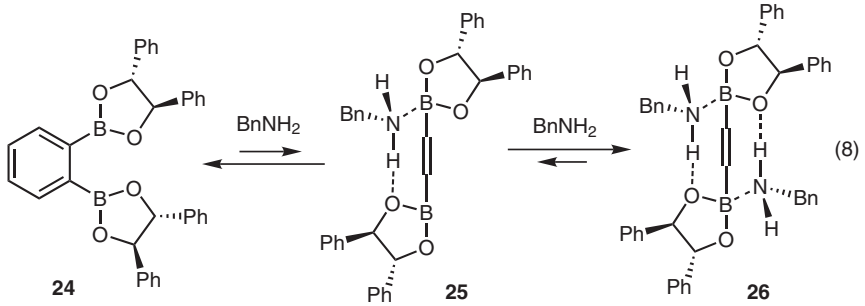




(8)

Figure 1.8 Bimolecular Lewis acid–base complexes with boronic esters. cat = catecholato

cation coordinates to five of the six ring oxygens and, interestingly, to one of the boronate oxygens (Figure 1.8). Using the same concept and a similar host, **20**, the primary amine benzylamine bound selectively in a 1:1 fashion to give B–N adduct **23** using the synergy of hydrogen bonds with the ether oxygens [70]. A borylated lyxofuranoside receptor displayed similar behavior [71]. As suggested by ^{1}H NMR spectroscopic studies, an *ortho*-phenyldiboronic ester (**24**) showed cooperative binding of two amine molecules in putative complex **26** (Equation 8, Figure 1.8) [72]. Other diboronate receptors bind to diamines selectively using the two boron centers for B–N coordination [73–75].

1.2.2.5 **Chemical Stability**

1.2.2.5.1 Ligand Exchange and Disproportionation

Several favorable factors contribute to the stability of boronic acids and their esters. Substitution of the carbon-containing group of boronic acids with other substituents is a slow process, and B–C/B–O bond metatheses to give the corresponding disproportionation products (trialkylborane, borinic acid or boric acid) is thermodynamically unfavored [24]. Similarly, thermodynamic considerations make the exchange of the hydroxyl substituents of boronic acids with other ligands quite unfavorable. Substitution with alcohols or diols to form boronic esters usually requires dehydration techniques to drive the reaction forward (Section 1.2.3.2.1). In general, from the B–X bond energies of all possible boronic acid derivatives (RBX_2), free boronic acids remain unchanged when dissolved in solutions containing other potential anionic ligands [24]. The only type of B–X bond stronger than a B–O bond is the B–F bond. Chemical methods to accomplish this type of exchange and other B–O bond derivatizations are described in Sections 1.2.3.6 and 1.2.3.7.

1.2.2.5.2 Atmospheric Oxidation

A significant thermodynamic drive for C–B bond oxidation comes as a direct consequence of the huge difference between B–O and B–C bond energies (Section 1.2.2.1). Heats of reaction for the oxidative cleavage of methylboronic acid with water and hydrogen peroxide are –112 and –345 kJ mol^{-1}, respectively [24]. Yet, fortunately for synthetic chemists, oxidative cleavage of the B–C bond of boronic acid derivatives with water or oxygen is a kinetically slow process, and most boronic acids can be manipulated in air and are stable in water over a wide pH range. This is particularly true for aryl- and alkenylboronic acids, and, in general, samples of all types of boronic acids tend to be significantly more stable when moist (Section 1.2.2.2) [40, 76, 77]. Presumably, coordination of water or hydroxide ions to boron protects boronic acids from the action of oxygen [40, 77]. Exceptionally, the highly electron-poor arylboronic acid 4-carboxy-2-nitrophenylboronic acid (**13**) was reported to undergo slow oxidation to the corresponding phenol when left in aqueous basic solutions (pH 9) [12]. Conversely, basic aqueous solutions of alkylboronate ions were claimed to be highly tolerant of air oxidation [40]. Free alkylboronic acids, however, are quite prone to slow atmospheric oxidation and variable amounts of the corresponding alcohols may form readily when dried samples are left under ambient air with no precautions. Likewise, solutions of arylboronic acids in tetrahydrofuran devoid of stabilizer may turn rapidly into the corresponding phenols. The propensity of alkylboronic acids to undergo autoxidation depends on the degree of substitution, with primary alkyl substituents being less reactive than secondary and tertiary alkyl substituents [76]. More potent oxidants such as peroxides readily oxidize all types of boronic acids and their corresponding esters (Section 1.5.2.1). Hence, this ease of oxidation must be kept in mind when handling boronic acids.

1.2.2.5.3 Protolytic Deboronation

Most types of boronic acids are highly resistant to protolysis of the C–B bond in neutral aqueous solutions, even at high temperatures. For example, *p*-tolylboronic acid was recovered unchanged after 28 hours in boiling water, but it was completely deboronated to toluene after 6 hours under pressure at 130–150 °C [78]. On the other hand, arylboronic acids can be quite readily deboronated in highly acidic or basic aqueous solutions [79]. In particular, ortho-substituted and especially electron-poor arylboronic acids are notorious for their propensity to protodeboronate under basic aqueous conditions – a process that can be exacerbated by exposure to light [59]. Consequently, competitive deboronation may plague some reactions of boronic acids like the Suzuki cross-coupling reaction (Section 1.5.3.1), which is often carried out under basic aqueous conditions. Under strongly acidic aqueous conditions, however, the more electron-rich arylboronic acids deboronate faster [80]. For example, *p*-carboxyphenylboronic acid is more tolerant than phenylboronic acid to the highly acidic conditions of ring nitration under fuming nitric acid and concentrated sulfuric acid [81]. Kuivila and co-workers [81, 82] have studies the effect of acid, temperature, and ring substitution of arylboronic acids on the kinetics of electrophilic protolytic deboronation with strong aqueous acid. A relatively complex behavior was found, and at least two possible pH-dependant mechanisms were proposed. In contrast to their behavior with aqueous acids, most arylboronic acids and esters appear to be very resistant to non-aqueous acids, as evidenced by their recovery from reaction processes using strong organic acids. For example, a phenolic methoxymethyl ether was deprotected with a 2:1 CH_2Cl_2–CF_3CO_2H mixture that left intact a pinacol boronic ester functionality [83]. Exceptionally, one report emphasized that arylboronic acids can be protodeboronated thermally by prolonged heating in refluxing ethereal solvents [84].

In contrast to arylboronic acids, early reports document the great stability of alkylboronic acids under aqueous acidic solutions. For example, various simple alkylboronic acids were unaffected by prolonged heating in 40% aqueous HBr or HI [40]. Like arylboronic acids, however, deboronation is observed in hot basic aqueous solutions [76]. Alkenylboronic esters undergo protonolysis in refluxing AcOH [85], and alkynylboronic acids were reported to be quite unstable in basic aqueous solutions (Section 1.3.5).

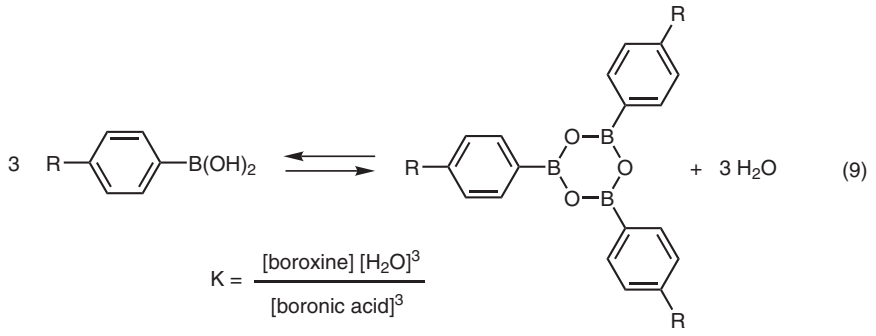
All types of boronic acids can be protodeboronated by means of metal-promoted C–B bond cleavage, and these methods are described separately in Section 1.5.1.

1.2.3
Boronic Acid Derivatives

For convenience in their purification and characterization, boronic acids are often best handled as ester derivatives, in which the two hydroxyl groups are masked. Likewise, transformation of the hydroxyl groups into other substituents such as halides may also provide the increased reactivity necessary for several synthetic applications. The next sections describe the most popular classes of boronic acid derivatives.

1.2.3.1 **Boroxines**

Boroxines are the cyclotrimeric anhydrides of boronic acids. They are isoelectronic to benzene and, by virtue of the vacant orbital on boron, may possess partial aromatic character. Several theoretical and experimental studies have addressed the nature and structure of these derivatives [86–91]; in particular, X-ray crystallographic analysis of triphenylboroxine confirmed that it is virtually flat [90]. Boroxines are easily produced by the simple dehydration of boronic acids, either thermally through azeotropic removal of water or by exhaustive drying over sulfuric acid or phosphorus pentoxide [40]. These compounds can be employed invariably as substrates in many of the same synthetic transformations known to affect boronic acids, but they are rarely sought as synthetic products. In one rare example of application, the formation of boroxine cross-linkages has been employed to immobilize blue-light emitting oligofluorene diboronic acids [92]. Samples of boroxines may also contain oligomeric acyclic analogues, and they are sensitive to autoxidation when dried exhaustively (Sections 1.2.2.2 and 1.2.2.5.2). A recent study examined the thermodynamic parameters of boroxine formation in water (Equation 9) [93]. Using ^{1}H NMR spectroscopy, the reaction was found to be reversible at room temperature, and the equilibrium constants, relatively small ones, were subject to substituent effects. For example, boroxines with a para electron-withdrawing group have smaller equilibrium constants. This observation was interpreted as an outcome of a back reaction (i.e., boroxine hydrolysis) facilitated by the increased electrophilicity of boron. Steric effects also come into play, as indicated by a smaller *K* for *ortho*-tolylboronic acid than for the para isomer. Variable temperature studies provided useful thermodynamic information, which was consistent with a significant entropic drive for boroxine formation due to the release of three molecules of water.



1.2.3.2 **Boronic Esters**

By analogy with carboxylic acids, replacement of the hydroxyl groups of boronic acids by alkoxy or aryloxy groups provides esters. By losing the hydrogen bond donor capability of the hydroxyl groups, boronic esters are less polar and easier to handle. They also serve as protecting groups to mitigate the particular reactivity of boron–carbon bonds. Most boronic esters with a low molecular weight are liquid at room temperature and can be conveniently purified by distillation. Exceptionally, the trity-

loxymethyl esters described above (**7**, Figure 1.2) are crystalline solids [17]. Figure 1.9 shows a selection of the most commonly encountered boronic esters, many of which are chiral and have also been used as inducers in stereoselective reactions (Chapters 6 and 8). Several macrocyclic oligomeric esters have also been described [94].

1.2.3.2.1 Stoichiometric Formation

The synthesis of boronic esters from boronic acids and alcohols or diols is straightforward (Equation 10, Figure 1.9). The overall process is an equilibrium, and the forward reaction is favored when the boronate product is insoluble in the reaction solvent. Otherwise, ester formation can be driven by azeotropic distillation of the water produced using a Dean-Stark apparatus, or, alternatively, with the use of a dehydrating agent (e.g., $MgSO_4$, molecular sieves). Boronic esters can also be made by transesterification of smaller dialkyl esters like the diisopropyl boronates, with distillation of the volatile alcohol by-product driving the exchange process. For cyclic esters made from the more air-sensitive alkylboronic acids, an alternate method involves treatment of a diol with lithium trialkylborohydrides [95]. Likewise, cyclic ethylboronates have been prepared by reaction of polyols with triethylborane at elevated temperatures [96]. One of the first reports on the formation of boronic esters from diols and

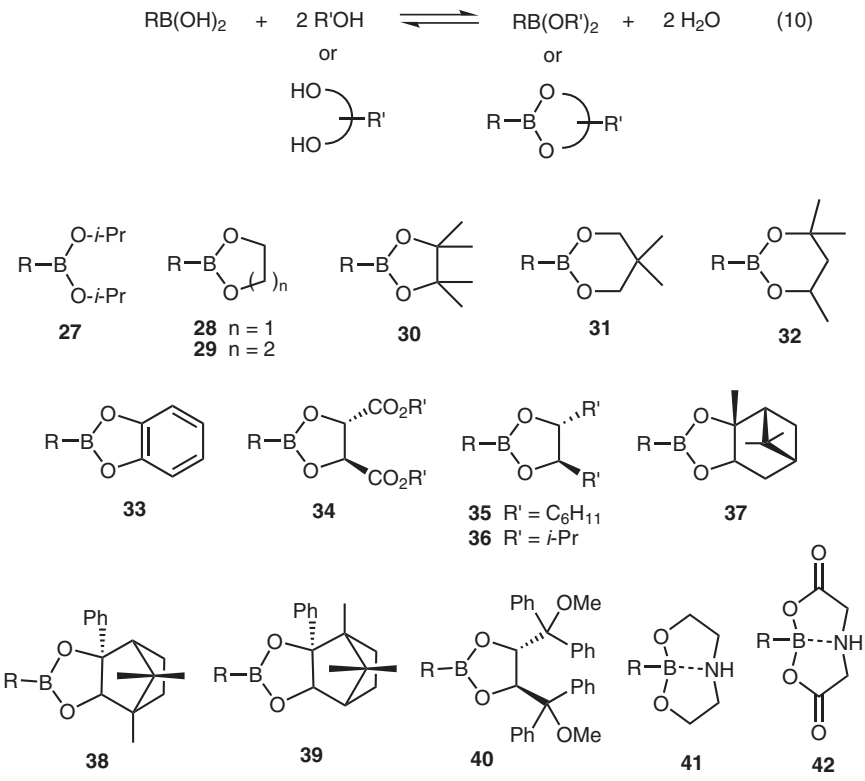


Figure 1.9 Common boronic esters.

polyols, by Kuivila and co-workers, described the preparation of several esters of phenylboronic acid by reaction of the latter, in warm water, with sugars like mannitol and sorbitol, and 1,2-diols like catechol and pinacol [97]. The desired non-polar boronic esters precipitated upon cooling the solution. Interestingly, *cis*-1,2-cyclohexanediol failed to provide the corresponding cyclic ester and the authors rationalized this observation on the basis of the unfavorable geometry of the diol substrate. Thus, whereas the two diols are not oriented in the same plane in the chair conformation (Equation 11, Figure 1.10), they can adopt such a favorable orientation only in the boat conformer, which is thermodynamically unfavorable [97].

Under anhydrous conditions (i.e., refluxing acetone), phenylboronic esters of *cis*-1,2-cyclopentanediol and *cis*-1,2-cyclohexanediol can be isolated [98]. The trans isomers, however, still fail to give a 1:1 adduct, and, based on elemental analysis and molecular weight determinations, give, rather, 1:2 adducts such as **43** (Equation 12). This observation was also explained in terms of the large energy required for the trans-diol to adopt a coplanar orientation, which would increase ring strain and steric interactions between axial atoms. Recently, the marked preference for the formation of boronic esters with cis-diols was exploited in the concept of dynamic combinatorial chemistry. In this study, phenylboronic acid was used as a selector to amplify and accumulate one out of nine possible dibenzoate isomers of *chiro*-inositol that exist under equilibrating conditions through base-promoted intramolecular acyl migration (Equation 13) [99]. Diethanolamine boronic esters (**41**, Figure 1.9) represent a useful class of boronic acid derivatives [100]. Other N-substituted derivatives were also characterized [101]. The internal coordination between the nitrogen lone pair and boron's

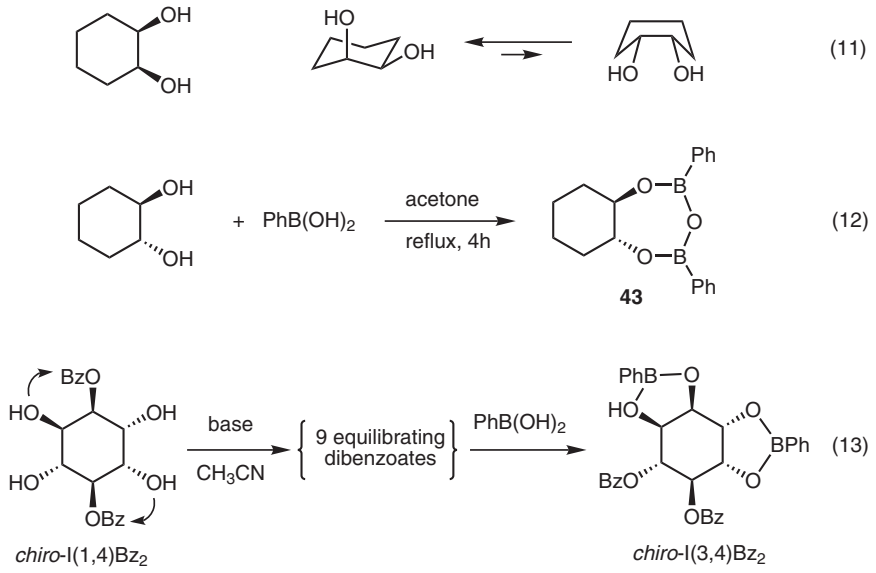


Figure 1.10 Specific examples of boronic ester formation with cyclic diols.

vacant orbital constitutes a rather unique structural characteristic of these tetrahedral derivatives. This coordination makes the hydrolysis reaction less favorable, and even stabilizes the boron atom against atmospheric oxidation. Analogous iminodiacetic acid derivatives (**42**) are even more robust (B–N $\Delta G^{\neq} > 90$ vs. 60 kJ mol^{-1} for **41**) [21]. Compared to the alkoxy groups of **41**, the electronic effect of the carboxyl groups leads to a more acidic boron atom, and hence a stronger B–N interaction. Diethanolamine boronic esters can be conveniently formed in high yields, often without any need for dehydration techniques, as they tend to crystallize out of solution. Indeed, diethanolamine adducts are solids, often crystalline, with sharp melting points, and can thus be used for purifying and characterizing boronic acids. The concept of internal coordination in diethanolamine esters has been exploited in the development of the DEAM-PS resin for immobilization and derivatization of boronic acids (Section 1.4.2.1).

1.2.3.2.2 Hydrolysis and Cleavage

Thermodynamically, the stability of B–O bonds in boronic acids and their ester derivatives is comparable (Section 1.2.2.1). Consequently, hydrolysis, in bulk water or even by simple exposure to atmospheric moisture, is a threatening process while handling boronic esters that are kinetically vulnerable to attack of water. In fact, hydrolysis is very rapid for all acyclic boronic esters such as **27** (Figure 1.9), and for small unhindered cyclic ones like those made from ethylene or propylene glycol (**28** and **29**), and tartrate derivatives (**34**) [102]. Catechol esters (**33**) are another class of popular derivatives as they are the direct products of hydroboration reactions with catecholborane (Section 1.3.4.4). Due to the opposing conjugation between the phenolic oxygens and the benzene ring, these derivatives are more Lewis acidic and are quite sensitive to hydrolysis. In the hydrolytic cleavage of catechol boronic esters from hydroborations, it is often necessary to carefully monitor the pH and buffer the acidity of the released catechol.

Conversely, hydrolysis can be slowed considerably for hindered cyclic aliphatic esters such as the C2-symmetrical derivatives **35** [103] and **36** [104], pinacol (**30**) [97], pinanediol (**37**) [105], Hoffmann's camphor-derived diols (**38** and **39**) [106], and the newer one **40** [107]. Indeed, many of these boronic esters tend to be stable to aqueous workups and silica gel chromatography. The robustness of the esters of *trans*-1,4-dimethoxy-1,1,4,4-tetraphenyl-2,3-butanediol (**40**) was demonstrated in its applications as a protecting group for alkenylboronic acids [107]. The resulting alkenylboronic esters are tolerant to a wide variety of reaction conditions (Section 1.3.8.5). Unfortunately, the bulky boronic esters **37**–**40** are very robust to hydrolysis, and their conversion back into boronic acids is notoriously difficult. Removal of the bulky pinanedioxy group in **37** exemplifies the magnitude of this particular problem. It is generally not possible to cleave a pinanediol ester quantitatively in water even under extreme pH conditions. Cleavage can be achieved by transborylation with boron trichloride [23, 108–112], which destroys the pinanediol unit, or by reduction to the corresponding borane using lithium aluminum hydride [113] (Equations 14 and 15, Figure 1.11). Both derivatives can be subsequently hydrolyzed to afford the desired boronic acid. Recently, a mild approach was developed to convert the robust DICHED

and pinanediol esters into trifluoroborate salts [114]. A two-phase transesterification procedure with phenylboronic acid has been described, but it is applicable only to small, water-soluble boronic acids [115]. Many of these procedures, such as the BCl_3-promoted method, were applied to the particular case of pinanediol esters of α-acylaminoalkylboronic acids [23, 112]. Using such a substrate, **44**, an oxidative method allowed the recovery of free boronic acid **45** in good yield from a destructive periodate cleavage, or by using the biphasic transesterification method in hexanes–water (pH 3) (Equations 16 and 17, respectively, Figure 1.11) [116].

Hydrolysis of a series of 5-, 6-, and 7-membered phenylboronic esters was studied by measuring the weight increase of samples subjected to air saturated with water vapor (i.e., under neutral conditions) [117]. Hydrolysis was confirmed by the observation of phenylboronic acid deposits. This early study confirmed that hindered esters such as phenylboron pinacolate hydrolyze at a much slower rate, and that 6-membered boronates are more resistant to hydrolysis than the corresponding 5-membered analogues. These results were interpreted in terms of the relative facility of boron–water complexation to form a tetracoordinate intermediate. Two factors were proposed: (1) the increase of steric effects on neighboring atoms upon formation of the hydrated complex and (2) the release of angle strain, which is optimal in the 5-membered boronates due to the decrease of the O–B–O and B–O–C bond angles

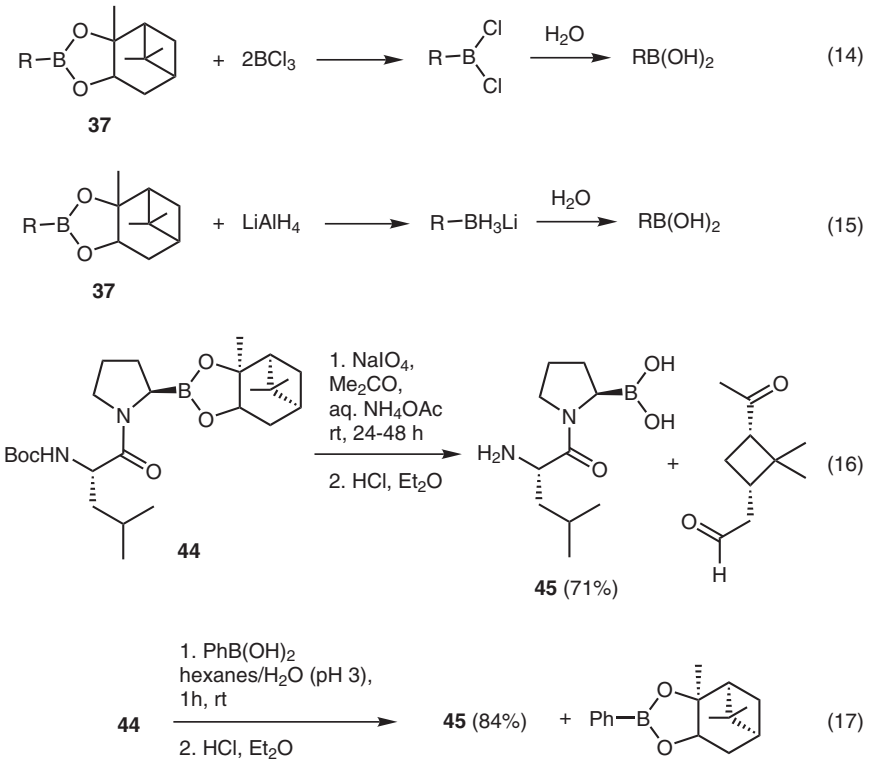
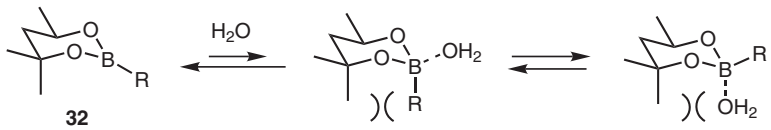


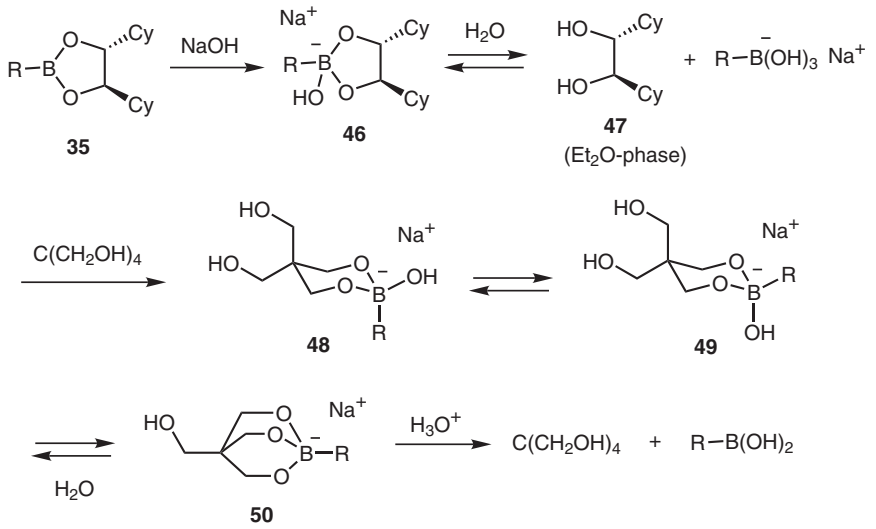
Figure 1.11 Cleavage of pinanediol boronic esters.

from ca. 120° to 109° upon going from a planar configuration to the tetracoordinate hydrated form with tetrahedral B and O atoms. Propanediol derivative **32** emphasizes the importance of steric hindrance to the coordination of water in order to minimize kinetic hydrolysis. Hydrolysis of **32** is slowed considerably compared to the unsubstituted 1,3-propanediol ester (**29**). The superior stability of esters **32** towards hydrolysis was attributed to the axial methyl groups, which develop a 1,3-diaxial interaction with the boron center in the approach of water from either face (Equation 18). Likewise, in contrast to the corresponding dimethyl ester, it was shown that atmospheric polymerization of 2-vinyl-4,4,6-trimethyl-1,3,2-dioxaborinane was largely prevented, presumably due to the hindered approach of oxygen to boron [118].



(18)

While developing a novel two-phase system for the basic hydrolysis of DICHED esters, **35**, Matteson has put forward a useful generalization on the process of thermodynamic hydrolysis of boronic esters (Scheme 1.1) [119]. Using a relatively dilute nonmiscible mixture of 1M aqueous sodium hydroxide and diethyl ether (conditions required to avoid precipitation of boronate salt **46**), an equilibrium ratio of 42:1 (**47** to **35**) in the ether phase was reached only after 18 hours even by using a large excess of sodium hydroxide with respect to the boronic ester **35**. By making use of soluble triols such as pentaerythritol to transesterify salt **46** into a more water-soluble salt (i.e., **48**/**49**/**50**), and thus facilitating the liberation of DICHED, a higher ratio of 242:1 was



Scheme 1.1 Hydrolysis of boronic esters by a two-phase system.

obtained. The free boronic acid could then be recovered by acidification of the aqueous phase containing a mixture of **48**–**50**, followed by extraction with ethyl acetate.

This new procedure, however, was not successful for the complete hydrolysis of pinanediol phenylboronic ester, providing an optimal pinanediol:boronic ester ratio of 3.5:1 in the ether phase. These results were interpreted in terms of the determining thermodynamic factors that control the reversible hydrolysis or transesterification of boronic esters. Entropic factors in the hydrolysis of cyclic esters are unfavorable as three molecules are converted into only two. In this view, transesterification with a diol, instead of hydrolysis, is overall even and thus more favorable. Other factors affecting the equilibrium are the effect of steric repulsions on enthalpy as well as the entropies of internal rotation of the free diols. trans-4,5-Disubstituted dioxaborolanes such as DICHED esters present minimal steric repulsions as the two cyclohexyl substituents eclipse C–H bonds. On the contrary, pinacol esters experience significant steric repulsion from the four eclipsing methyl groups. Consequently, it is not surprising that they can be transesterified easily with trans-DICHED [17, 120]. In this scenario, the exceptional resistance of pinanediol esters to thermodynamic hydrolysis would be due to the rigid cyclic arrangement whereby the two diols are preorganized in a coplanar fashion to form a boronic ester with essentially no loss of entropy from internal rotation of the free pinanediol. Other types of esters including DICHED [121] and the robust pinacol esters of peptidyl boronates [122] have also been converted into boronic acids through transesterification with diethanolamine in organic solvent, followed by acidic aqueous hydrolysis. This method, however, is effective only if the resulting diethanolamine ester crystallizes from the solution so as to drive the equilibrium forward. As stated above, transesterification of cyclic boronic esters with diols is often slow, and particularly so in organic solvents. Wulff and coworkers found that several boronic acids possessing proximal basic atoms or substituents (e.g. **15**, Figure 1.7) lead to an unusually large neighboring group effect, and the transesterification equilibria is reached much faster with these boronic esters as a result of a rapid proton transfer [123]. Boronic acids like **15** are internally coordinated (^{11}B NMR = 14.6 ppm), and beneficial neighboring effects in these *ortho*-aminomethylbenzeneboronic acids are at play in the aqueous binding of carbohydrates (Chapter 12).

1.2.3.2.3 Boronic Acid–Diol (Sugar) Equilibrium in Water

The reversible formation of boronic esters by the interaction of boronic acids and polyols in water was first examined in the seminal study of Lorand and Edwards [49]. This work followed an equally important study on the elucidation of the structure of the borate ion [124]. By measuring the complexation equilibrium between phenylboronic acid and several model diols and monosaccharides using the method of pH depression, ester formation was shown to be more favorable in solutions of high pH where the boronate ion exists in high concentrations (Equation 19, Figure 1.12). This study also confirmed the Lewis acid behavior of boronic acids and the tetracoordinate structure of their conjugate base, i.e., the hydroxyboronate anion (Section 1.2.2.4). Another conclusion is that free boronic acids have lower Lewis acid strengths than their neutral complexes with 1,2-diols. For example, the pK_a of PhB(OH)$_2$ decreases

from 8.8 to 6.8 and 4.5 upon formation of cyclic esters with glucose and fructose, respectively [125]. To explain the favorable thermodynamic effect seen at high pH (Equation 19) in comparison to neutral pH (Equation 20), it was hypothesized that the formation of hydroxyboronate complexes of 1,2-diols is accompanied by a significant release of angle strain, resulting from the rehybridization of boron from sp^2 to sp^3 (i.e., 120° vs. 109° bond angles) [49].

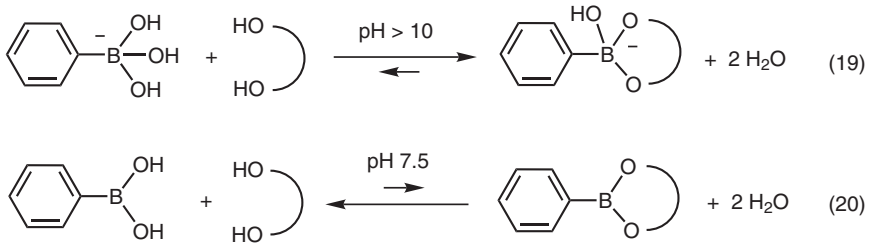


Figure 1.12 Equilibrium formation of boronic esters from diols at high (Equation 19) and neutral (Equation 20) pH in water.

Pizer and co-workers reported a series of investigations on the equilibria and mechanism of complexation between boric acid or boronic acids with polyols and other ligands in water. Early work by this group [53] and others [126] showed that the stability constants of complexes increase when the aryl substituent on the boronic acid is electron poor, which is consistent with the proposal of Lorand and Edwards that views formation of hydroxyboronate complexes as the drive for release of angle strain. Using methylboronic acid and simple 1,2- and 1,3-diols, equilibrium constants were measured both by pH titration and ^{11}B NMR spectroscopy [127]. Constants of 2.5, 5.5 and 38 were found for 1,3-propanediol, 1,2-ethanediol and 1,2,3-propanetriol respectively, with the latter binding preferentially with a 1,2-diol unit. Kinetic studies performed by the temperature-jump relaxation method revealed forward and reverse rate constants, and established that the lower stability constants of six-membered boronic esters compared to the five-membered ones is the result of a faster reverse reaction for the former [127]. Quite importantly, this work confirmed that the tetracoordinate hydroxyboronate anion is much more reactive than the trigonal neutral boronic acid in forming esters with diols (at least 10^4 times faster), with forward rate constants in the range 10^3–10^4 M^{-1} s^{-1}. It was suggested that the high reactivity of the boronate anion could be interpreted in terms of an associative transition state involving proton transfer and hydroxide displacement within a pentacoordinated boron. In the past decade, interest in the interaction between boronic acids and cis-diols has developed tremendously due to applications in the development of receptors and sensors for saccharides (Section 1.6.4 and Chapter 12). As with simple polyols discussed above, the binding of carbohydrates to boronic acids is subject to the same geometrical requirement for a coplanar diol unit. In fact, in water, boronic acid receptors bind to glucose in the furanose form, which presents a very favorable, coplanar 1,2-diol [128]. This observation concurs with the absence of complexation between boronic acids and non-reducing sugars (glycosides) and the low affinity of

1→4 linked oligosaccharides such as lactose [129, 130]. Fluorescent catechol derivatives such as the dye alizarin red S (ARS) also form covalent adducts with boronic acids in water, and this equilibrium has recently been used as a competitive color- and fluorescence-based assay for both qualitative and quantitative determination of saccharide binding [131]. Using the ingenious ARS assay, Springsteen and Wang presented an interesting cautionary tale from discrepancies found in the measurements of boronic acid–diol binding constants based on the above-mentioned method of pH depression. The latter method may not always reliably provide the true overall equilibrium constants. Indeed, these measurements are complicated by the multiple states of ionization of the boronic acid and the resulting ester (neutral trigonal or tetrahedral hydroxyboronate), the pronounced effect of the solvent, pH and buffer components, and the concentration of these species on the equilibrium [125].

1.2.3.3 **Dialkoxyboranes and other Heterocyclic Boranes**

Several cyclic dialkoxyboranes, such as 4,4,6-trimethyl-1,3,2-dioxaborinane **51** [132], 1,3,2-benzodioxaborole (catecholborane) **52** [133], pinacolborane **53** [134], have been described (Figure 1.13). Dialkoxyboranes can be synthesized simply by the reaction between equimolar amounts of borane and the corresponding diols. These borohydride reagents have been employed as hydroborating agents, in carbonyl reduction, and more recently as boronyl donors in cross-coupling reactions. Dialkoxyboranes have also been invoked as intermediates in the hydroboration of β,γ-unsaturated esters [135]. Sulfur-based heterocyclic boranes were reported, including 1,3,2-dithiaborolane **54** [136]. Acyloxyboranes such as Yamamoto's tartaric acid derived CAB catalyst (**55**) [137] and related oxazaborolidinones such as **56**, derived from N-sulfonylated amino acids, have been used as chiral promoters for cycloadditions and aldol reactions of silyl enol ethers [138]. Synthetic applications of these catalysts are described in detail in Chapter 10.

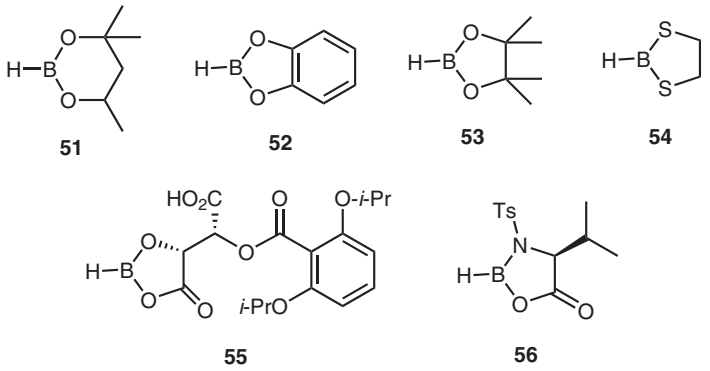
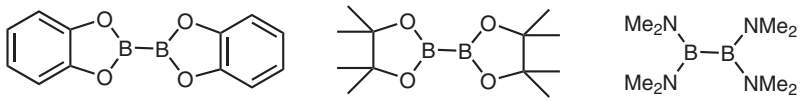


Figure 1.13 Common dialkoxyboranes and heterocyclic analogues.

1.2.3.4 Diboronyl Esters

Various synthetically useful diboronyl esters such as B_2cat_2 (**57**) or B_2pin_2 (**58**) have been described (Figure 1.14) [139]. These reagents are now commercially available, albeit their cost remains quite prohibitive for preparative applications. They can be accessed by condensation of a diol with the tetrakis(dimethylamino)diboron precursor (**59**), which is also commercially available and can be made in three steps from boron tribromide [140]. Recently, a shorter and more practical synthesis of B_2cat_2 was described [141]. The discovery that diboronyl compounds can be employed with transition metal catalysts in various efficient cross-coupling and addition reactions can be considered one of the most significant advances in boronic acid chemistry in the past decade. The chemistry of diboronyl compounds has been reviewed recently [139], and is discussed in several sections of this chapter and in Chapter 2.



57 **58** **59**

Figure 1.14 Common diboronyl reagents.

1.2.3.5 Azaborolidines and other Boron Heterocycles

Numerous heterocyclic derivatives of boronic acids have been described, and useful X-ray crystallographic data have been obtained for many of these compounds. Some representative examples are described in this section (Figure 1.15). Benzodiazaborole products (**60**) of 1,2-phenylenediamine and free boronic acids form readily in refluxing toluene [142, 143]. Both aliphatic and aromatic acids are applicable, and it was claimed that the resulting adducts are easier to recrystallize than diethanolamine boronates. An intramolecular adduct, **61**, was also reported [144]. These benzodiazaboroles are air-stable, and the adduct of phenylboronic acid hydrolyzes only slowly in aqueous solutions. With anhydrous hydrogen chloride in toluene, a dihydrochloride salt was formed. The unusual stability of adducts **60** was further supported by their formation by exchange of tartrate esters with 1,2-phenylenediamine at room temperature in benzene. Control studies showed that the equilibrium lies much towards the diazaborole, which is surprising in light of thermodynamic factors such as the much higher energy of covalent B–O bonds than B–N bonds (Section 1.2.2.1). As both ethylenediamine and aniline itself did not form similar covalent adducts under the same conditions, it was suggested that the favorable geometry of 1,2-phenylenediamine, as well as the stability of the resulting five-membered ring and its partial aromatic character, were responsible for the highly favorable formation of adducts **60** [142]. Diazaborolidines from aliphatic 1,2-diamines, however, are not prepared with such ease. For example, several chiral ones evaluated as chiral proton sources had to be prepared from dichloroboranes [145].

Amino acids can condense with boronic acids to form 1:1 chelates of type **62** [146]. The tetracoordinate structure of these adducts is very apparent by NMR due to the formation of a new stereocenter at boron. Interestingly, 4-boronophenylalanine (**63**),

a potential BNCT agent, was shown to dimerize to form head-to-tail paracyclophane derivative **64** in reversible fashion in DMSO (Equation 21, Figure 1.15) [147]. This dimer is prevalent at low concentrations (<50 mM), while oligomeric mixtures predominate at higher concentrations. Amino acid adducts of boronic acids are hydrolytically unstable, and **64** was indeed found to revert to free **63** upon addition of water to the solution. Purine analogue **65** also hydrolyzed readily in aqueous ethanolic solutions [148]. The addition product **66** between anthranilic acid and phenylboronic acid has been reported [149]. Salicylhydroxamic acid adducts of arylboronic acids are more resistant and were proposed as components of an affinity system for bioconjugation [150] (Section 1.6.8). Both B-alkyl and B-aryl oxazaborolidinones **67**, made from N-sulfonylated amino acids such as tryptophan, have been employed as chiral Lewis acids in several synthetic transformations (Chapter 10) [151], and in crystallization-induced asymmetric transformations [152]. Aminoalcohols can form oxazaborolidines by condensation with boronic acids under anhydrous conditions. Chiral oxazaborolidines derived from reduced amino acids (e.g., **68**) have been a popular class of Lewis acids for cycloadditions (Chapter 10) [153], and as catalysts and reagents for the enantioselective reduction of ketones and imine derivatives [154], which is described in detail in Chapter 11.

In addition to the benzoboroxole described in Section 1.2.2.1 (**8**, Figure 1.2) [18, 155, 156], there are several other examples of "internal" heterocyclic derivatives in which an ortho substituent of an arylboronic acid closes onto the boronic acid with either a dative or a covalent bond [157]. For example, *ortho*-anilide derivatives **69** and the corresponding ureas (**70**), in a putative internally chelated form A, were shown to

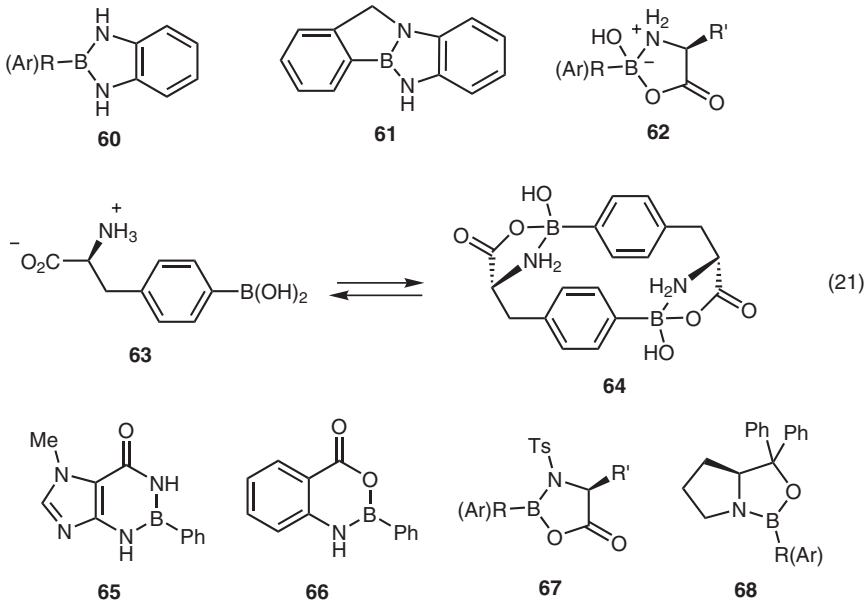
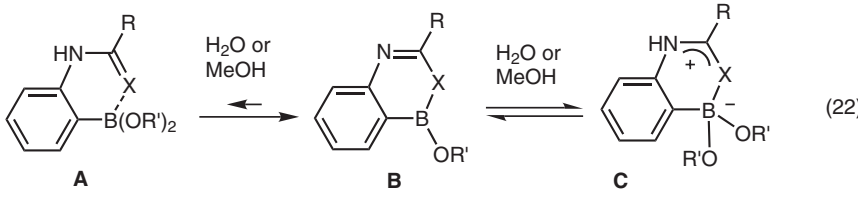


Figure 1.15 Examples of azaborolidines and other heterocyclic analogues.

exist mainly in their cyclic monodehydrated form B (Equation 22, Figure 1.16) [158]. This is probably true even in aqueous or alcohol solutions owing to the partial aromatic character of these boron-containing analogues of purine heterocycles. In fact, these compounds can even add one molecule of water or alcohol by 1,4-addition and thus exist in equilibrium with form C. One such derivative, **71**, was obtained from recrystallization in methanol, and X-ray crystallographic analysis proved its zwitterionic structure with a tetrahedral boronate anion. A class of related derivatives made from 2-formylphenylboronic acid and hydrazines was also characterized [157], and the boroxine of one internally chelated derivative, **72**, was studied by X-ray crystallography [159]. Other examples of heterocyclic derivatives include pyrimidine analogue **73** and cyclodimer **74** [160].



69 X = O,
70 X = NH, NR
R = H, NH_2, alkyl or aryl
R' = H , CH_3, or CMe_2CMe_2

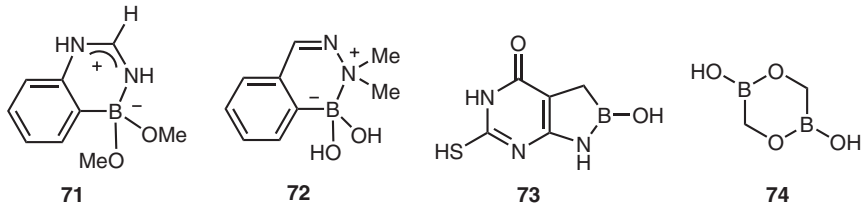


Figure 1.16 Hemi-heterocyclic "internal" boronic ester derivatives.

1.2.3.6 **Dihaloboranes and Monoalkylboranes**

Highly electrophilic dihaloboranes can undergo reactions that do not affect boronic acids and esters. For example, oxidative amination of the B–C bond of boronate derivatives requires the transformation of boronic esters into the corresponding dichlorides (Section 1.5.2.2). Of several methods described for the preparation of alkyl- and aryl-dichloroboranes, only a few conveniently employ boronic acids and esters as substrates. They can be accessed either by iron trichloride-catalyzed exchange of the boronic ester with BCl_3 (Equation 23, Figure 1.17) [161] or by treatment of the corresponding monoalkylborane with TMSCl [162] or acidification with anhydrous HCl in dimethyl sulfide (Equation 24) [163]. The requisite monoalkyl and monoaryl borohydride salts can be made by treating boronic esters with $LiAlH_4$ [164], and the use of HCl in dimethyl sulfide leads to the isolation of the stable $RBCl_2$-SMe_2 adducts (Equation 24) [163]. Both methods can be performed without detectable epimerization on

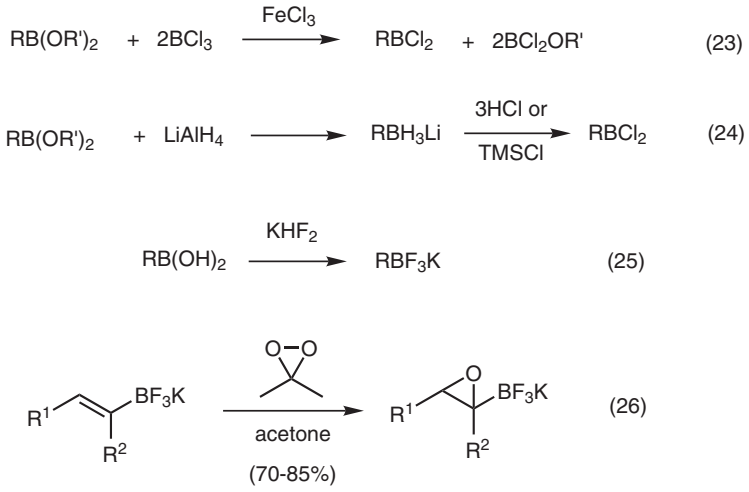


Figure 1.17 Synthesis of dichloroboranes, monoalkylboranes, and trifluoroborate salts.

chiral boronic esters originating from the asymmetric hydroboration of alkenes [161, 163].

1.2.3.7 **Trifluoroborate Salts**

Organotrifluoroborate salts are a new class of air-stable boronic acid derivatives that can be easily prepared according to a procedure described by Vedejs and co-workers (Equation 25, Figure 1.17) [165]. Boronic esters also react to give the desired salts [114]. These crystalline derivatives are easy to handle, and are competent substrates in many of the same reaction processes that employ free boronic acids. Their applications have been reviewed recently [166]. Notable examples include the Suzuki cross-coupling reaction [167], rhodium-catalyzed 1,4-addition [168], copper-promoted couplings to amines and alcohols [169], and allylation of aldehydes [170]. It was recently reported that trifluoroborate salts are conveniently transformed into dichlororoboranes by treatment with $SiCl_4$ in THF [171]. The incompatibility of boron–carbon bonds with several oxidants limits the possibilities to further transform compounds containing a boronic acid (ester) functionality. Taking advantage of strong B–F bonds, the use of organotrifluoroborate salts may be viewed as a way to protect boron's vacant orbital from an electrophilic reaction with a strong oxidant. Molander and Ribagorda have recently provided a clear testimony of this significant advantage provided by trifluoroborate salts. In this protocol, 1-alkenyltrifluoroborate salts were epoxidized cleanly with preservation of the carbon–boron bonds in good yields and high purity with dimethyldioxirane (Equation 26, Figure 1.17) [172]. The latter was clearly superior to *m*-CPBA and other oxidants tested. Significantly, under the same conditions, 1-alkenylboronic acids and the corresponding pinacol esters do not lead to the desired epoxide. Instead, the aldehyde resulting from carbon–boron oxidation and

other unidentified oxidation products are obtained. In view of their unique properties, interest in the chemistry of trifluoroborate salts is expected to grow further.

1.3 Synthesis of Boronic Acids and their Esters

The increasing importance of boronic acids as synthetic intermediates has justified the development of new, mild and efficient methods to provide access to a large pool. Of particular interest is the synthesis of arylboronic acids substituted with a wide range of other functional groups. As a consequence of their growing popularity and improvements in methods available for their preparation, many functionalized boronic acids have become available from several commercial sources. Although several methods, like the oxidation or hydrolysis of trialkylboranes, have significant historical and fundamental relevance, this section is devoted mainly to modern methods of practical value to synthetic chemists.

1.3.1 Arylboronic Acids

Arylboronic acids remain the most popular class of boronic acids. Their popularity in medicinal chemistry is due in large part to their role as cross-coupling partners for the synthesis of biaryl units (Section 1.5.3.1), which are present in the structure of several pharmaceutical drugs. Several methods, summarized generically in Figure 1.18, are now available for the synthesis of complex arylboronic acids and the following section presents an overview of these methods with selected examples in Table 1.3.

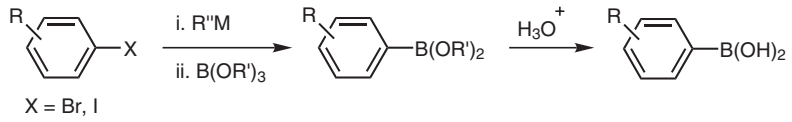
1.3.1.1 Electrophilic Trapping of Arylmetal Intermediates with Borates

One of the first and, probably, still the cheapest and most common way of synthesizing arylboronic acids involves the reaction of a hard organometallic intermediate (i.e., lithium or magnesium) with a borate ester at low temperature. The corresponding zinc and cadmium species are much less effective [173].

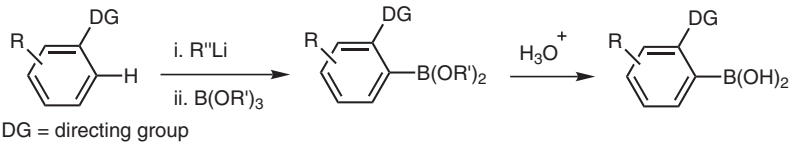
1.3.1.1.1 By Metal–Halogen Exchange with Aryl Halides

Provided the aryl halide substrate is compatible with its transformation into a strongly basic and nucleophilic arylmetal reagent, relatively simple aryl, alkenyl and even alkylboronic acids can be made from a sequence of metal–halogen exchange followed by electrophilic trapping with a trialkylborate. The first such methods for preparing phenylboronic acid, which involved the addition of methylborate to an ethereal solution of phenylmagnesium bromide at –15 °C, became notorious for providing a low yield of desired product [174]. Boron trifluoride was also employed instead of borates [175]. In the early 1930s, Johnson and co-workers developed the first practical and popular method for preparing phenylboronic acid and other arylboronic acids with an inverse addition procedure meant to minimize the undesirable formation of

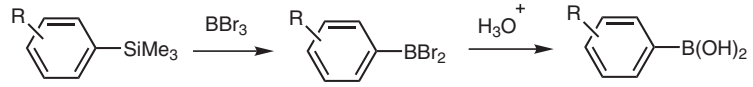
1.3.1.1.1 Electrophilic borate trapping of arylmetal intermediates from aryl halides



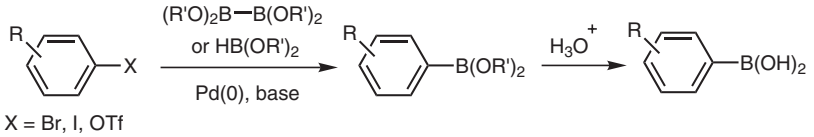
1.3.1.1.2 Electrophilic borate trapping of arylmetal intermediates from directed ortho-metallation



1.3.1.2 Transmetallation of arylsilanes and arylstannanes



1.3.1.3 Transition metal-catalyzed coupling between aryl halides/triflates and diboronyl reagents



1.3.1.4 Direct boronylation by transition metal-catalyzed aromatic C-H functionalization

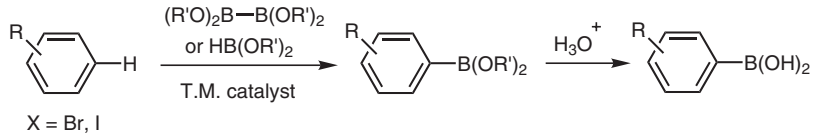


Figure 1.18 Common methods for the synthesis of arylboronic acids (esters).

borinic acid by-product [176, 177]. In this variant, phenylmagnesium bromide is added to a solution of tri-*n*-butylborate at –70 °C. Specifically, in the reaction of an arylmagnesium bromide with a trialkylborate, exhaustive formation of undesired borinic acid and borane via a second and third displacement on the intermediate boronate ester is prevented by precipitation of the magnesium trialkoxyphenylborate salt (**75**, M = MgX, in Equation 27, Figure 1.19). The latter is also thought not to dissociate into the corresponding boronic ester and metal alkoxide at low temperatures, which is key in protecting the desired boronate ester from a second displacement by the Grignard reagent (Equation 28). Then, the free boronic acid is obtained following a standard aqueous workup to hydrolyze the labile boronic ester substituents. Such procedures have been used successfully in the kilogram-scale preparation of important arylboronic acids [178, 179].

Table 1.3 Selected examples of preparative methods for arylboronic acids and esters. pin = pinacolato ($OCMe_2CMe_2O$).

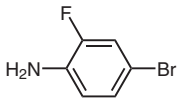
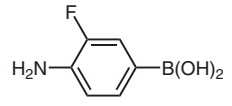
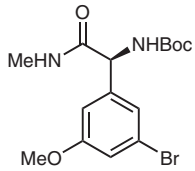
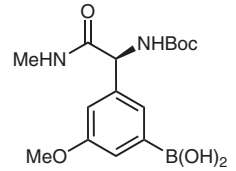
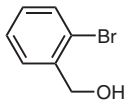
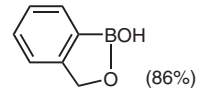
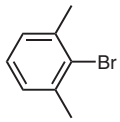
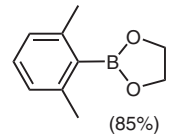
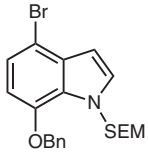
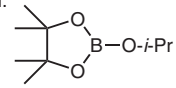
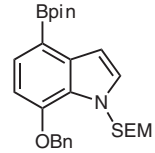
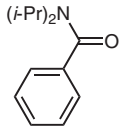
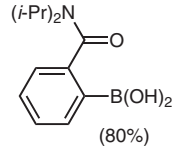
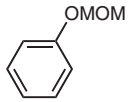
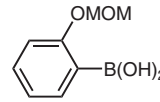
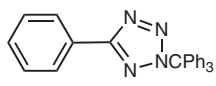
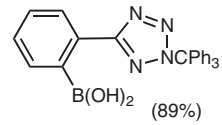
Entry	Substrate	Conditions	Product	Reference
1		1. i. *n*-BuLi (2 eq), THF, 0 °C ii. TMSCl (2 eq) 2. i. *t*-BuLi (2.2 eq), Et_2O, -78 °C ii. $B(OMe)_3$ (xs), -78 °C iii. 0.1N aq. HCl	 (45%)	183
2		i. MeMgCl (5 eq) THF, 0 °C ii. *t*-BuLi (5 eq), -78 °C iii. $B(OMe)_3$ (10 eq), 0 °C	 (80%)	184
3		i. *n*-BuLi (2 eq) Et_2O, 0 °C, 2 h; -78 °C ii. $B(OMe)_3$ (1 eq) iii. aq. HCl	 (86%)	18
4		i. *i*-PrMgBr, THF, -40 °C ii. $B(OMe)_3$, THF, -78 °C iii. $HOCH_2CH_2OH$, toluene	 (85%)	186
5		i. *t*-BuLi, THF, -78 °C ii. 	 (68%)	187
6		i. s-BuLi, TMEDA THF, -78 °C ii. $B(OMe)_3$ ii. 5% aq. HCl	 (80%)	192
7		i. s-BuLi, TMEDA THF, -78 °C ii. $B(OMe)_3$ ii. 5% aq. HCl		193
8		i. *n*-BuLi (1 eq) THF, < -20 °C ii. $B(O\text{-}i\text{-}Pr)_3$ (1.3 eq) ii. *i*-PrOH-NH_4Cl-H_2O	 (89%)	195

Table 1.3 Continued

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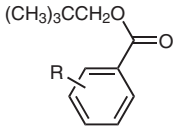
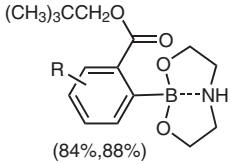
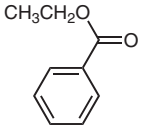
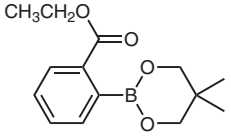
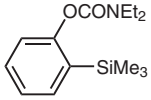
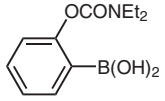
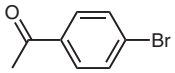
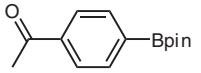
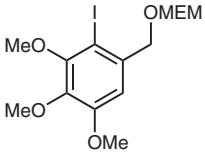
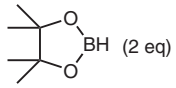
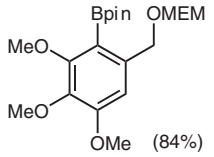
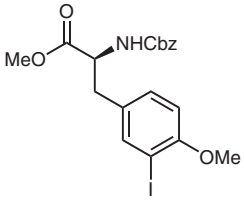
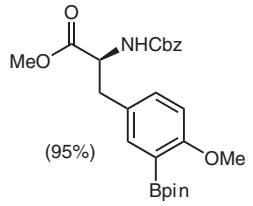
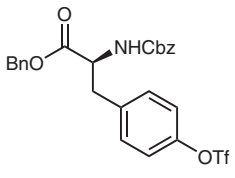
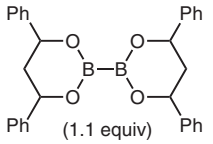
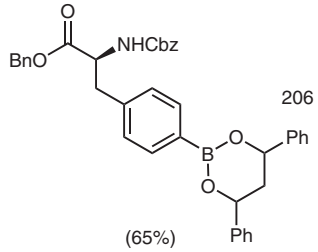
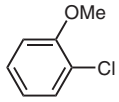
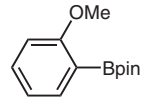
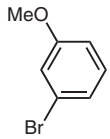
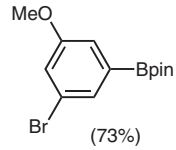
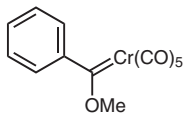
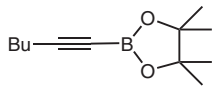
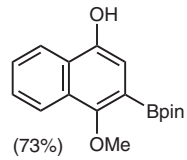
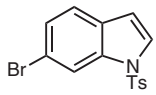
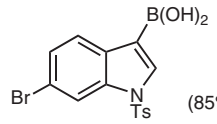
9	 R = *p*-Br or *o*-Br	i. LDA (1.2 eq) $B(O\text{-}i\text{-}Pr)_3$ (2.6 eq), THF ii. diethanolamine (1.1 eq)	 (84%,88%)	196
10		i. LTMP (1.5 eq) $B(O\text{-}i\text{-}Pr)_3$ (2 eq) THF, -78 °C ii. $HOCH_2CMe_2CH_2OH$	 (92%)	197
11		i. BBr_3 (1.5 eq) CH_2Cl_2, -78 °C to RT ii. 5% aq. HCl	 (>85%)	193
12		B_2pin_2 (1.1 eq) $PdCl_2(dppf)$ (3 mol%) KOAc (3 eq), DMSO, 80 °C, 1 h	 (80%)	200
13		 (2 eq) Et_3N (3 eq) $Pd(OAc)_2$ (5 mol%) PCy_2(o-biph) (10 mol%) 80 °C, 0.5 h	 (84%)	202
14		B_2pin_2 $PdCl_2(dppf)$ (3 mol%) KOAc (3 eq), DMSO, 80 °C, 3 h	 (95%)	205
15		 (1.1 equiv) $PdCl_2(dppf)$ (8 mol%) KOAc, DMF, 100 °C, 3 h	 (65%)	206

Table 1.3 Continued

Entry	Substrate	Conditions	Product	Reference
16		B_2pin_2 (1.1 eq) $Pd(dba)_2$ (3 mol%) PCy_3 (7.2 mol%), KOAc (1.5 eq) dioxane, 80 °C, 48 h	 (70%)	207
17		B_2pin_2 (1.1 eq) 1/2[IrCl(COD)]$_2$ + bpy (3 mol%) benzene, 80 °C, 16 h	 (73%)	213
18		 THF, 45 °C, 16 h	 (73%)	217
19		1. $Hg(OAc)_2$, AcOH, H_2O, $HClO_4$ 2. BH_3-THF 3. H_2O	 (85%)	187

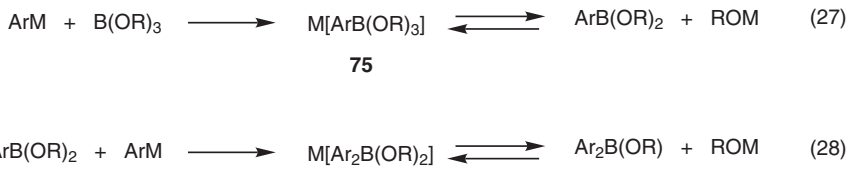


Figure 1.19 Equilibrium involved in the reaction between arylmetal intermediates (Li or Mg) and borates.

Isolation of free boronic acids using an aqueous work up may lead to low yields, especially for small or polar ones, which tend to be water-soluble even at a low pH (Section 1.4). In such cases, it is often better to isolate the desired boronic acid as an ester. In an improved procedure that does not involve an aqueous work-up, Brown and Cole reported that the reaction of several types of organolithium intermediates with triisopropylborate was very effective for the synthesis of arylboronic esters [180]. To help minimize the possible formation of borinic acids and boranes by multiple displacements (i.e., Equation 28 in Figure 1.19), the reaction protocol involves the slow addition of the organolithium to a solution of triisopropylborate in diethyl ether cooled to –78 °C. The use of smaller borate esters such as trimethylborate gave large proportions of multiple addition products (i.e., borinic acid and borane). With triiso-

propylborate, however, the clean formation of lithium alkoxyboronate salt (**75**, M = Li, R = *i*-Pr, Figure 1.19) was demonstrated by NMR spectroscopy, and the boronic ester can be obtained in high purity as the final product upon addition of anhydrous hydrogen chloride at 0 °C. An improvement to this procedure involves pyrolysis or the use of acid chlorides to breakdown the lithium triisopropylboronate salt, thereby avoiding the generation of free isopropanol and lithium chloride and facilitating the isolation of the boronic ester [181]. Recently, an "in-situ" quench variant whereby triisopropylborate is present in the flask prior to the addition of butyllithium was described; in many cases this simpler procedure afforded higher yields of aryl- and heteroaryl boronic acids compared to the sequential addition procedure [182]. Provided the requisite aryllithium reagent is readily accessible, all these procedures provide the corresponding isopropyl boronic esters in high yields. In addition to arylboronic esters, alkenyl, alkynyl, alkyl and even (α-haloalkyl)boronic esters were made this way [180]. If so desired, the free boronic acid may be obtained by hydrolysis of the ester. The metal–halogen exchange route can even be applied to functionalized substrates containing acidic hydrogen atoms, provided either temporary protection is effected (entry 1, Table 1.3) or a suitable excess of organometallic reagent is employed (entries 2 and 3). All isomers of hydroxybenzeneboronic acid were synthesized from the corresponding bromophenols using this method [185].

Recently, a new convenient procedure to synthesize arylboronic esters from Grignard reagents and trimethylborate was described [186]. This method involves a nonaqueous workup procedure in which the resulting solution of aryldimethoxyboronate is evaporated to eliminate the excess $B(OMe)_3$, and the residual solid is refluxed overnight in a solution of diol in toluene. In particular, several examples of ethylene glycol arylboronic esters were described with this method (e.g., entry 4, Table 1.3). Alternatively, the robust pinacol ester can be obtained directly by electrophilic quench of the aryllithium intermediate with a pinacol borate ester (entry 5). The use of bis(diisopropylamino)boron chloride as trapping agent in the reaction of both organolithium and magnesium compounds provides the corresponding bis(diisopropylamino)boranes, which can be easily transformed into the corresponding boronic esters and oxazaborolidines by exchange with a diol or an aminodiol [188].

1.3.1.1.2 By Directed ortho-Metallation

The metallation of arenes functionalized with coordinating ortho-directing groups such as amines, ethers, anilides, esters and amides is yet another popular way to access arylmetal intermediates that can be trapped with borate esters. Early work showed the suitability of ortho-lithiation of N,N-dialkylated benzylamines in the synthesis of *ortho*-methylamino-benzeneboronic acids [189–191]. Sharp and Snieckus further demonstrated the efficiency of this method in the preparation of *ortho*-carboxamido phenylboronic acids (entry 6, Table 1.3) [192]. This protocol was then generalized to many other substrates. For example, methoxymethoxybenzene (entry 7) and pivaloylaniline were treated with *s*-BuLi in the presence of TMEDA in THF at –78 °C, and the resulting ortho-lithiated intermediates quenched with trimethyl borate followed by an aqueous acidic workup described above (Section 1.3.1.1.1), to give the corresponding arylboronic acids in good yields [193, 194]. Although the crude

boronic acids could be used directly in Suzuki cross-coupling reactions, they were characterized as their stable diethanolamine adducts. The ortho-metallation route to arylboronic acids constitutes a reliable process in pharmaceutical chemistry where it can be applied to heterocyclic intermediates such as a tetrazole required in the synthesis of the antihypertensive drug Losartan (entry 8, Table 1.3) [195]. The use of esters as directing groups is more problematic as the metallated intermediate can undergo condensation with the benzoate substrate, giving a benzophenone. In one protocol, the metallation step is performed in the presence of the electrophile [196]. This in situ metallation-boronylation procedure employs LDA as base, and neopentyl esters were found to be particularly suitable because of their stability in the presence of this base. Most importantly, LDA is compatible with borate esters under the conditions employed, and its inertness to bromide-substituted benzoates provides another significant advantage over the use of BuLi for the deprotonation step. Thus, a solution of bromo-substituted neopentyl benzoate esters and excess triisopropylborate treated with LDA (1.1–1.5 equiv.) in THF led to the isolation of crude *ortho*-carboxy arylboronic acids, which were isolated as diethanolamine adducts in high yields (entry 9, Table 1.3). A limitation of this method using LDA as base is the requirement for an electron-withdrawing substituent to activate the arene substrate. Neopentyl benzoate, for example, does not undergo directed metallation and gives, rather, the corresponding diisopropyl carboxamide. A recent variant of this in situ trapping procedure using 2,2,6,6-tetramethylpiperidide (LTMP) as the base led to a more general methodology, allowing the presence of other substituents normally incompatible with standard ortho-metallation procedures with alkyllithium bases [197]. For example, ethyl benzoate, benzonitrile, fluoro- and chlorobenzene were transformed in high yield into the corresponding ortho-substituted boronic acids as neopentylglycol esters. As demonstrated in particular in the case of ethyl benzoate (entry 10), the use of LTMP as base is quite advantageous because LDA fails to metallate this substrate and provides instead the carboxamide product of addition to the ester.

1.3.1.2 **Transmetallation of Aryl Silanes and Stannanes**

One of the earliest methods for preparing aromatic boronic acids involved the reaction between diaryl mercury compounds and boron trichloride [198]. As organomercurial compounds are to be avoided for safety and environmental reasons, this old method has remained unpopular. In this respect, trialkylaryl silanes and stannanes are more suitable and both can be transmetallated efficiently with a hard boron halide such as boron tribromide [199]. The apparent thermodynamic drive for this reaction is the higher stability of B–C and Si(Sn)–Br bonds of product compared to the respective B–Br and Si(Sn)–C bonds of substrates. Using this method, relatively simple arylboronic acids can be made following an aqueous acidic workup to hydrolyze the arylboron dibromide product [193]. For example, some boronic acids were synthesized more conveniently from the trimethylsilyl derivative than by a standard ortho-metallation procedure (entry 11, Table 1.3).

1.3.1.3 Coupling of Aryl Halides with Diboronyl Reagents

The traditional method involving the trapping of aryllithium or arylmagnesium reagents with borate esters is limited by the functional group compatibility of these hard organometallic species as well as the rigorously anhydrous conditions required. In search of milder conditions amenable to a wider scope of substrates and functionalities, Miyaura and co-workers found that diboronyl esters such as B_2pin_2 (**58**, Figure 1.14) undergo a smooth cross-coupling reaction with aryl bromides, iodides, and triflates under palladium catalysis [200]. This new reaction process is described in Chapter 2; thus only a brief summary is presented here. A detailed mechanism has been proposed [139b, 200], and several diboronyl reagents are now commercially available, including diborylpinacolate (B_2pin_2). Despite the obvious appeal of this cross-coupling method [139], the prohibitive price of the diboronyl reagents currently restrains its use for the large-scale preparation of boronates. Standard conditions for the coupling reaction involve $PdCl_2$(dppf) as catalyst, with potassium acetate as the base in a polar aprotic solvent [200]. The mildness of these conditions is evidenced by the use of carbonyl-containing substrates such as benzophenones (entry 12, Table 1.3) or benzaldehydes [83], which would be unsuitable in the Brown–Cole procedure using organolithium intermediates. The cheaper reagent pinacolborane (**53**, Figure 1.13) can also serve as an efficient boronyl donor in this methodology (entry 13) [201]. Cedranediolborane has also been proposed as an alternative to pinacolborane, which gives pinacol esters that are notoriously difficult to hydrolyze (Section 1.2.3.2.2) [203]. The scope of haloarene substrates in coupling reactions with diboronyl esters or pinacolborane is very broad. A recent example described the preparation of peptide dimers using a one-pot borylation/Suzuki coupling [204]. Hindered or electron-rich aryl halides may also be used with high efficiency (entries 13, 14, Table 1.3). Of particular significance is the use of pinacolborane with aryltriflates, which can be made with ease from phenols [201]. For instance, 4-borono-phenylalanine is now easily accessible from tyrosine using this approach (entry 15). This example also shows that the use of diboronyl reagents with hydrolytically labile substituents is advantageous if the desired product is the free boronic acid. Aryl chlorides are more attractive substrates than bromides and iodides due to their low cost and wider commercial availability. In this regard, the development of modified conditions with $Pd(dba)_2$ and tricyclohexylphosphine as catalyst system has expanded the scope of this coupling methodology to aryl chlorides – even electron-rich ones (entry 16, Table 1.3) [207]. Alternatively, a microwave-promoted procedure for aryl chlorides using a palladium/imidazolium system has been described [208]. Recently, a similar procedure employed aryldiazonium salts as substrates [209].

1.3.1.4 Direct Boronylation by Transition Metal-catalyzed Aromatic C–H Functionalization

In terms of atom-economy, a very attractive strategy for accessing arylboronic acids is the direct boronylation of arenes through a transition metal promoted C–H functionalization. In addition to the catalyst, a suitable boron donor is required, and both diboronyl esters and dialkoxyboranes are very appropriate in this role. The concept of this type of direct borylation was first demonstrated on alkanes using photochemical

conditions [210]. For arene substrates, several research groups, including those of Smith [211], Hartwig [212], Miyaura/Hartwig [213] and Marder [214] have recently reported a number of efficient procedures using iridium and rhodium catalysts (entry 17, Table 1.3). This new reaction process has also generated much interest for its mechanism [215]. Regioselectivity remains a major challenge in aromatic C–H activation with mono- and polysubstituted arenes, and, not surprisingly, new advances are reported at a rapid pace [216]. This recent and emerging approach to the synthesis of boronic acid derivatives is discussed in detail in Chapter 2.

1.3.1.5 **Other Methods**

Harrity and co-workers described the application of 2-substituted 1-alkynylboronic esters in the Dötz cycloaddition of Fisher chromium carbene complexes, affording in a highly regioselective fashion a novel class of hydroxy-naphthyl boron pinacolates (entry 18, Table 1.3) [217]. These reaction products also provided, upon treatment with ceric ammonium nitrate, the corresponding quinone boronic esters.

1.3.2
Diboronic Acids

The preparation of all three substitution patterns of benzenediboronic acid has been reported (Figure 1.20). Whereas the preparation of the 1,4- and 1,3-benzenediboronic acids **76** and **77** from the corresponding dibromides were well described [157a, 218], that of the ortho isomer **78** is more tedious [72, 219]. Several other mono- and polycyclic aromatic diboronic acids, such as **79** [150], **80** [220], and **81** [221], have been described.

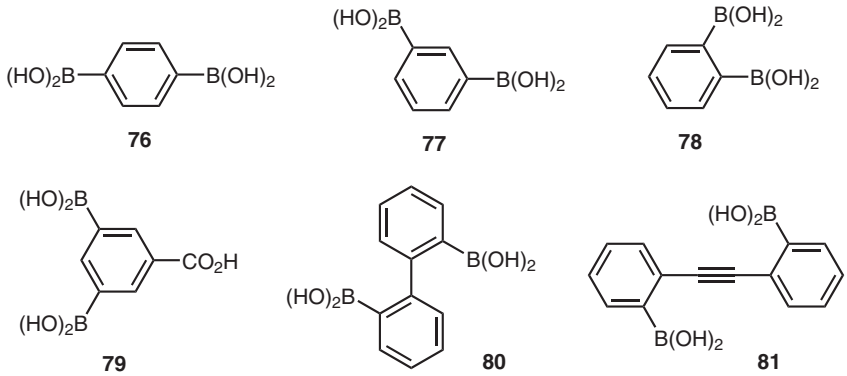


Figure 1.20 Selected examples of diboronic acids.

1.3.3
Heterocyclic Boronic Acids

Heterocyclic aromatic boronic acids, in particular pyridinyl, pyrrolyl, indolyl, thienyl, and furyl derivatives, are popular cross-coupling intermediates in natural product synthesis and medicinal chemistry. The synthesis of heterocyclic boronic acids has been reviewed recently [222], and will not be discussed in detail here. In general, these compounds can be synthesized using methods similar to those described in the above section for arylboronic acids. Of particular note, all three isomers of pyridineboronic acid have been described, including the pinacol ester of the unstable and hitherto elusive 2-substituted isomer, which is notorious for its tendency to protodeboronate [223]. Improvements and variants of the established methods for synthesizing heterocyclic boronic acids have been constantly reported [13, 182]. For example, a Hg-to-B transmetallation procedure was recently employed to synthesize a highly functionalized indolylboronic acid (entry 19, Table 1.3) [187].

1.3.4
Alkenylboronic Acids

Alkenylboronic acids constitute another class of highly useful synthetic intermediates. They are particularly popular as partners in the Suzuki–Miyaura cross-coupling reaction for the synthesis of dienes and other unsaturated units present in many natural products (Section 1.5.3.1). Several methods are available for the synthesis of a wide range of alkenylboronic acids with different substitution patterns. These approaches are summarized in Figure 1.21 and are described in the sub-sections below.

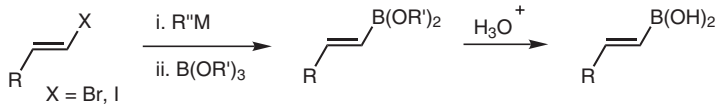
1.3.4.1 Electrophilic Trapping of Alkenymetal Intermediates with Borates

Alkenylboronic acids can be synthesized from reactive alkenylmetal species in a way similar to that described above for arylboronic acids (Section 1.3.1.1.1) [224]. Typically, alkenyl bromides or iodides are treated sequentially with *n*-BuLi and a trialkylborate (entry 1, Table 1.4). A nonpolar trienylboronic acid was synthesized using this approach [226]. As described in Section 1.2.2.2, small boronic acids tend to be highly soluble in water and may be difficult to isolate when made using the traditional approach involving an aqueous workup. In these cases, exemplified with the polymerization-prone ethyleneboronic acid synthesized from vinylmagnesium bromide, it has proved more convenient to isolate the product as a dibutyl ester by extraction of the acidic aqueous phase with butanol [227]. Recently, alkoxy-functionalized butadienyl- and styrenyl boronic esters were synthesized from α,β-unsaturated acetals by treatment with Schlosser's base and subsequent trapping with triisopropylborate (entry 2) [228].

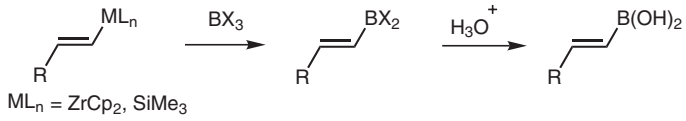
1.3.4.2 Transmetallation Methods

The treatment of trialkylsilyl derivatives with boron halides described in Section 1.3.1.2 is applicable to alkenyltrimethylsilanes [229]. It was employed as a method for

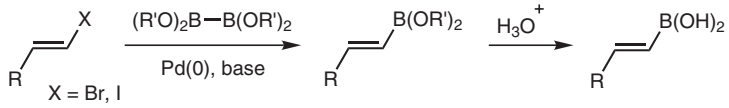
1.3.4.1 Electrophilic trapping of alkenylmetal intermediates with borates



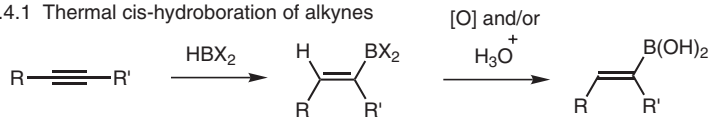
1.3.4.2 Transmetallation methods



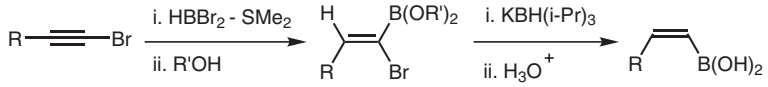
1.3.4.3 Transition metal catalyzed coupling between aryl halides/triflates and diboronyl reagents



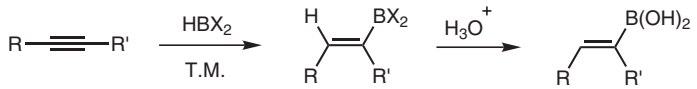
1.3.4.4.1 Thermal cis-hydroboration of alkynes



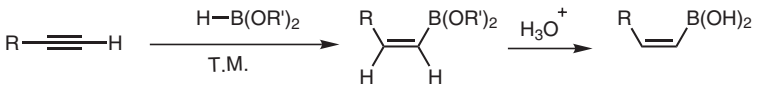
1.3.4.4.2 Indirect trans-hydroboration using alkynyl bromides



1.3.4.4.3 Transition metal-catalyzed cis-hydroboration of alkynes



1.3.4.4.4 Rhodium and iridium catalyzed trans-hydroboration of alkynes



1.3.4.5 Alkene metathesis

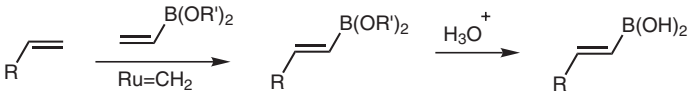


Figure 1.21 Common methods for the synthesis of alkenylboronic acids (esters).

Table 1.4 Selected examples of preparative methods for alkenylboronic acids and esters. pin = pinacolato ($OCMe_2CMe_2O$), cat = catecholato

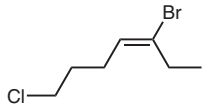
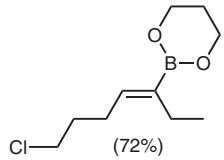
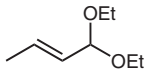
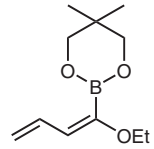
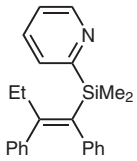
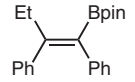
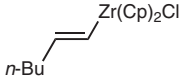
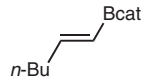
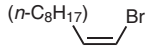
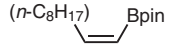
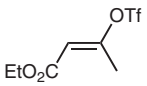
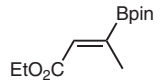
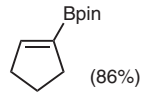
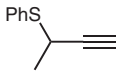
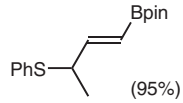
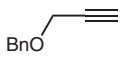
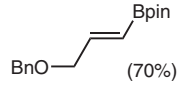
Entry	Substrate	Conditions	Product	Reference
1		i. *s*-BuLi, THF, -78 °C ii. $B(OR')_3$, -78 °C, 1 h iii. HCl/Et_2O, -78 °C to rt iv. H_2O v. $HO(CH_2)_3OH$	 (72%)	225
2		i. *n*-BuLi/KO-*t*-Bu (2.5 eq), THF, -95°C, 2 h ii. B(O-*i*-Pr)$_3$ (2 eq) -95 °C to rt iii. H_2O, extraction iv. $HOCH_2CMe_2CH_2OH$ (1 eq) toluene, rt, 12 h	 (93%)	228
3		1. BCl_3 (2.2 eq) CH_2Cl_2, -40 °C, 5 h 2. pinacol, Et_3N	 (82%, *Z*/*E* 98:2))	231
4		catBCl CH_2Cl_2, 0 °C	 (57%)	232
5		B_2pin_2 (1.1 eq) $PdCl_2$(dppf) (3 mol%) PPh_3 (6 mol%) KOPh (1.5 eq), toluene, 50 °C, 5 h	 (74%)	234
6		B_2pin_2 (1.1 eq) $PdCl_2(PPh_3)_2$ (3 mol%) PPh_3 (6 mol%) KOPh (1.5 eq), toluene, 50 °C, 1 h	 (93%, >99% Z:E)	235
7		HBpin (1.5 eq) $PdCl_2$(dppf) (3 mol%) $AsPh_3$ (12 mol%), Et_3N (3 eq), dioxane, 80 °C, 16 h	 (86%)	236
8		i. Cy_2BH (1 eq), DME, rt, 1 h ii. Me_3NO (2 eq), reflux iii. $HOCMe_2CMe_2OH$ (1 eq), rt, 12 h	 (95%)	244
9		i. Cy_2BH (1 eq), DME, rt, 1 h ii. Me_3NO (2 eq), reflux iii. $HOCMe_2CMe_2OH$ (1 eq), rt, 12 h	 (70%)	244

Table 1.4 Continued.

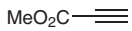
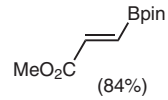
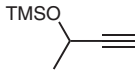
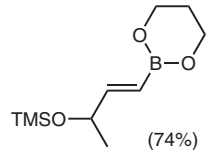
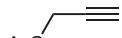
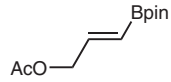
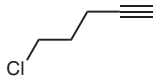
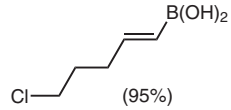
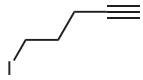
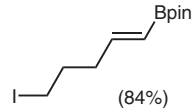
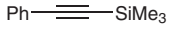
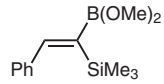
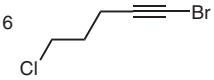
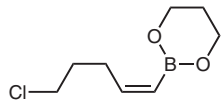
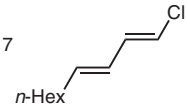
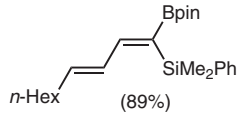
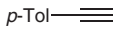
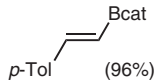
Entry	Substrate	Conditions	Product	Reference
10		i. Ipc_2BH, THF, -35 °C to 0 °C ii. CH_3CHO (10 eq), 0 to 40 °C iii. $HOCMe_2CMe_2OH$ (1 eq), rt, 12 h	 (84%)	246
11		i. Ipc_2BH, THF, -35 °C to rt, 5 h ii. CH_3CHO (xs), 0 °C; reflux 12 h iii. $HO(CH_2)_3OH$	 (74%)	247
12		i. **87** (1 eq) ii. H_2O, rt, 0.5 h iii. aq. CH_2O (1 eq), rt, 1 h iv. $HOCMe_2CMe_2OH$ (1.1. eq), rt, 12 h	 (55%, 97:3 regio)	248
13		i. CBH (1 eq), 70 °C, 1 h ii. H_2O, 25 °C, 1 h iii. filtration	 (95%)	249b
14		HBpin (2 eq), CH_2Cl_2, 25 °C, 6 h	 (84%)	134
15		i. $HBCl_2$ (1 eq), BCl_3 (1 eq) pentane, -78 °C; rt, 12 h ii. MeOH, Et_3N, 0 °C	 (46%)	253
16		i. $HBBr_2$-SMe_2, CH_2Cl_2 ii. MeOH, pentane iii. K(*i*-PrO)$_3$BH, Et_2O, 0 °C to rt, 0.5 h iv. H_2O, 0 °C v. $HO(CH_2)_3OH$	 (89%)	256
17		i. *n*-BuLi (1.05 eq), THF, -90 °C, 15 min ii. $PhMe_2SiB(OCMe_2)_2$, warm up to rt, 12 h	 (89%)	259
18		HBcat (1 eq), $Cp_2Ti(CO)_2$ (4 mol%) C_6H_6, 25 °C, 2 h	 (96%)	262

Table 1.4 Continued.

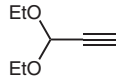
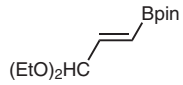
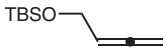
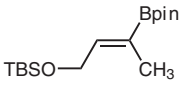
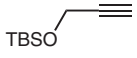
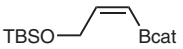
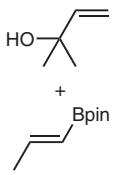
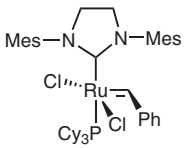
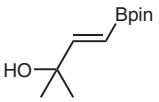
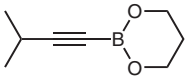
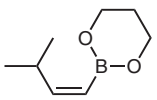
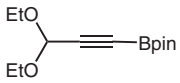
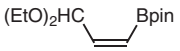
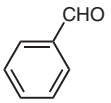
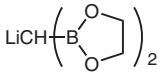
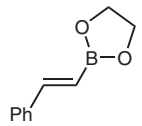
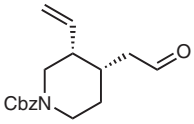
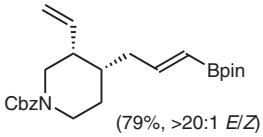
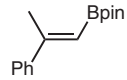
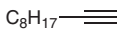
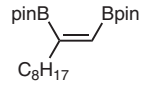
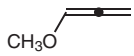
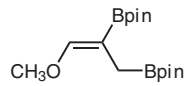
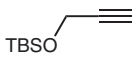
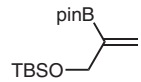
Entry	Substrate	Conditions	Product	Reference
19		HBpin (1.05 eq), $HZrCp_2Cl$ (5 mol%) CH_2Cl_2, 25 °C, 24 h	 (82%)	263
20		HBpin (1.5 eq) $Pt(dba)_2$ (3 mol%) $P(t\text{-}Bu)_3$ (6 mol%) toluene, 50 °C, 2 h	 (82%)	267
21	 (1.2 eq)	HBcat (1 eq) $[Rh(cod)Cl]_2$ (1.5 mol%) PPr_3 (6 mol%) Et_3N (1 eq) cyclohexane, rt, 2 h	 (71%, 99% *Z*)	268
22	 (1 equiv each)	 (5 mol%) CH_2Cl_2, reflux	 (61%, > 20:1 E:Z)	272
23		i. H_2, Lindlar, pyridine 1,4-dioxane, rt, 1.5 h ii. H_2O iii. $HO(CH_2)_3OH$, pentane	 (83%, 95% *Z*)	276
24		i. $HZrCp_2Cl$ (1.2 eq) THF, 25 °C, 0.5 h ii. H_2O, 0.5 h	 (82%)	277
25		 THF/CH_2Cl_2 -78 °C, 3 h	 (87%, >93% *E*)	279
26		$Cl_2CHBpin$ (2 eq) $CrCl_2$ (8 eq) LiI (4 eq) THF, 25 °C	 (79%, >20:1 *E*/*Z*)	284

Table 1.4 Continued.

Entry	Substrate	Conditions	Product	Reference
27		trans-[RhCl(CO)(PPh_3)$_2$] (5 mol%) B_2pin_2 (0.67 eq) 3:1 toluene-CH_3CN, 80 °C, 3 d	 (90%)	286
28	 (1.1 equiv)	B_2pin_2 (1 eq) $Pt(PPh_3)_4$ (3 mol%) DMF, 80 °C, 24 h	 (86%)	288
29	 (1.5 equiv)	B_2pin_2 (1 eq) $Pt(dba)_2$ (10 mol%) PCy_3 (10 mol%) toluene, 50 °C, 18 h	 (85%)	290
30		B_2pin_2 (1.1 eq) CuCl (1.1 eq) KOAc (1.1 eq) $P(t\text{-}Bu)_3$ (1.1 eq) DMF, rt, 16 h	 (62%, 91:9 regiosel.)	291

preparing ethylene boronic esters [230]. Recently, isomerically pure tetrasubstituted alkenylboronic esters were synthesized by this approach, following an esterification of the intermediate dichloroborane with pinacol (entry 3, Table 1.4) [231]. *trans*-Alkenylboronic acids can also be synthesized from zirconocene intermediates obtained from the hydrozirconation of terminal alkynes (entry 4) [232].

1.3.4.3 Transition-metal Catalyzed Coupling between Alkenyl Halides/Triflates and Diboronyl Reagents

Alkenyl halides and triflates are suitable substrates in the palladium-catalyzed borylation reaction described above for aromatic substrates (Section 1.3.1.3). In this reaction, the geometry of the starting alkenyl halide is preserved in the product, and several functionalities are tolerated in the substrate. At the outset, however, Miyaura and co-workers found that the conditions utilized for aryl halide substrates led to low yields of the desired alkenylboronate due to competing reactions such as the formation of the homo-coupled product of Suzuki cross-coupling [233]. To improve the rate of transmetallation between the diboronyl reagent (B_2pin_2) and the oxidative addition Pd(II) intermediate, stronger bases were evaluated. In the optimal procedure, potassium phenoxide was the most effective base, with a less polar solvent (toluene) than that used with aryl halides, and triphenylphosphine as ligand in place of dppf. Alkenyl bromides and triflates were superior to iodides, and generally afforded good yields of products (70–90%). The mildness of these conditions opened up a rather

impressive scope of suitable substrates [234], including (*Z*)-alkenes (entry 5, Table 1.4), and both acyclic and cyclic ones with functionalities such as alkyl halides, silyl-protected alcohols, and carboxylic esters (entry 6) [235]. Pinacolborane was effective in the borylation of alkenyl halides under a new set of optimal conditions (entry 7) [236]. No competing hydroboration was observed, but *Z*-configured substrates are inverted under these reaction conditions.

1.3.4.4 **Hydroboration of Alkynes**

1.3.4.4.1 Thermal cis-Hydroboration

Since its discovery by Brown and Rao in 1956 [237], hydroboration chemistry has been a central reaction in the preparation of organoboron compounds [238]. cis-Hydroboration of terminal alkynes provides ready access to *trans*-2-substituted alkenylboronic acids [239], and several borane reagents have been used for this purpose (Figure 1.22). Non-differentiated internal alkynes usually give mixtures of regioisomeric alkenylboron compounds. With terminal alkynes, however, the hydroboration is highly regioselective and adds boron at the terminal carbon. Likewise, whereas small borane reagents tend to undergo a double hydroboration of the alkyne substrate, more hindered boranes allow the hydroboration process to stop with ease after one addition, avoiding further hydroboration of the desired product into a diboroalkane [239]. Thus, the bulky dialkylborane reagents disiamylborane (**82**) [239], thexylborane (**83**) [240], dicyclohexylborane (**84**) [241], and 9-BBN (**85**) [242] all react with terminal alkynes to provide 2-substituted dialkylalkenylboranes in a very high regioselectivity. The corresponding alkenylboronic acid may be obtained after an appropriate oxidative workup, which is generally performed with a mild and selective oxidant for the two sp^3 C–B bonds. To this end, trimethylamine oxide was found most suitable [243], leaving not only the alkenyl boron–carbon bond intact but also a selenide and a sulfide substituent (entry 8, Table 1.4) [244]. In the hydrolysis of the resulting alkenylboronate, the ensuing separation of the desired boronic acid from the alcohol by-product originating from the oxidation of the dialkylborane is not always straightforward. Hoffmann and Dresely described a procedure with dicyclohexylborane in which the boronic acid is esterified in situ as a pinacolate after the oxidation step, then purified by distillation to eliminate the residual cyclohexanol [244]. This way, several functionalized (*E*)-1-alkenylboronates were isolated – the use of DME, a polar coordinating solvent, was essential when using a propargylic ether as substrate (entry 9). Otherwise, no reaction occurred, possibly due to the coordination of Cy_2BH to the basic ether. For substrates that may be sensitive to the oxidative workup, or to avoid the cyclohexanol by-product, diisopinocampheylborane (**86**, Figure 1.22) [245] offers a milder alternative. With this reagent, the alkyne is hydroborated and then subjected to a gentle oxidative dealkylation using acetaldehyde to afford a diethyl alkenylboronic ester along with two equivalents of pinene [246, 247]. The crude diethyl alkenylboronate can be transesterified with diols such as pinacol to yield the corresponding pinacol ester, which in most cases must be purified by distillation or chromatography. Although several highly functionalized alkenylboronates were synthesized using this method (entries 10 and 11), it is often difficult to completely elim-

inate the pinene by-product by distillation. Recently, the new reagent di(isopropylprenyl)borane, **87**, was described [248]. Much like reagent **86**, it features a mild neutral workup, which can be done with aqueous formaldehyde or water (entry 12).

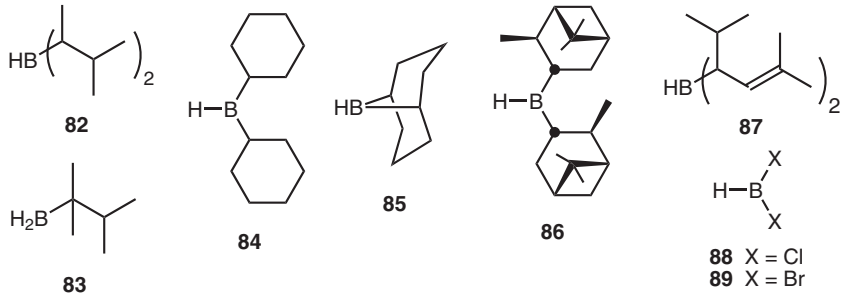


Figure 1.22 Common hydroborating agents for alkynes.

The use of 4,4,6-trimethyl-1,3,2-dioxaborinane (**51**, Figure 1.13) [132], catecholborane (**52**) [249], pinacolborane (**53**) [134], or the more reactive 1,3,2-dithiaborolane (**54**) [136] provides the boronic acid derivative directly after a hydrolytic workup with no oxidation step. Yet, these methods are not without disadvantages. Dialkoxyboranes are less reactive than the dialkylboranes described above. For example, alkyne hydroborations with catecholborane are often performed at temperatures as high as 100 °C. In this regard, dialkylboranes such as Cy_2BH were found to catalyze these hydroborations at room temperature [250]. Because dialkylboranes are more reactive than catecholborane, it was suggested that this catalytic process involves exchange of the resulting alkenyl group with catecholborane to recycle the dialkylborane. Moreover, although catecholborane was employed with highly functionalized substrates [251], it does not tolerate acetal or ether functionalities at the propargylic carbon [244, 247], and the acidic catechol released in the aqueous workup needs to be neutralized and removed from the mixture (entry 13). By producing the robust pinacolate ester in a single operation, the use of pinacolborane (**53**) is quite advantageous although the addition also tends to be sluggish (entry 14). Dibromoborane (**89**, Figure 1.22), in the form of a methyl sulfide complex, conveniently gives access to 1-alkenylboronic acids bearing alkyl or aryl substituents at the 2-position following alcoholysis of the intermediate alkenyldibromoborane [252]. Several other functionalities, however, are not well tolerated by this reagent. The related dichloloroborane (**88**) undergoes a regioselective hydroboration with silylacetylenes, giving the (*E*)-1-trimethylsilyl-1-alkenylboronic ester after methanolysis (entry 15) [253]. Dichloroborane is difficult to handle, but a simple variant, presumed to generate it in situ by reaction of trimethylsilane with boron trichloride, was also shown to hydroborate alkynes [254]. Alternatively, a recent report demonstrated the suitability of the stable and commercially available Cl_2BH–dioxane complex for the preparation of 1-alkenylboronic acids [255].

1.3.4.4.2 Indirect trans-Hydroboration using Alkynyl Bromides

All the above hydroboration methods provide terminal *trans*-alkenylboronic acids by a highly regioselective syn addition of the B–H bond across the terminal alkyne. To provide *cis*-alkenylboronic acids, Brown and Imai developed an ingenious two-step method based on the regioselective hydroboration of bromoalkynes with dibromoborane (Figure 1.21) [256]. In this procedure, the resulting (*Z*)-1-bromo-alkenyldibromoboranes are transformed into the corresponding esters through simple alcoholysis. The isolated boronates are then treated with potassium triisopropoxyborohydride (KIPBH) to effect a stereospecific bromide substitution by inversion of configuration, thereby affording the *cis*-alkenylboronic esters. Whereas dibromoborane presents a limited scope of chemoselectivity, KIPBH is relatively mild. For example, it tolerates a primary alkyl chloride on the substrate (entry 16, Table 1.4). Furthermore, an extension of this approach employing organolithium or Grignard reagents in place of KIPBH leads to the stereoselective preparation of (*E*)-1-substituted-1-alkenylboronic esters that could not obtained via the hydroboration of alkynes [257, 258]. Recently, a similar nucleophilic substitution mechanism has also been proposed in a new method involving the addition of alkenyllithium intermediates to the diboronyl reagent B_2pin_2 or the related dimethylphenylsilyl(pinacolato)borane [259]. In this reaction, which accomplishes a geminal difunctionalization of formal alkenylidene-type carbenoids, 1,1-diboronylalkenes or 1-silyl-1-alkenylboronates are produced (entry 17).

1.3.4.4.3 Transition Metal-catalyzed cis-Hydroboration

Since the discovery of the rhodium-catalyzed hydroboration of alkenes by Männig and Nöth in 1985 [260], this method has generally not provided satisfactory results when applied to alkynes [261]. Hartwig and He, however, found that dicarbonyltitanocene effectively catalyzes the hydroboration of alkynes with catecholborane without the contamination of by-products of catecholborane decomposition usually observed under rhodium catalysis (entry 18, Table 1.4) [262]. By taking advantage of the superior stability of pinacolborane over catecholborane, Pereira and Srebnik developed a very convenient zirconocene-catalyzed procedure for the pinacolboration of terminal alkynes (entry 19) [263]. This method, which features lower reaction temperature and times than the non-catalyzed variant of Knochel and co-workers [134], provides the (*E*)-1-alkenylboronates as their convenient pinacolate esters in high yields and regioselectivity. Other transition metal catalysts, such as $Rh(CO)(Ph_3P)_2Cl$ and $NiCp(Ph_3P)Cl$, are also effective in conjunction with pinacolborane as the hydroborating agent [264]. Like the non-catalyzed hydroboration, internal alkynes tend to give mixtures of regioisomers. Using thioalkynes, however, a nickel-catalyzed catecholboration method afforded the 2-alkylthio-1-alkenylboronates in high regioselectivity [265]. An early study described one example of $Pd(PPh_3)_4$-catalyzed catecholboration of an enyne to afford an allenylboronate [266].

Miyaura and co-workers also reported the $Pt(dba)_2$-catalyzed pinacolboration of terminal allenes; the regioselectivity was highly dependent on the nature of the added phosphine ligand [267]. For example, whereas the bulky tris(2,4,6-trimethoxyphenyl)phosphine often led to substantial amounts of the external Markovnikov prod-

uct, the use of tris(*t*-butyl)phosphine provided the internal hydroboration product as single isomer (entry 20, Table 1.4). Notably, the resulting 1-substituted-1-alkenylboronate would not be available using the uncatalyzed hydroboration of terminal allenes or terminal alkynes.

1.3.4.4.4 Rhodium- and Iridium-catalyzed trans-Hydroboration

Direct alkyne hydroboration methods, whether catalyzed or not, afford *trans*-alkenylboronic acids by a highly regioselective syn addition of the reagent's B–H bond across the terminal alkyne. The indirect Brown method to effect formal trans-hydroboration (Section 1.3.4.4.2) is limited by the need for a bromoalkyne and the harshness of the dibromoborane reagent employed. To fill this important methodological void and allow for a direct, mild formation of *cis*-alkenylboronic acids, Miyaura and co-workers sought a true "trans-hydroboration" method. They found that the hydroboration of alkynes with either catecholborane or pinacolborane in the presence of triethylamine and catalytic amounts of rhodium or iridium phosphine complex provides good to high yields of (*Z*)-1-alkenylboronic esters in a very high selectivity (entry 21, Table 1.4) [268]. Interestingly, deuterium-labeling experiments showed that the internal cis-hydrogen substituent comes from the terminal alkyne and not from the borane. Based on this information, a mechanism involving migration of the acetylenic hydrogen, and proceeding through a metal-vinylidene complex, was proposed to explain the selectivity of this unique "trans-hydroboration" method [268].

1.3.4.5 **Alkene Metathesis**

Recently, the advent of efficient catalysts for alkene metathesis has opened up new opportunities for the synthesis of alkenylboronic acids. For example, ring-closing metathesis of dienylboronic acids provides cyclic alkenylboronic acids that would be difficult to obtain otherwise [269]. Chemoselectivity in cross-metathesis chemistry is a significant problem that severely limits the synthesis of acyclic alkenes using these novel catalysts [270]. With most terminal alkenes, mixtures of disubstituted alkene products are obtained, and often with a low *E*/*Z* selectivity. Exceptionally, a number of alkene substrates are prone to undergo a highly chemoselective cross-metathesis with other terminal alkenes [270]. Fortunately, ethylene and 1-propenyl pinacol boronic esters are such favorable substrates [271, 272]. For example, Grubbs and coworkers discovered that the latter undergoes a clean cross-metathesis with terminal alkenes, catalyzed by a ruthenium alkylidene, to provide the (*E*)-1-alkenylboronic ester products in high selectivity (entry 22, Table 1.4) [272]. This methodology was tested in the synthesis of complex molecules such as epothilone analogues [273]. Ene-yne metathesis reactions based on alkynylboronic ester annulation strategies provide polysubstituted 2-butadienyl boronic esters [274, 275].

1.3.4.6 **Other Methods**

Though conceptually simple, photochemical *E* to *Z* isomerization of double bonds is not an efficient approach for accessing geometrically pure alkenylboronic esters [253, 258]. Alkynylboronic esters, however, can be selectively hydrogenated over Lindlar's catalyst [276]. 1,4-Dioxane was found to be the optimal solvent for providing (*Z*)-1-

alkenylboronates with stereochemical purity over 95% (entry 23, Table 1.4). Likewise, highly pure (*Z*)-1-alkenylboron pinacolates were isolated from the corresponding alkynylboronates and a sequence of regioselective hydrozirconation and aqueous protonolysis (entry 24) [277]. The synthesis of alkenylboronates using other types of additions and cycloadditions of alkynylboronates are described in Chapter 9.

Matteson and Majumdar have reported a Peterson-type olefination of the anion derived from a α-trimethylsilylmethylboronic ester ($LiCH(SiMe_3)Bpin$) [278]. Addition of the latter onto aldehydes provided the corresponding alkenylboronic esters as a mixture of geometrical isomers (~70:30 *Z*/*E*). No further optimization was reported towards controlling the *E*/*Z* selectivity in this potentially useful and unique method for synthesizing alkenylboronic acids from aldehydes. The corresponding lithiomethylenediboronic esters tend to provide mixtures favoring the *E* isomer (entry 25) [279, 280], and this approach to access alkenylboronic acids from aldehydes was employed in the total syntheses of natural products such as palytoxin [281] and the macrolide antibiotic rutamycin B [282]. A variant of the traditional Takai reaction, using $Cl_2CHBpin$, provides *trans*-1-alkenylboronic esters from aldehydes [283]; this procedure was recently employed in a synthesis of quinine (entry 26) [284].

Pinacol and 2-methyl-2,4-pentanediol esters of ethylene boronic acid are efficient substrates for Heck couplings with aryl and alkenyl halides, giving 2-aryl- and 2-butadienylboronates, respectively, with minimal side-product from Suzuki coupling [285]. Marder and co-workers have developed a dehydrogenative borylation of vinylarenes to access 2,2-disubstituted-1-alkenylboronates that are not accessible by standard alkyne hydroboration chemistry [286]. By using the catalyst precursor $RhCl(CO)(PPh_3)_2$ and B_2pin_2 or B_2neop_2, the authors found conditions that prevent significant competitive hydrogenation or hydroboration of the product. For example, (*E*)-Ph(Me)C=CH(Bpin) was obtained from α-methylstyrene in high yield and high geometrical selectivity (entry 27, Table 1.4). A mechanism that accounts for the beneficial role of acetonitrile as co-solvent was proposed. To access similar 2,2-disubstituted-1-alkenylboronates, a two-step sequence of bromoboration/Negishi coupling was described [287].

Diboronyl compounds add onto terminal and internal alkynes under platinum catalysis to provide *cis*-1,2-diboronylalkenes [288]. For example, $Pt(PPh_3)_4$ catalyzes the addition of bis(pinacolato)diboron (**58**) to 1-decyne, affording the corresponding alkenylbisboronate (entry 28, Table 1.4). Several other metal complexes tested, including palladium, rhodium and nickel complexes, failed to promote the same reaction. Mechanistically, the reaction's catalytic cycle is thought to be initiated by the oxidative addition of Pt(0) into the B–B bond, followed by a cis-boro-platination of the alkyne, and the cycle is terminated by the reductive elimination of the alkenyl-Pt(II)-Bpin unit to give the product and regenerate the Pt(0) catalyst [289]. Allenes also react similarly (entry 29) [290]. In a related process, B_2pin_2 was found to add to terminal alkynes at room temperature in the presence of stoichiometric copper(I) chloride and potassium acetate as the base [291]. It was proposed that a boron-to-copper transmetallation is involved, giving a putative boryl-copper species (CuBpin). The reaction provides a variable ratio of 1-boronyl and 2-boronyl alkenes, depending on the additive employed, which can either be a phosphine or LiCl (entry 30). Recently, Mu-

rakami and co-workers reported a palladium-catalyzed silaboration of allenes, affording 2-boronyl-allylsilanes [292]. The same group also described a palladium- and nickel-catalyzed intramolecular cyanoboronation of homopropargylic alkynes [293].

1.3.5 Alkynylboronic Acids

Like their aryl and alkenyl counterparts, alkynylboronic acids can be made by displacement of magnesium or lithium acetylides with borate esters. For example, Matteson and Peacock have described the preparation of dibutyl acetyleneboronate from ethynylmagnesium bromide and trimethyl borate [294]. The C–B linkage is stable in neutral or acidic hydrolytic solvents but readily hydrolyzes in basic media such as aqueous sodium bicarbonate. Brown and co-workers eventually applied their organolithium route to boronic esters to the particular case of alkynylboronic esters, and in this way provided a fairly general access to this class of compounds [295].

1.3.6 Alkylboronic Acids

Compared to aryl- and alkenylboronic acids, alkylboronic acids and esters have found limited use as synthetic intermediates aside for their oxidation into alcohols (Section 1.5.2.1). This is due in part to their inferior shelf-stability. In addition, their transmetallation with transition metal catalysts such as palladium is presumed to be more difficult than that of the unsaturated and aromatic boronic acid derivatives [296]. For example, alkylboronic acids have long been known to be reluctant substrates in the Suzuki-cross-coupling reaction, and they have become efficient in this application only very recently with the use of special bases and the advent of new and highly active catalyst systems (Section 1.5.3.1). Perhaps the most synthetically useful class of alkylboronic acids are the α-haloalkyl derivatives popularized by Matteson (Section 1.3.8.4), and their elegant chemistry is described in Chapter 8.

Alkylboronic acids and esters can also be synthesized from the trapping of organomagnesium and organolithium intermediates with borates. Methylboronic esters, for example, are made using the condensation of methyllithium and triisopropylborate [180]. Likewise, the useful α-chloromethylboronate reagents **90** can be made with the in situ trapping variant whereby butyllithium is added to a mixture of ICH_2Cl and triisopropylborate [297]. The corresponding bromides (**91**) [298] and iodides (**92**) [299] were also reported. Both catalyzed and uncatalyzed hydroboration of alkenes serve as powerful methods to access enantiopure alkylboronic esters. Because a selective oxidation of two of the resulting three B–C bonds following hydroboration with dialkylboranes is difficult, a hydroboration route to alkylboronic acids and esters is limited to reagents such as Ipc_2BH (**86**), dihaloboranes, and dialkoxyboranes (e.g., catechol- and pinacolborane). The asymmetric hydroboration of alkenes with Ipc_2BH or $IpcBH_2$ (Equation 29, Figure 1.23) [300, 301], or using chiral rhodium catalysts [302], constitutes well-established routes to access chiral alkylboronic esters or the corresponding alcohols or amines after a stereospecific oxidation of the B–C bond (Sec-

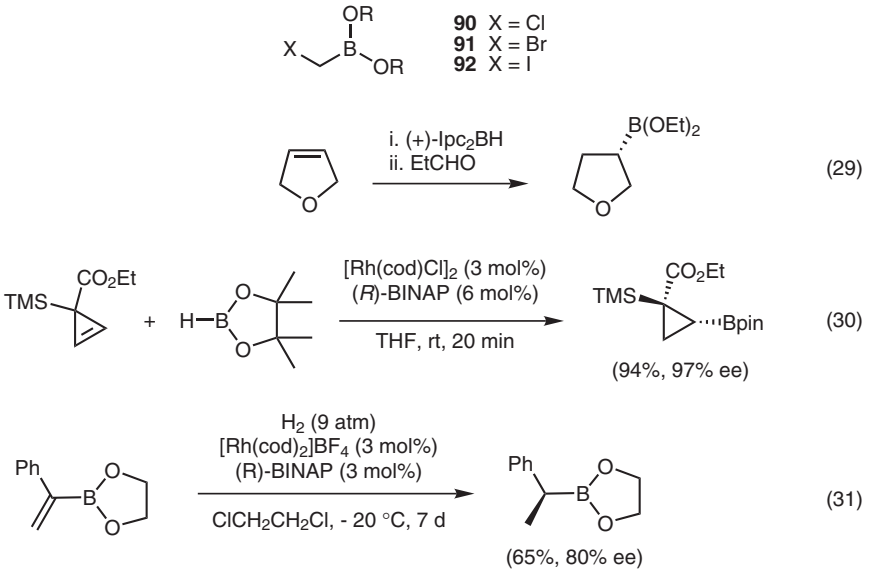
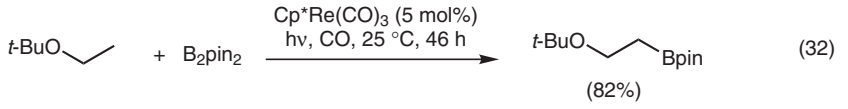


Figure 1.23 Alkylboronic acids (esters): selected examples of enantioselective preparative methods.

tions 1.5.2.1 and 1.5.2.2). Chiral cyclopropylboronic esters were obtained by catalytic enantioselective pinacolboration of cyclopropenes (Equation 30) [303]. Stereoisomerically pure alkylboronic esters can also be obtained through less common methods such as the hydrogenation of chiral alkenylboronic esters [304], and even with enantioselective variants using chiral catalysts (Equation 31) [305]. Other types of additions and cycloadditions of alkenylboronic esters are discussed in detail in Chapter 9. The aforementioned Matteson asymmetric homologation of (α-haloalkyl)boronic esters is another popular strategy to access new alkylboronic esters (Section 1.3.8.4 and Chapter 8). Alkylboronic acids have also been obtained by a regioselective rhenium-catalyzed C–H activation/boronylation reaction (Equation 32) [210b].

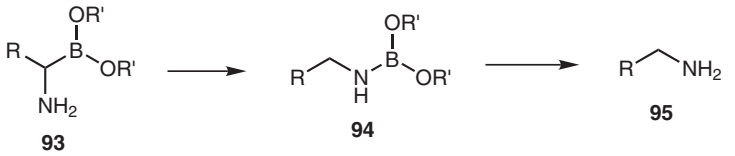


1.3.7
Allylic Boronic Acids

Because of their tremendous utility as carbonyl allylation agents (Section 1.5.3.2), several methodologies have been developed for synthesizing allylic boronic acids and their various esters. The preparation and reactions of allylic boronic esters are discussed in detail in Chapter 6.

1.3.8 Chemoselective Transformations of Compounds containing a Boronic Acid (Ester) Substituent

New boronic acid derivatives can be made by the derivatization of compounds that already contain a boronic acid(ester) functionality. The scope of possible transformations, however, relies on the compatibility of these reaction conditions with the boronate group, and in particular the oxidatively labile C–B bond. One seminal example illustrating the limitations imposed by the intrinsic reactivity of boronic acids is that of α-aminoalkylboronic acids, the boron analogues of amino acids (Section 1.3.8.4) [306]. The synthesis of these important derivatives remained an elusive goal for several years. The reason for the instability of compounds of type **93** is the incompatibility of free α-amino groups possessing hydrogen substituents, which undergo a spontaneous 1,3-rearrangement to give the homologated amine **94** (Equation 33) [111].



(33)

Eventually, this undesired process was prevented through rapid acetylation of the amino group or its neutralization as a salt [111]. This undesirable rearrangement was later exploited in a method for mono-N-methylation of primary amines [307]. As exemplified with the formation of ethylene by debromoboronation of 2-bromoethaneboronic acid, alkylboronic acids with a leaving group in the β-position are unstable under basic conditions [308]. Matteson has provided a detailed overview on the chemical compatibility of boronic acids and esters – a review that is undoubtedly of great help in avoiding trouble when derivatizing a boronic acid containing compound [309]. Therefore, only selected examples of boronate-compatible transformations are discussed in this section.

1.3.8.1 Oxidative Methods

The sensitivity of the B–C bond of boronic acids and esters to oxidation was discussed in Section 1.2.2.5.2. Although basic hydrogen peroxide and other strong oxidants rapidly oxidize B–C bonds, a certain degree of selectivity is possible. For example, sulfide and alcohol functionalities can be oxidized selectively without affecting the boronate group (Equations 34 and 35, Figure 1.24) [244]. However, epoxidation of alkenylboronic esters fails – but it can be achieved indirectly from trifluoroborates salts (Equation 26, Figure 1.17) [172]. The permanganate oxidation method is commonly employed to access carboxy-substituted arylboronic acids from methyl-substituted precursors [310]. Radical bromination of methyl-substituted arylboronic acids provides a route to the corresponding hydroxymethyl and formyl derivatives (Equations 36–38) [155]. Bromination of *p*-tolylboronic acid, followed by alkylation of aceta-

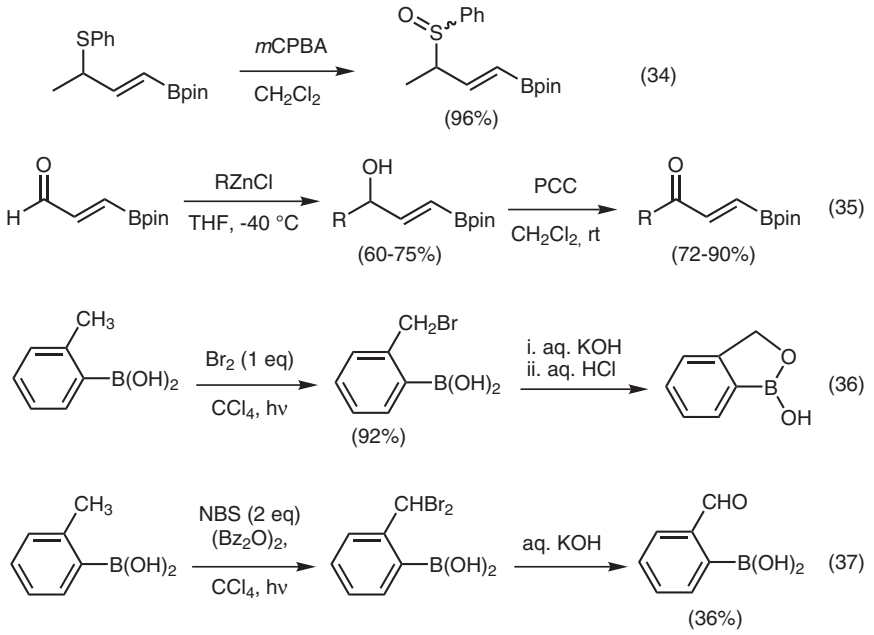


Figure 1.24 Chemoselective oxidation reactions involving boronic acid derivatives.

minomalonic ester, hydrolysis and decarboxylation, afforded the first synthesis of 4-borono-phenylalanine [155].

1.3.8.2 **Reductive Methods**

Care must be taken in using strong hydride reagents as they can transform boronic esters into dihydridoboranes (Section 1.2.3.6). Subsequent hydrolysis, however, can restore the boronic acid. Hindered alkenylboronates are tolerant of DIBALH (Scheme 1.3 below) [107]. Catalytic hydrogenation methods appear to be quite compatible with boronate groups, as shown by the examples of Figure 1.25 (Equations 38 and 39) [311, 312].

1.3.8.3 **Generation and Reactions of α-Boronyl-substituted Carbanions and Radicals**

Carbanions adjacent to a boronate group can be generated by two general approaches, direct deprotonation or metallation by replacement of an α-substituent. Direct deprotonation of simple alkylboronic esters like 2,4,4,5,5-pentamethyl-1,3,2-dioxaborolane [**96** with $(RO)_2 = OCMe_2CMe_2O$, Equation 40 in Figure 1.26] is not possible even with strong bases like LDA or lithium 2,2,6,6-tetramethylpiperidide (LiTMP) [280]. An activating group must be present next to the boronate; a phenyl [280], thioether [313], trimethylsilyl [278, 314], triphenylphosphonium [314], or another boronate group [280] are all suitable in this role (i.e., **97–100**, Equation 40). Relatively hindered bases and a large boronic ester are preferable to favor C–H abstraction over

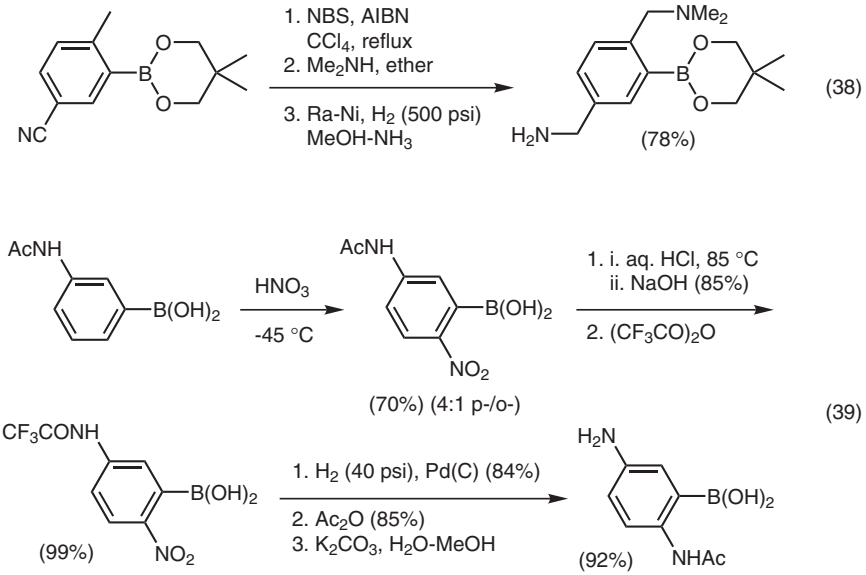


Figure 1.25 Chemoselective reduction reactions involving boronic acid derivatives.

the formation of a B–N ate adduct. For example, the carbanion of bis(1,3,2-dioxaborin-2-yl)methane [**100** with $(RO)_2 = O(CH_2)_3O$] can be generated by treatment with LiTMP (one equivalent) and one equivalent of the additive tetramethylethylenediamine (TMEDA) in tetrahydrofuran (–78 to 0 °C) [280]. Some of these species can be alkylated efficiently with primary halides and tosylates. Propanediol bisboronate **100** [$(RO)_2 = O(CH_2)_3O$] and the useful α-phenylthio derivative **101**, deprotonated with LDA, can even be alkylated twice in a sequential manner (Equation 41) [313]. The anion of **101** was also reacted with epoxides and lactones, and more recently it was used in the synthesis of functionalized boronic acid analogues of α-amino acids [315]. The carbanions of gem-diboronic esters **100** and trimethylsilylmethyl pinacolboronate [**99** with $(RO)_2 = OCMe_2CMe_2O$] undergo other transformations and also behave as substituted Wittig-like reagents by adding to aldehydes or ketones to provide alkenylboronates (e.g., entry 25, Table 1.4), which can also be oxidized and hydrolyzed to provide the homologated aldehydes [279, 316]. One drawback to the use of **100** is its preparation, which provides a low chemical yield. The corresponding carbanion can also be accessed by reaction of tris(dialkoxyboryl)methanes with an alkyllithium, but this approach lacks generality [317]. bis(1,3,2-Dioxaborin-2-yl)methane [**100** with $(RO)_2 = O(CH_2)_3O$] is suggested to be slightly more acidic than triphenylmethane (pK_a 30.6 in DMSO) [280], which confirms the rather weak stabilizing effect of a boronate group compared to a carboxyester (pK_a of dimethylmalonate ~13). Calculation of the Hückel delocalization energies confirmed that a boronate group is indeed slightly more stabilizing than a phenyl group (pK_a of diphenylmethane = 32.6 in DMSO), and the calculation of B–C π-bond orders indicated a very high degree of

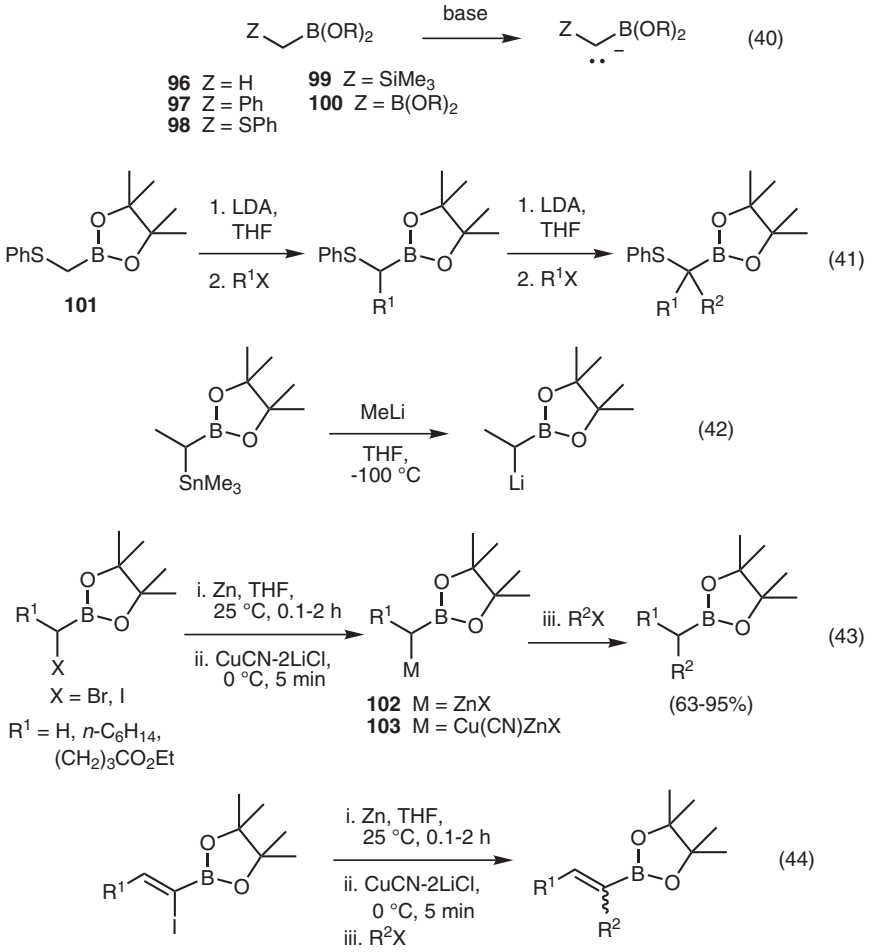


Figure 1.26 Formation and reactions of boronyl-substituted carbanions.

B–C conjugation in the carbanion [280]. This result appears to contradict the apparently modest degree of B–C π-overlap in alkenyl and aryl boronates discussed in Section 1.2.2.1; however, the latter cases concerned neutral species.

Other methods for the generation of α-boronyl carbanions include examples such as the lithiation of an α-trimethylstannyl derivative (Equation 42, Figure 1.26) [318], and the formation of the corresponding organozinc or organocopper species from α-bromo or α-iodo alkylboronates (Equation 43) [319]. In the latter cases, as demonstrated by Knochel, the mildness of the zinc and copper organometallic intermediates expands the range of compatible functional groups compared to the corresponding organolithium intermediates described above. Thus, reagents **102** and **103**, even with a carboxyester-containing side chain as R^1 substituent, were reacted with various electrophiles such as allylic halides, aldehydes, and Michael acceptors in good to excellent

yields (Equation 43). Likewise, the related sp^2 1,1-bimetallics can be generated from 1-iodoalkenylboronic pinacol esters, albeit with loss of stereochemical integrity of the olefin geometry (Equation 44) [320]. In one example, the Negishi coupling of a 1-iodozincalkenylboronate with an alkenyl iodide partner led to the formation of a 2-boronylbutadiene.

1.3.8.4 Reactions of (α-Haloalkyl)boronic Esters

One of the most powerful methods for modifying alkylboronic esters involves the nucleophilic attack and 1,2-rearrangement on (α-haloalkyl)boronic esters (**104**) (Figure 1.27). The addition of organometallic species to these boronic esters induces a facile boron-promoted displacement (Equation 45). Heteroatom-containing nucleophiles as well as organometallic reagents can be employed in this substitution reaction. Conversely, the addition of α-haloakyl carbanions to alkyl- and alkenylboronic esters leads to the same type of intermediates, and constitutes a formal one-carbon homologation of boronic esters (Equation 46). Sulfides from the addition of carbanions of α-thioethers can also undergo this rearrangement in the presence of mercuric salts [321]. A very efficient asymmetric variant of this chemistry was developed to allow the synthesis of chiral α-chloroalkylboronates, which can further undergo substitution reactions with a broad range of nucleophiles [322]. These α-chloroboronates are obtained in a very high enantiomeric purity through the Matteson asymmetric homologation reaction, which features the $ZnCl_2$-promoted addition of dichloromethyllithium to the boronates of pinanediol and a number of C2-symmetrical 1,2-diols. This elegant methodology was used in the synthesis of complex natural products, and is a cornerstone in the design and preparation of α-acylaminoboronic acid enzyme inhibitors.

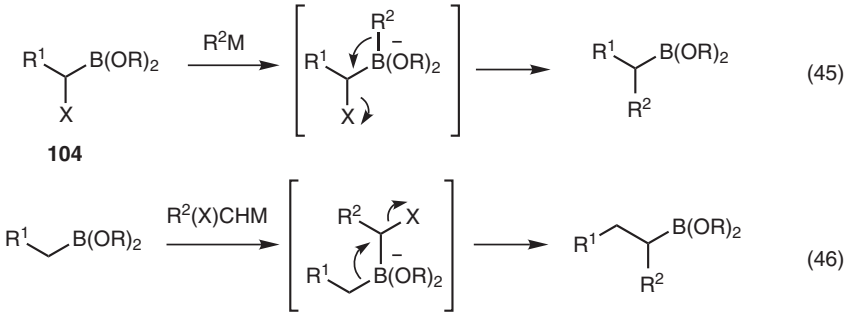
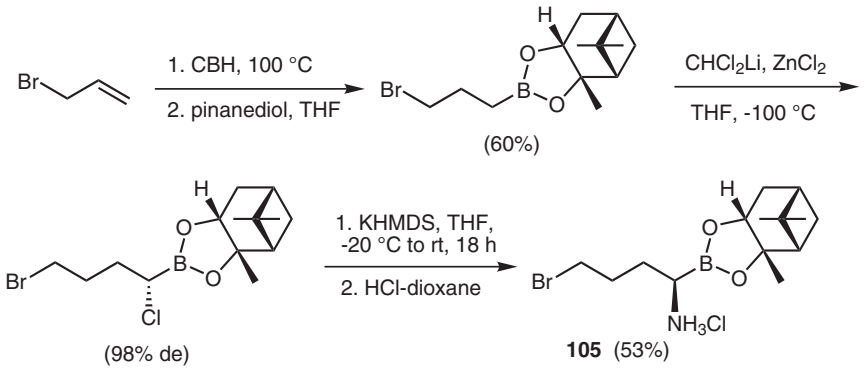


Figure 1.27 Substitution reactions of (α-haloalkyl)boronic esters.

As exemplified with the synthesis of **105** (Scheme 1.2), the latter compounds are obtained via the displacement α-chloroalkylboronates with the hexamethyldisilazide anion. This example also emphasizes the powerful neighboring group effect of boron, which allows selectivity in the addition of Cl_2CHLi in the presence of a primary alkyl bromide [323]. Other applications of (α-haloalkyl)boronates in stereoselective synthesis are detailed in Chapter 8.



Scheme 1.2 Application of the Matteson asymmetric homologation to the synthesis of chiral α-aminoboronic esters.

1.3.8.5 **Other Transformations**

Several other reactions can be performed on free boronic acids and the corresponding esters. Nitration of free arylboronic acids under fuming nitric acid and concentrated sulfuric acid has been known since the 1930s [324], albeit the use of low temperatures (e.g., Equation 39, Figure 1.25) is recommended in order to minimize protodeboronation (Section 1.2.2.5.3) [312, 325]. Other successful transformations of arylboronic acids include diazotization/hydrolysis [177], bromination [8], and nucleophilic aromatic substitutions [177]. Some alkenylboronates can be isomerized to allylboronates in high yields under Ru or Ir catalysis [326]. Schrock carbene formation is compatible with arylboronates [83], and radical additions to allyl or vinylboronates provide usefully functionalized alkylboronic esters [327]. Pinacol alkenylboronates are robust enough to tolerate a number of transformations, such as ester hydrolysis and a Curtius rearrangement (Equation 47, Figure 1.28) [328]. The scope of compatible transformations can be further increased with the help of a bulky boronate ester to effectively protect the susceptible boron center in oxidations, reductions, and other reactions (e.g. Scheme 1.3) [107]. Chapter 9 describes more addition and cycloaddition chemistry of alkenylboronic acid derivatives, including radical additions, cyclopropanation, and [4+2] cycloadditions.

Alkylboronic esters can also tolerate a wide range of conditions, and problems, if any, are usually encountered in the purifications steps rather than with the actual chemistry. The synthesis of 2-amino-3-boronopropionic acid, the boronic acid analogue of aspartic acid (**106**, Scheme 1.4), which included reactions such as carbethoxyester hydrolysis, a Curtius rearrangement, and hydrogenolysis, convincingly illustrates the range of possibilities [329]. Unlike the α-aminoalkylboronic acids described above, homologous compound **106** is stable and is thought to exist as an internal chelate or a chelated dimer in aqueous solutions. Lithiations in the presence of a boronic acid or the corresponding ester are difficult due to the electrophilic properties of the boron atom [330]. In this regard, protection of the boronyl group as a diethanolamine ester allowed the synthesis of *para*- and *meta*-chlorosulfonyl aryl-

boronic acids via a clean bromine/lithium exchange followed by trapping with sulfur dioxide (Equation 48, Figure 1.28) [331].

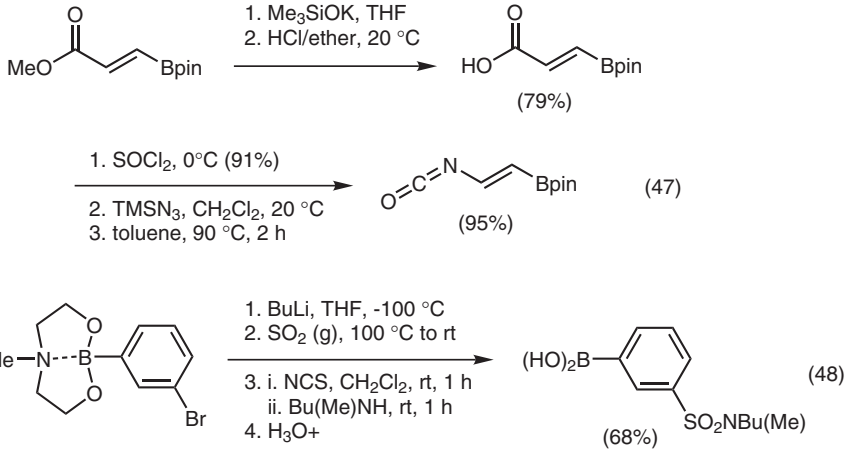
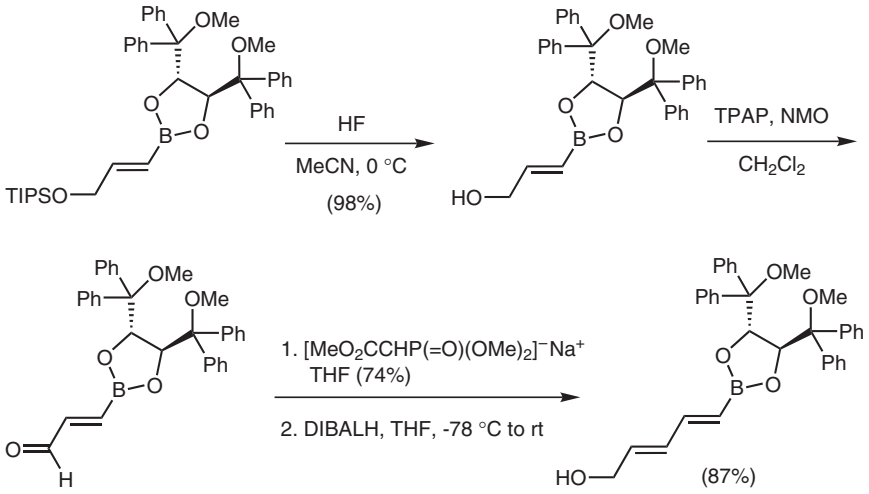
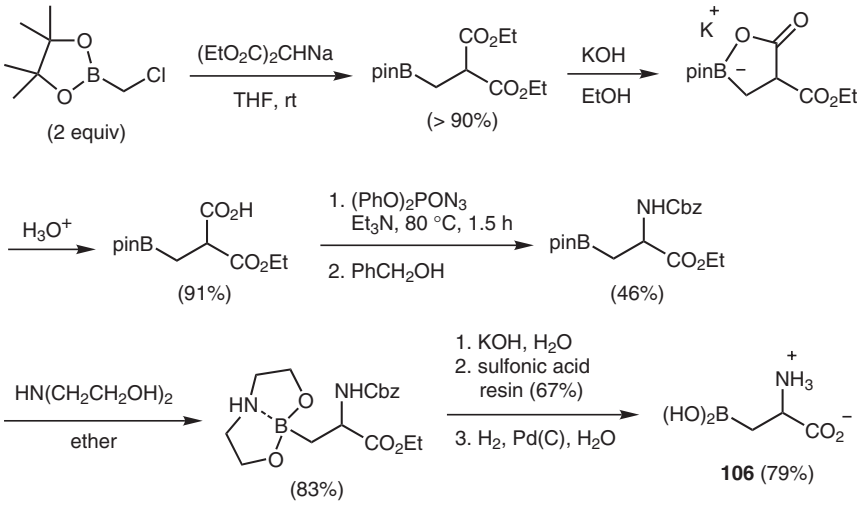


Figure 1.28 Other chemoselective reactions involving boronic acid derivatives.



Scheme 1.3 Sequence of transformations on a boronate-protected alkenylboronic acid.



Scheme 1.4 Synthesis of the boronic acid analogue of aspartic acid (**106**).

1.4
Isolation and Characterization

As discussed in Section 1.2.2.2, the polar and often amphiphilic character of boronic acids tends to make their isolation and purification difficult. In some cases, nonpolar organic solvents may be used to precipitate small boronic acids dissolved in a polar organic solvent. At higher pH where the hydroxyboronate species predominates (Section 1.2.2.4.1), however, boronic acids may be entirely miscible in water. For this reason, when extracting boronic acids from aqueous solutions, it is desirable to adjust the pH of the water phase to neutral or slightly acidic, and to use a polar organic solvent for an efficient partition. In addition to these potential difficulties in isolating boronic acids, their tendency to form oligomeric anhydrides further complicates characterization efforts. To palliate to these problems, boronic acids are often purified and characterized as esters. The following section provides a summary of useful methods and generalizations for the isolation and characterization of boronic acids and boronic esters.

1.4.1
Chromatography and Recrystallization

Most boronic acids can be recrystallized with ease. The choice of recrystallization solvent, however, greatly affects the relative proportions of free boronic acid and its corresponding anhydrides in the purified solid. Santucci and Gilman found that acids are usually obtained from aqueous solutions (i.e. water or aqueous ethanol), and anhydrides predominate when non-polar recrystallization solvents like ethylene dichlo-

ride are employed [332]. Recrystallization in benzene gives some dehydration, but to a lesser extent. Several other solvents have been used for the recrystallization of arylboronic acids. Much like carboxylic acids, most boronic acids interact strongly with silica gel. Depending on the degree of hydrophobicity of the boron substituent, chromatography and TLC on silica gel may be possible despite the high retentivity of boronic acids. A highly lipophilic trienylboronic acid was conveniently purified by silica gel chromatography [226]. Some polar boronic acids literally stick to silica and can hardly be eluted, even with eluents containing methanol or a small proportion of acetic acid. In other cases, filtration through a short plug of silica using acetone as co-eluent [333], or the use of a polar eluent mixture of CH_2Cl_2 and EtOAc, were found suitable [325].

1.4.2
Solid Supports for Boronic Acid Immobilization and Purification

Recently, the increasing popularity of boronic acids as synthetic intermediates has motivated the development of solid supports and linkers to allow their immobilization and facilitate purification operations or derivatization (Figure 1.29). The appeal of these methods is particularly apparent in view of the difficulties often encountered in isolating pure boronic acids from both aqueous and organic solvent systems.

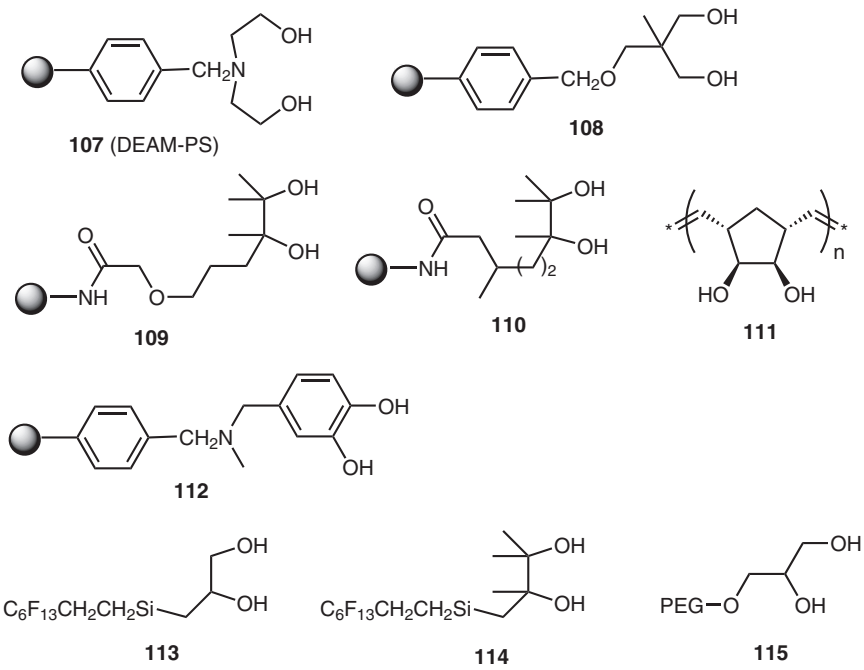


Figure 1.29 Diol-based supports for boronic acid immobilization and purification.

1.4.2.1 **Diethanolaminomethyl Polystyrene**

Diol-based insoluble polystyrene resins that can form supported boronate esters are obvious choices for immobilizing boronic acids. Hall and co-workers reported the first such example of solid support for boronic acids, the diethanolaminomethyl polystyrene resin (DEAM-PS, **107** in Figure 1.29) [334, 335]. The immobilization of alkyl, alkenyl, and arylboronic acids with this resin is straightforward, consisting simply of mixing a slight excess of DEAM-PS, as a suspension, in an anhydrous solution containing the boronic acid [334a]. Tetrahydrofuran is the solvent of choice as it dissolves most boronic acids. Notably, no azeotropic removal of the water released is needed, which is a benefit of B–N coordination in the resulting boronate adducts and of the highly hydrophobic nature of this polystyrene support. This simple procedure can be employed to scavenge or purify boronic acids from crude mixtures (Equation 49, Figure 1.30). Following resin washings, the desired boronic acid can be recovered upon treatment of the resin with a 5–10% solution of water in THF. A wide variety of arylboronic acids were immobilized with the DEAM-PS resin, and it has even been employed successfully in the derivatization of functionalized boronic acids [335]. Thus, amino-substituted arylboronic acids supported onto DEAM-PS were transformed into anilides and ureas, bromomethyl-substituted ones were reacted with amines, formyl-substituted ones were subjected to reductive amination with aldehydes, and carboxy-substituted phenylboronic acids were transformed into amides [335]. All these transformations afforded new arylboronic acid derivatives in very high purity directly after cleavage from the resin. The advantages of this solid-supported approach in avoiding the usual partitions between aqueous-organic solvent mixtures are best illustrated in the preparation of the BNCT candidate **118** (Equation 50, Figure 1.30), an amphoteric boronic acid soluble in aqueous solutions over the entire pH range (at pH > 8, the hydroxyboronate species is predominant, and at lower pH the amine is protonated). After immobilization of *p*-carboxyphenylboronic acid onto DEAM-PS to afford **116**, amide coupling with *N*,*N*-diethylethylenediamine followed by simple resin washings afforded the supported product **117**, which was released from the support to give **118** in very good yield and high purity (Equation 50) [335]. DEAM-PS supported boronic acids were also employed in the interesting concept of resin-to-resin transfer reactions (RRTR), whereby a phase transfer agent is used in situ to allow the transfer of one supported substrate to another resin-supported substrate. This convergent solid-phase synthetic strategy was applied to the Suzuki cross-coupling [336] and the borono-Mannich reactions [337]. These strategies are yet another benefit of the ease of boronic acid immobilization and cleavage when using DEAM-PS, which constitutes a significant advantage of this commercially available resin compared to most other diol-based resins described below.

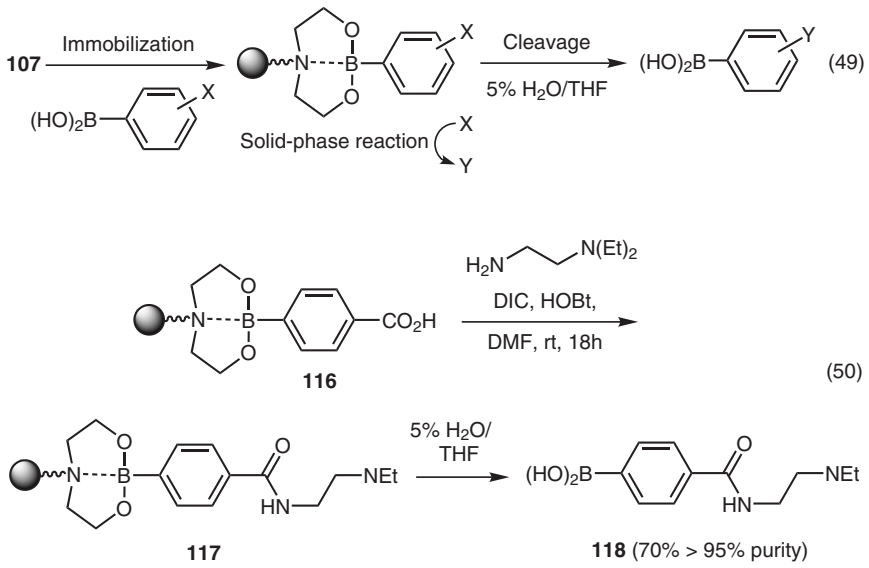


Figure 1.30 Solid-phase immobilization and derivatization of boronic acids using *N*,*N*-diethanolaminomethyl polystyrene (DEAM-PS, **107**).

1.4.2.2 **Other Solid-supported Diol Resins**

A macroporous polystyrene resin functionalized with a 1,3-diol unit, **108**, has been described by Carboni and co-workers [338]. Although the immobilization and subsequent cleavage of boronic acids both require harsher conditions than DEAM-PS, this support has also proven useful in the derivatization of functionalized boronic acids, as well as in several elegant C–C bond forming/release procedures [339] and a traceless cleavage of arenes [340]. Analogous pinacol-like linkers **109** and **110** were also described, although pre-attachment of the boronic acid prior to immobilization was required in these examples [341, 342]. The use of a ROMPgel diol (**111**) in the immobilization of allylboronates was reported to simplify the purification of the homoallylic alcohol products resulting from aldehyde additions [343]. More recently, a catechol resin (**112**) was found to be effective in the immobilization and derivatization of functionalized arylboronic acids [344].

1.4.2.3 **Soluble Diol Approaches**

Fluorous phase purification methodologies using fluoroalkyl-tagged substrates combine the advantages of homogenous reaction conditions of solution-phase reactions with the ease of purification of solid-phase methods. In this regard, a new class of pinacol-like and other diol-based polyfluoroalkyl linkers such as **113** and **114** were described [345]. The resulting fluorous boronates were employed in various transformations, and allowed a facile purification by simple partition between fluorous and organic solvents. A dendritic high-loading polyglycerol, **115**, was shown to be effec-

tive in immobilizing arylboronic acids and in facilitating the purification of biaryl products from homogeneous Suzuki cross-coupling reactions [346].

1.4.3 Analytical and Spectroscopic Methods for Boronic Acid Derivatives

1.4.3.1 Melting Points and Combustion Analysis

The difficulty in measuring accurate and reproducible melting points for free boronic acids has long been recognized [347]. Rather than true melting points, these measurements are often more reflective of dehydration or decomposition points [185, 348]. The lack of reproducibility for a given boronic acid may originate from the water contents of the sample used, which affects the acid–anhydride transition. Moreover, as mentioned above, the water content also depends on the recrystallization solvent [332]. For these reasons, it is often more appropriate to report melting points of boronic acids as their diethanolamine ester (Section 1.2.3.2.1). Likewise, combustion analysis of free boronic acids may provide inaccurate results depending on the recrystallization method employed.

1.4.3.2 Mass Spectrometry

One useful diagnostic information in the mass spectrometric analysis of boronic acid derivatives is the observation of boron's isotopic pattern, which is constituted of ^{10}B (20% distribution) and ^{11}B (80%). However, unless other functionalities help increase the sensitivity of a boronic acid containing compound, it is often difficult to obtain intense signals with most ionization methods due to the low volatility of these compounds. This problem is exacerbated by the facile occurrence of gas-phase dehydration and anhydride (boroxine) formation in the ion source. To minimize these thermal reactions and improve volatility, cyclic boronates such as the 1,2-ethanediol, 1,3-propanediol, and pinacol esters are employed. These derivatives were even made on an analytical scale [349]. Fragmentation patterns of various para-substituted arylboronic esters of 1,2-ethanediol were studied using electron impact ionization and several deboronative fragmentation pathways were observed [350]. The nature of the para substituent was found to have a marked influence. In another study by GC-MS, ortho substituents were found to interact strongly during fragmentation [349]. Boropeptides, a popular class of enzyme inhibitors (Section 1.6.5), and phenylboronic acid were characterized by positive-ion ammonia chemical ionization with different diols as bench-top derivatization agents [351].

1.4.3.3 Nuclear Magnetic Resonance Spectroscopy

Boron compounds, including boronic acid derivatives, can be conveniently analyzed by NMR spectroscopy [352]. Of the two isotopes, ^{11}B is the most abundant (80%) and possesses properties that are more attractive towards NMR. These attributes include its lower resonance frequency, spin state (3/2) and its quadrupole moment, a wide range of chemical shifts, and its higher magnetic receptivity (16% of ^{1}H). When analyzing boronic acids in non-hydroxylic solvents by NMR spectroscopy, it is often necessary to add a small amount of deuterated water (e.g. one or two drops) to the sam-

ple in order to break up the oligomeric anhydrides. Alternatively, analysis in anhydrous alcoholic solvents such as methanol will allow detection of the in situ formed methanolic ester. Observation of the ^{11}B nucleus against a reference compound (e.g. BF_3) is straightforward with modern instruments, and can be especially revealing of the electronic characteristics [33] and coordination state of the boronate moiety. The boron resonance of free boronic acids and tricoordinate ester derivatives is generally detected in the 25–35 ppm range, and tetracoordinate derivatives such as diethanolamine esters resonate at around 10 ppm [353]. In ^{13}C analysis, carbons next to the ^{11}B atom tend to be broadened – often beyond detection limits. Consequently, with aromatic boronic acids the signal of the quaternary carbon bearing the boron atom, which is already depleted by a long relaxation time, is very difficult to observe over the background noise.

1.4.3.4 Other Spectroscopic Methods

Despite their limited structure determination capabilities, ultraviolet and infrared spectroscopy were determinant characterization techniques in the early days of boronic acid research [332]. Notable IR absorptions are the strong H-bonded OH stretch (3300–3200 cm^{-1}), and a very strong band attributed to B–O stretch (1380–1310 cm^{-1}). IR is particularly diagnostic of the presence of boronic anhydrides. Upon anhydride (boroxine) formation, the OH stretch disappears and a new strong absorption appears at 680–705 cm^{-1} [68].

1.5 Overview of the Reactions of Boronic Acid Derivatives

1.5.1 Metallation and Metal-catalyzed Protodeboronation

In 1882, Michaelis and Becker described the preparation of phenylmercuric chloride (**119**) from the reaction of phenylboronic acid and aqueous mercuric chloride (Equation 51, Figure 1.31) [198b]. Benzylboronic acid was transformed into benzylmercuric chloride in the same manner, and both compounds were found to resist hydrolysis under the conditions of their preparation. Mechanistic studies later showed that this reaction proceeds through the hydroxyboronate ion [354]. Catechol and pinacol alkenylboronic esters can also be easily transformed into the corresponding organomercurial derivative with retention of configuration (Equation 52) [355, 356]. One of the early realizations concerning the reactivity of arylboronic acids was that several metal ions [other than Hg(II)] can induce protodeboronation in water, presumably via the intermediacy of an arylmetal species (Equation 51). Thus, Ainley and Challenger found that hot solutions of copper sulfate, cadmium bromide, and zinc chloride produce benzene [324]. As phenylboronic acid is stable to dilute hydrochloric acid, it was deduced that the deboronation occurred through the formation of intermediates similar to **119** (Figure 1.31) and their reaction with water, and not from the possible release of acid by hydrolysis of the metal salt. Instead of giving benzene,

cupric chloride and bromide were found to provide the respective phenyl chloride and bromide [324]. Halide salts of beryllium, magnesium, and calcium did not react with phenylboronic acid [324]. Arylboronic acids were transformed into arylthallium derivatives in similar fashion [357], and alkylboronic acids were unreactive under the same conditions [78]. Ammonical solutions of silver nitrate also induce protodeboronation of arylboronic acids, with production of silver oxide [176]. Aliphatic boronic acids behave differently and tend, rather, to undergo a reductive coupling to give dimeric alkane products [76]. Kuivila and co-workers studied the mechanism of metal ion catalysis in the aqueous protodeboronation of arylboronic acids [358]. Substituent effects and the influence of pH were investigated, and both base and cadmium catalysis pathways were evidenced for this reaction. The order of effectiveness of the different metal ions at effecting aqueous deboronation was established as Cu(II) > Pb(II) > Ag(I) > Cd(II) > Zn(II) > Co(II) > Mg(II) > Ni(II).

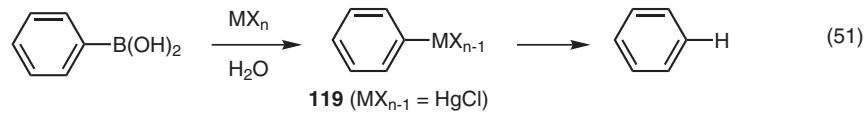


Figure 1.31 Transmetallation-protodeboronation of boronic acids.

From a synthetic chemistry standpoint, reaction of the metallated intermediates with electrophiles other than a proton is more attractive. Indeed, one of the most important recent developments in boronic acid chemistry strove from the discoveries that transition metals such as palladium(0), rhodium(I), and copper(I) can oxidatively insert into the B–C bond and undergo further chemistry with organic substrates. These processes are discussed in Sections 1.5.3 and 1.5.4.

1.5.2 Oxidative Replacement of Boron

1.5.2.1 Oxygenation

The treatment of arylboronic acids and esters with alkaline hydrogen peroxide to produce the corresponding phenols was first reported more than 75 years ago [324]. The oxidation of alkyl- and alkenyl- boronic acid derivatives leads to alkanols [40] and aldehydes/ketones, respectively [85, 257, 279, 316]. With α-chiral alkylboronates, the reaction proceeds by retention of configuration (Equation 53, Figure 1.32) [359, 121]. In fact, the oxidation of boronic acids and esters is a synthetically useful process, mainly in the preparation of chiral aliphatic alcohols via asymmetric hydroboration reactions [300, 302], or from Matteson homologation chemistry [322]. Paradoxically, the

oxidation of arylboronic acids is not a popular and economical approach for preparing phenols. It was recently reported, however, that a one-pot C–H activation/borylation/oxidation sequence gives access to meta-substituted phenols that would be difficult to obtain by other means (Equation 54) [360]. The mechanism of the aqueous basic oxidation of phenylboronic acid was investigated by Kuivila [361]. The rate is first order each in boronic acid and hydroperoxide ion, which led the authors to propose the mechanism of Equation 55 (Figure 1.32). The transition state features a boron-to-oxygen migration of the ipso carbon. Milder oxidants, such as anhydrous trimethylamine *N*-oxide [362], oxone [363], and sodium perborate [364, 365], can also be employed for the oxidation of most types of boronic acid derivatives. Notably, perborate was reported to give a cleaner oxidation of alkenylboronic acids into aldehydes compared to hydrogen peroxide [316]. Interestingly, the combined use of diacetoxyiodobenzene and sodium iodide under anhydrous conditions transforms

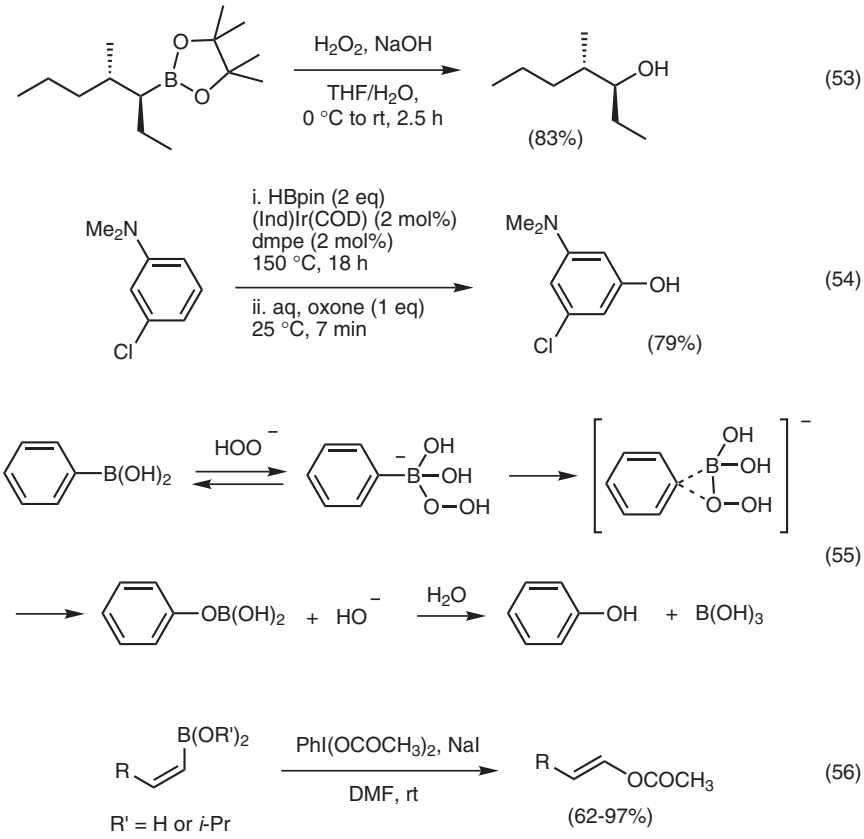


Figure 1.32 Oxidation of boronic acids (esters).

alkenylboronic acids and esters into enol acetates in a stereospecific manner (Equation 56) [366].

1.5.2.2 **Amination**

Aryl azides can be accessed indirectly from arylboronic acids via in situ generated aryllead intermediates (Equation 57, Figure 1.33) [367]. A mild procedure for ipso-nitration of arylboronic acids was recently developed (Equation 58), and a mechanism proposed [368]. The common methods and reagents for electrophilic amination, however, do not affect boronic acids and their esters. These processes require the intermediacy of more electrophilic boron substrates such as borinic acids or dichloroboranes. For example, enantiomerically pure propanediol boronates, which are accessible from the asymmetric hydroboration of alkenes with Ipc_2BH followed by acetaldehyde-promoted workup and transesterification, can be treated sequentially with MeLi and acetyl chloride. The resulting borinic ester is sufficiently electrophilic to react at room temperature with the amination reagent hydroxylamine-O-sulfonic acid with retention of stereochemistry to give primary amines in essentially 100% optical purity (Equation 59) [369]. The preparation of optically pure secondary amines from alkyl azides requires the intermediacy of the highly electrophilic dichloroboranes (Equation 60) [163], which can be made from boronic esters or monoalkylboranes as described in Section 1.2.3.6. A convenient one-pot procedure was described

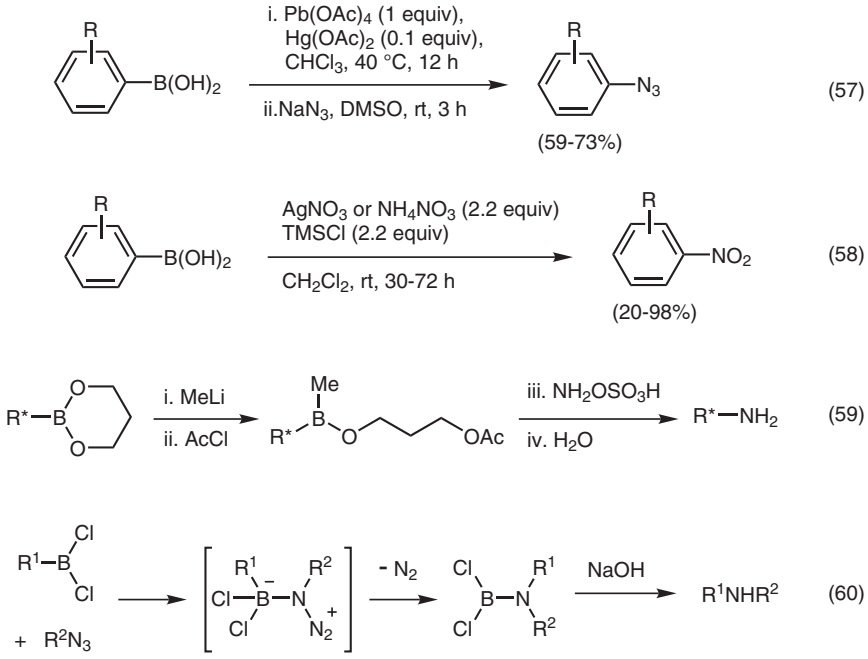


Figure 1.33 Oxidative amination of boronic acid derivatives.

with bis(isopropylamino)borane substrates, which can generate the corresponding dichloroboranes in situ by treatment with dry HCl [370]. Intramolecular variants of the reaction with alkylazides give access to pyrrolidines and piperidines [371].

1.5.2.3 **Halogenation**

1.5.2.3.1 Arylboronic Acids and Esters

As described above, cuprous chloride and bromide provide the corresponding ipso-substituted phenyl halides from benzeneboronic acid [324]. Likewise, arylboronic acids are halodeboronated regioselectively by the action of aqueous chlorine, bromine, and aqueous iodine containing potassium iodide [324]. Alkylboronic acids do not react under the same conditions [40]. Kuivila and co-workers have studied the kinetics of brominolysis in aqueous acetic acid and found that bases catalyze the reaction [372]. This observation and a Hammett plot of ten arylboronic acids [373] are consistent with a proposed electrophilic ipso-substitution mechanism involving the usual weakening effect of the C–B bond through formation of a boronate anion (Equation 61, Figure 1.34). *N*-Bromo- and *N*-iodosuccinimides convert arylboronic acids into the corresponding aryl halides in good to excellent yields [374]. Most arylboronic acids react in refluxing acetonitrile whereas the most activated ones such as 2-methoxyphenylboronic acid are iodinated at room temperature. Boronic esters provide significantly lower yields, and *N*-chlorosuccinimide is essentially unreactive, even in the presence of bases. Recently, the use of 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) under catalysis by sodium methoxide was shown to be an efficient bromodeboronation method for arylboronic acids when acetonitrile is used as solvent (Equation 62, Figure 1.34) [375]. The corresponding reagent DCDMH leads to the isolation of aryl chlo-

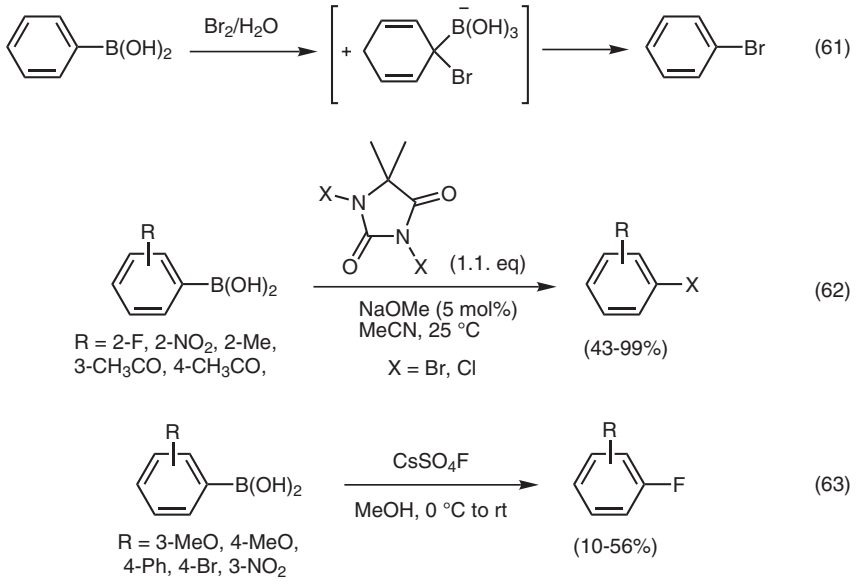


Figure 1.34 Halogenation of arylboronic acids.

rides. Aryl fluorides can be obtained in rather modest yield by treatment of arylboronic acids with cesium fluoroxysulfate ($CsSO_4F$) in methanol (Equation 63) [376]. Aryl(phenyl)iodonium salts are formed by treatment of arylboronic acids with trifluoromethanesulfonic acid and diacetoxyiodobenzene in dichloromethane [377].

1.5.2.3.2 Alkenylboronic Acids and Esters

The sequential treatment of alkenylboronic esters with bromine in ethereal anhydrous solvent, then with sodium hydroxide or alkoxides in a one-pot fashion, provides the corresponding alkenyl bromides with inversion of olefin geometry (Equations 64 and 65, Figure 1.35) [378–380]. A reasonable mechanism to account for the inversion is based on the formation of a vicinal dibromide followed by a trans bromodeboronation promoted by the addition of the base (Equation 64) [380]. The related iodinolysis process is complementary, giving alkenyl iodides with retention of olefin geometry (Equations 66 and 67) [381–383]. The procedure involves the simultaneous action of iodine and aqueous sodium hydroxide, and a tentative mechanism involving the syndeboronation of an iodohydrin intermediate has been proposed to explain the stere-

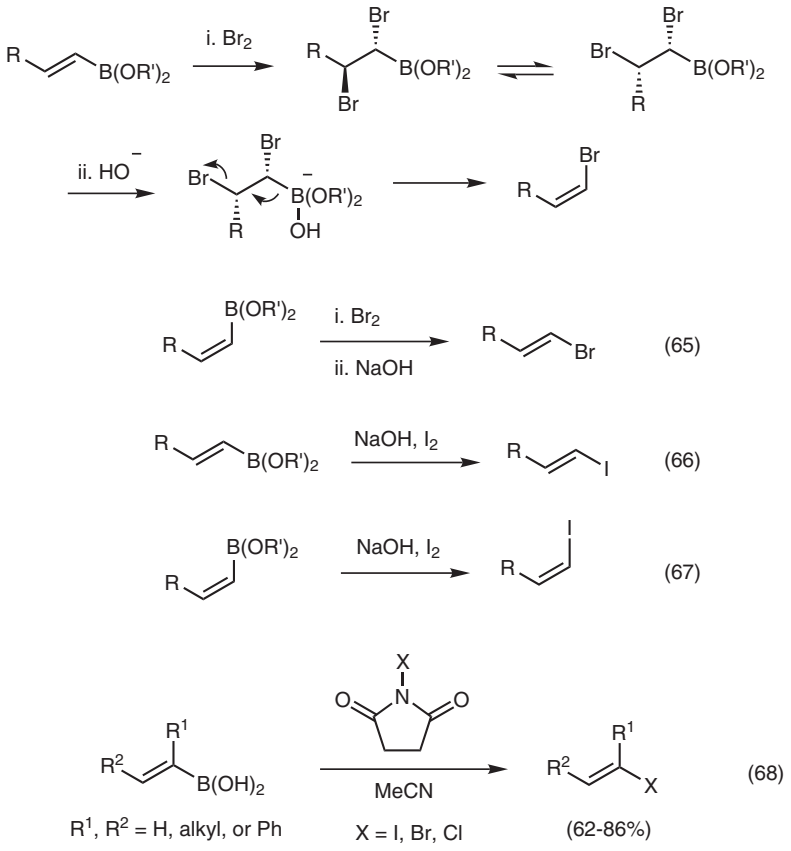


Figure 1.35 Halogenation of alkenylboronic acids (esters).

ochemistry of this reaction [380]. Like the bromination process, however, in most cases a sequential treatment of the alkenylboronic acid with iodine, then with sodium hydroxide, provides the corresponding alkenyl iodides by inversion of geometry [380]. In both cases, boronic acids can be used directly with only one equivalent of halogen, whereas boronic esters can be transformed effectively with at least two equivalents of the requisite halogen. The use of ICl and sodium acetate was also demonstrated [384]. Indeed, the combination of ICl and sodium methoxide as base was more efficient with hindered pinacol alkenylboronates, and both isomers can be obtained selectively from a single (*E*)-1-alkenylboronate, depending on the order of addition of the reagents [385]. A mechanism involving the boronate ion was invoked in this variant as well, and, notably, a pinacol alkylboronic ester failed to react. Petasis and Zavialov reported a mild halogenation procedure for various types of alkenylboronic acids using halosuccinimides as reagents (Equation 68, Figure 1.35) [386]. The reactions proceed in acetonitrile at room temperature to provide high yields of alkenyl halide products with retention of olefin geometry. The stereoselectivity was tentatively explained through a pseudo-intramolecular substitution mechanism within a tetracoordinate boron intermediate. The chlorination variant with *N*-chlorosuccinimide, however, requires the use of triethylamine as base. Alkenylboronic acids were also chlorinated with chlorine by inversion olefin geometry [387].

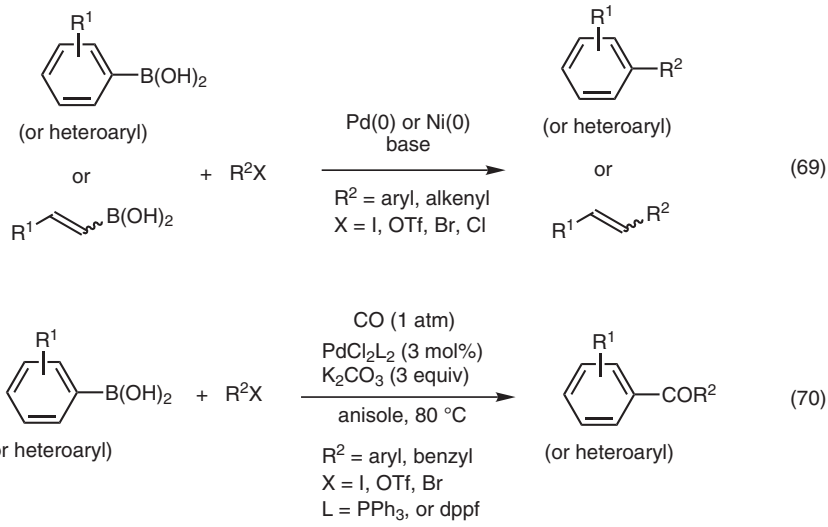


Figure 1.36 Transition metal-catalyzed coupling of boronic acids (esters) with carbon halides/triflates (Suzuki cross-coupling reaction).

1.5.3 Carbon–Carbon Bond forming Processes

1.5.3.1 Palladium-catalyzed Cross-coupling with Carbon Halides (Suzuki Coupling)

A 1979 *Chemical Communications* paper by Miyaura and Suzuki reported findings generally regarded as the most important discovery in the recent history of boronic acid chemistry [388]. This paper described a Pd(0)-catalyzed coupling between alkenyl boranes or catecholates and aryl halides, in the presence of a base, providing arylated alkene products in high yields. Soon thereafter, a seminal paper on the synthesis of biaryls by coupling of phenylboronic acid with aryl bromides and halides was reported (Equation 69, Figure 1.36) [389]. Since then, significant improvements have been made through an optimization of the different reaction parameters such as catalyst, ligands, base, solvent, and additives. These advances have been reviewed regularly [390].

The accepted mechanism for the aqueous basic variant involves oxidative addition of the halide substrate to give a Pd(II) intermediate, followed by a transmetallation, and a final reductive elimination that regenerates the catalyst (Figure 1.37) [391–393]. The two key catalytic intermediates have been observed by electrospray mass spectrometry [394]. Although the exact role and influence of the base remains unclear [395], the transmetallation is thought to be facilitated by base-mediated formation of the tetracoordinate boronate anion [396], which is more electrophilic than the free boronic acid (Sections 1.5.1 and 1.5.2). A useful carbonylative variant has also been developed to access benzophenones (Equation 70) [397], which can also be produced from the coupling of acid chlorides [398] or anhydrides [399]. A variant of this method allows the preparation of α,β-unsaturated esters from alkenylboronic esters [243]. In all of these reactions, one dreaded limitation with some ortho-substituted and electron-poor arylboronic acids is the possible occurrence of a competitive protolytic deboronation, which is exacerbated by the basic conditions and the use of a transition metal catalyst (Section 1.5.1). Methods to minimize this side reaction were developed; in particular the use of milder alternative bases [400] such as fluoride salts [401], and

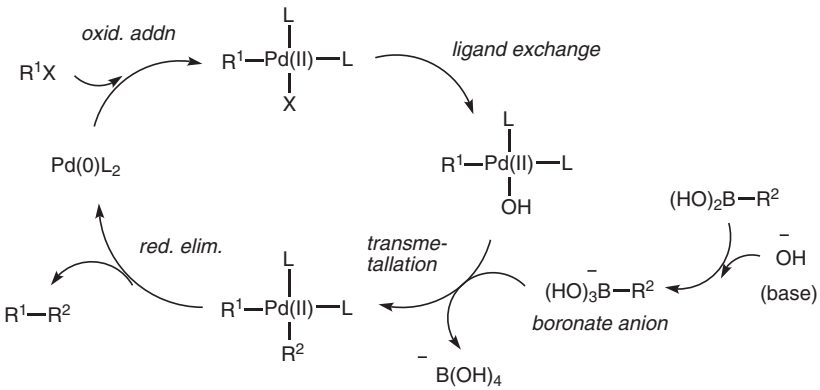


Figure 1.37 Accepted mechanism for the Suzuki cross-coupling reaction under aqueous conditions.

non-aqueous conditions [402]. Competitive homo-coupling of the arylboronic acid can also compete, but it can also be an attractive process for making symmetrical biaryls [403]. Despite these impediments, the venerable Suzuki–Miyaura cross-cou-

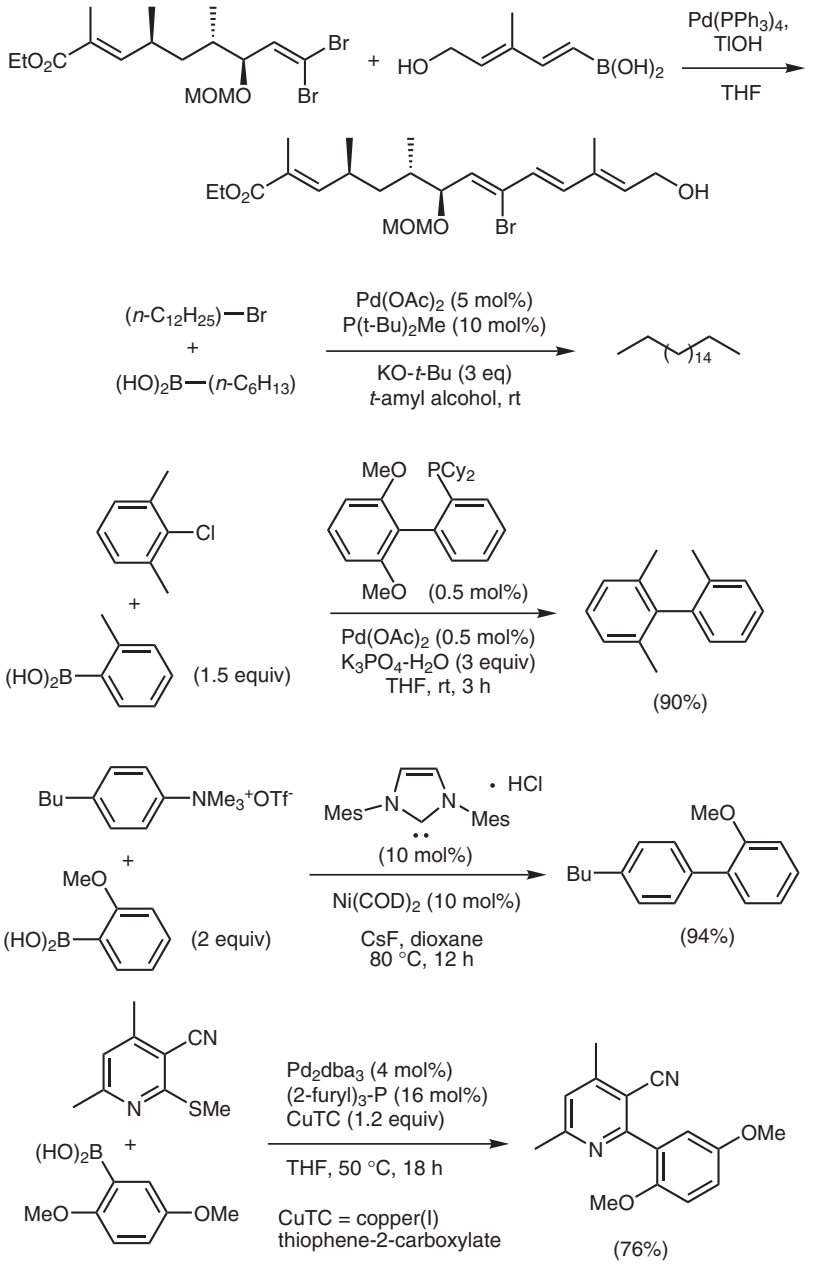


Figure 1.38 Selected examples of Suzuki-cross coupling reactions.

pling reaction has become the most versatile method to synthesize a broad range of biaryl compounds that find widespread uses as pharmaceutical drugs and materials. The reaction is particularly useful in combination with orthometallation approaches to generate the arylboronic acid substrate [404].

Alkenylboronic acids and esters are also very useful substrates (Equation 71, Figure 1.38) [405], in particular to access substituted olefins and dienyl moieties commonly encountered in several classes of bioactive natural products [282, 406]. To this end, Kishi and co-workers examined the influence of the base, and developed an optimal variant using thallium hydroxide [281]. Recently, allylic alcohols were found to couple directly with alkyl and alkenyl boronic acids without the aid of a base [407]. In rare cases, the Suzuki reaction has been applied to the use of alkylboronic acids [296, 408], including cyclopropylboronic acids [409]. Hitherto notorious for their tendency to undergo β-hydride elimination, alkyl bromides are now suitable as electrophiles under carefully optimized conditions that even allow Csp^3–Csp^3 couplings with alkylboronic acids (Equation 72) [410]. The Suzuki reaction has also been applied very successfully in solid-phase chemistry and combinatorial library synthesis [411]. It has been applied industrially [412], especially in medicinal chemistry, e.g. in the production of the antihypertensive drug losartan [195].

In the past few years alone, several new and further improved catalysts and ligands have been developed for difficult substrates such as aryl chlorides, which are cheaper and more available than bromides [413]. Amongst other advances, new phosphine-based systems developed by Fu [414], Buchwald [415], and others [416] even allow room-temperature couplings with aryl chlorides. For example, Buchwald and co-workers recently reported a universal palladium catalyst system, based on a rationally designed ligand with unprecedented stability and scope, for couplings of hindered aryl chlorides at room temperature (Equation 73, Figure 1.38) [417]. Phosphine free systems based on N-heterocyclic carbene ligands perform very well with hindered boronic acids and electrophiles [418]. Other transition metals catalyze the reaction, notably nickel [419] and ruthenium [420], albeit the range of suitable substrates seems more limited. Interestingly, advantageous ligand-free couplings [421] and even the surprising claim of palladium-free couplings have been reported [422]. Other classes of substrates such as aryltosylates [423] and arylammonium salts [424] (Equation 74) were recently uncovered to further expand the scope of this cross-coupling chemistry. Likewise, arylsulfonium salts [425], thioesters [426], and thioethers [427] are suitable electrophilic substrates. For example, heteroaromatic thioethers couple to arylboronic acids under base-free conditions promoted by copper(I) thiophene-2-carboxylate (Equation 75) [428]. More recent developments in the synthesis of biaryl products by the coupling of aromatic boronic acids with aromatic electrophiles are described in detail by Professor Suzuki in Chapter 3.

1.5.3.2 **Allylation of Carbonyl Compounds**

The addition of allylboronates to aldehydes was first discovered in 1974 [429]. This reaction has since found tremendous use in the stereoselective synthesis of acetate and propionate units embodied in numerous natural products (Equation 76, Figure 1.39) [430]. The tartrate-based chiral allylboronates, for example, have become one of the

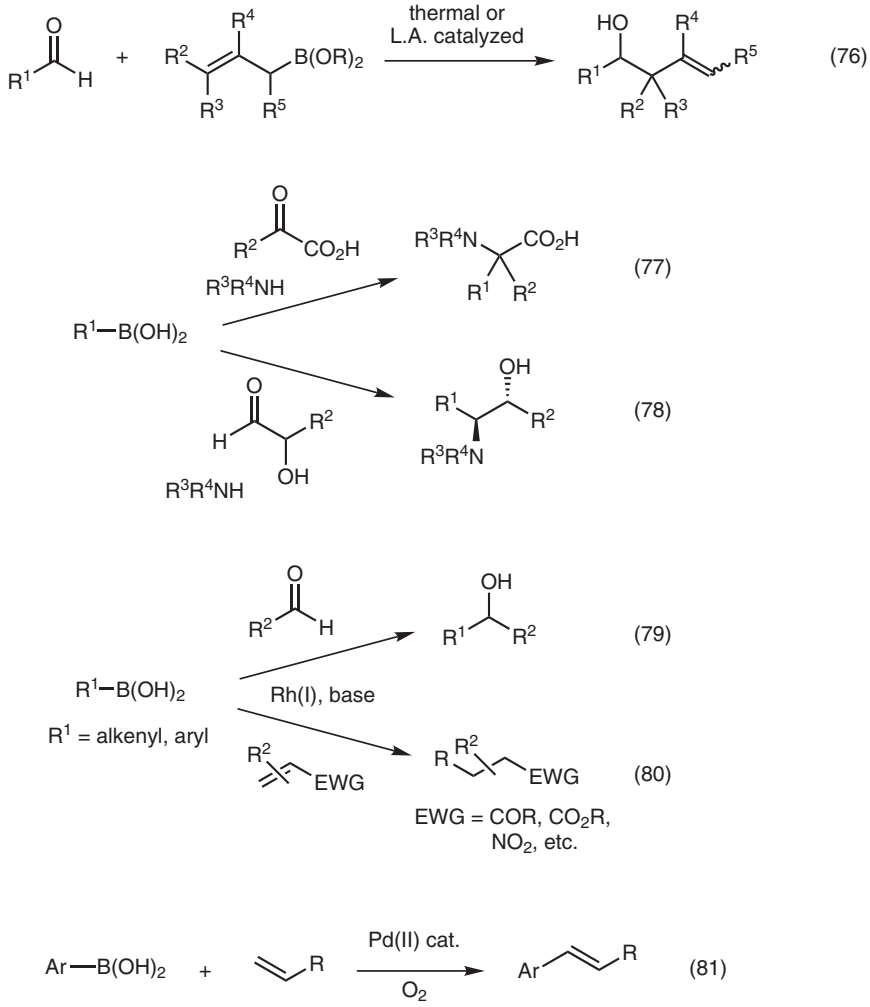


Figure 1.39 Other C–C bond forming reactions involving boronic acids (esters).

most recognized classes of chiral reagents in organic synthesis [102]. One of the most recent developments of this reaction is the discovery that additions of allylboronates to aldehydes can be catalyzed by Lewis acids [431]. The dramatic rate acceleration observed allows a substantial decrease of the reaction temperature, which in turn leads to outstanding levels of diastereo- and enantioselectivity with camphordiol-based reagents [432]. The preparation of allylboronates and their most recent synthetic applications are described in Chapter 6.

1.5.3.3 Uncatalyzed Additions to Imines and Iminiums

In 1997, Petasis and Zavialov described a novel uncatalyzed three-component reaction between α-ketoacids, amines and boronic acids, providing a novel synthetic route to α-amino acids (Equation 77, Figure 1.39) [433]. The use of α-hydroxyaldehydes lends access to β-aminoalcohols in high yields and excellent stereoselectivity (Equation 78) [434]. Both alkenyl and aryl boronic acids can be employed. This powerful new reaction process and variants thereof are described in Chapter 7.

1.5.3.4 Rhodium-catalyzed Additions to Aldehydes and Alkenes

Another recent breakthrough in organoboron chemistry is the exciting discovery that rhodium(I) complexes catalyze the addition of boronic acids to carbonyl compounds [435] and a wide range of alkene substrates (Equations 79 and 80, Figure 1.39) [436]. The latter process can even provide enantioselectivities over 99% in 1,4-additions to enones [437]. Very recently, cinnamaldehydes were found to give an anomalous self-conjugate reduction/cross-coupling tandem reaction [438], and arylboroxines reportedly undergo a catalytic asymmetric addition to *N*-tosylarylimines [439]. Palladium and nickel catalysts promote similar additions of boronic acids onto unactivated alkynes [440], allenes [441], and 1,3-butadienes [442]. These new reactions of boronic acids are reviewed in detail in Chapter 4.

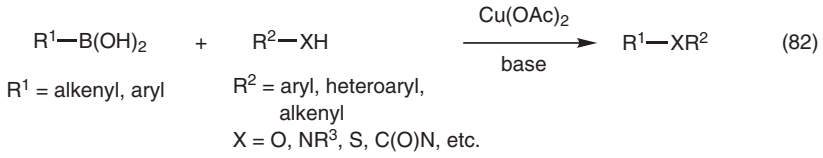
1.5.3.5 Heck-type Coupling to Alkenes and Alkynes

Several reports have highlighted the ability of boronic acids to undergo rhodium- [443], ruthenium- [444], iridium- [445], or palladium-catalyzed [446] addition–dehydrogenation reactions on alkenes (Equation 81, Figure 1.39) [446c]. Similar couplings to terminal alkynes were reported [447].

1.5.4 Carbon–Heteroatom Bond forming Processes

1.5.4.1 Copper-catalyzed Coupling with Nucleophilic Oxygen and Nitrogen-containing Compounds

In 1998, groups led by Chan, Evans, and Lam independently reported their observations that copper diacetate promotes the coupling of aryl and heteroaryl boronic acids to moderately acidic heteroatom-containing functionalities like phenols, thiols, amines, amides, and various heterocycles (Equation 82, Figure 1.40) [448–450]. The potential of this mild and general method was convincingly exemplified with the syntheses of the diaryl ether units of a thyroxine intermediate (Equation 83) [449] and the teicoplanin aglycon related to vancomycin [184]. This new reaction has since been extended to other classes of substrates and, in particular, to applications in solid-phase synthesis [451]. A mechanism was suggested based on transmetallation of the boronic acid with $Cu(OAc)_2$ followed by ligand exchange with the nucleophilic substrate, and reductive elimination to give the coupling product [448]. This new reaction of boronic acids constitutes the main topic of Chapter 5.



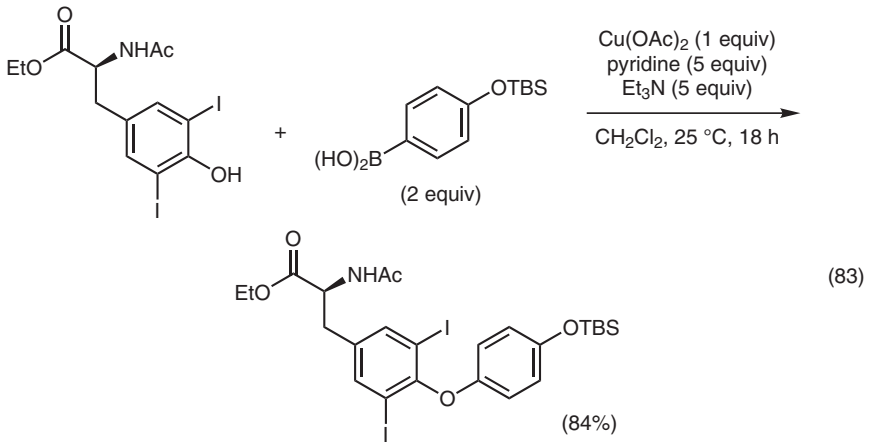


Figure 1.40 Copper-catalyzed coupling of boronic acids with nucleophilic oxygen and nitrogen-containing compounds.

1.5.5 Other Reactions

The B–C bond of alkynylboronic esters is labile enough to allow their uncatalyzed nucleophilic addition to enones, and an asymmetric variant has been developed using binaphthyl alkynylboronates (Equation 84, Figure 1.41) [452]. 1,3-Dicarbonyl compounds are arylated with arylboronic acids in the presence of lead tetraacetate and catalytic $Hg(OAc)_2$ under in situ conditions that promote a rapid boron–lead transmetallation (Equation 85) [453]. Allylic carbonates [454] and even amines [455] provide cross-coupling products with boronic acids under nickel catalysis. The metalation of *ortho*-bromobenzeneboronic esters was recently shown to be an effective route to benzyne complexes of Group 10 metals (e.g., Ni, Pd) [456]. Arylboronic acids have been employed as aryl source in enantioselective zinc-promoted additions to aldehydes [457]. Likewise, arylboronic esters were used in a ruthenium-catalyzed ortho-arylation of aromatic ketones via C–H activation/functionalization (Equation 86) [458], or in a dealkoxylation/functionalization [459]. Cyclobutanones undergo a C–C bond insertion/functionalization with arylboronic acids (Equation 87) [460]. Boronic acids have been employed in multicomponent reaction processes other than the Petasis reaction (Section 1.5.3.3). For example, they react with diazocyclopentadiene and a rhenium(I) tricarbonyl complex to give new monoalkylated cyclopentadienyl rhenium

complexes [461]. Jamison and co-workers reported a nickel-catalyzed three-component reaction between alkynes, imines, and organoboron compounds such as alkenyl and aryl boronic acids [462]. The resulting allylic amines are obtained in high regioselectivity. A palladium-catalyzed three-component reaction between allenes, organic halides and boronic acids was reported [463]. A chemo- and regioselective Ru(II)-catalyzed cyclotrimerization involving alkynylboronates and two other alkynes can be

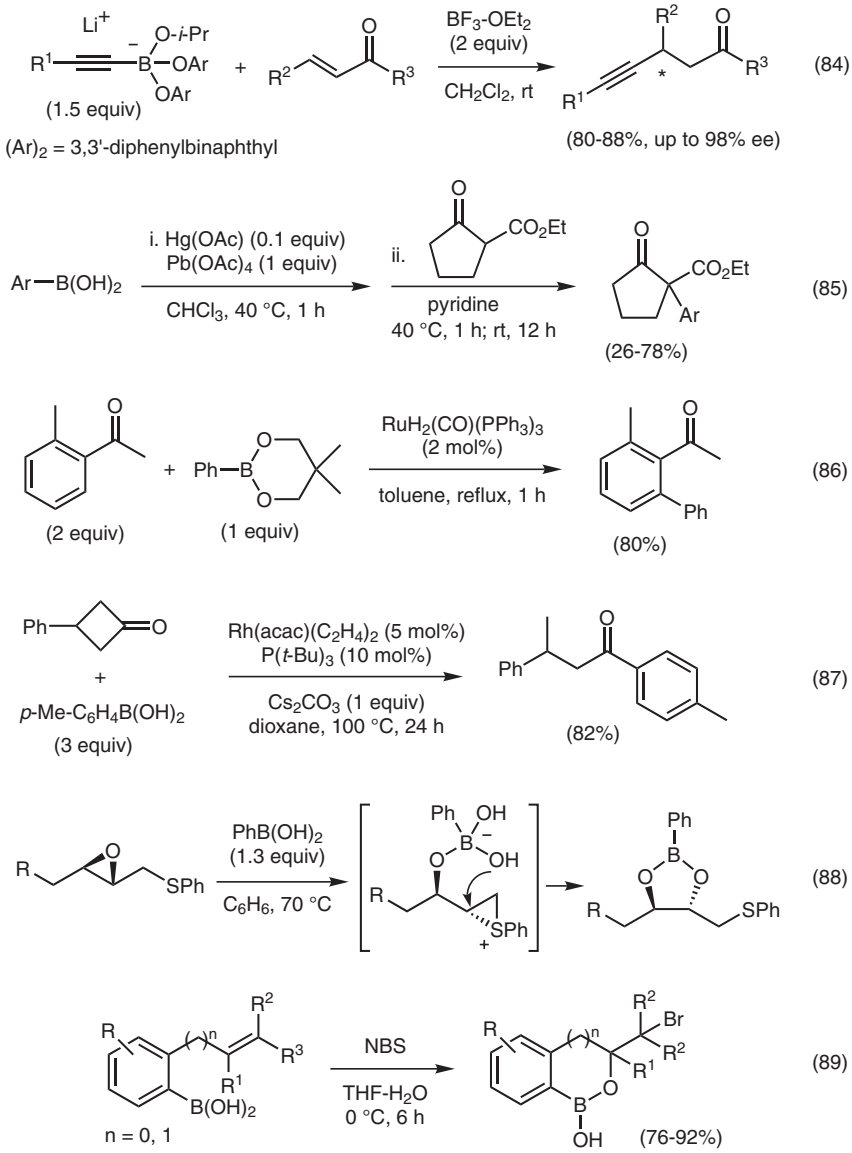


Figure 1.41 Selected examples of other reactions of boronic acid derivatives.

turned into a four-component synthesis of polysubstituted arenes when combined with a one-pot Suzuki coupling (Chapter 9) [464].

Under favorable conditions, the hydroxyl group of boronic acids can serve as a nucleophile. For example, epoxy-sulfides are opened stereoselectively by phenylboronic acid to afford diol products (Equation 88, Figure 1.41) [465]. A new variant of this process makes use of a palladium catalyst [466]. Boronic acids have been employed recently as internal nucleophiles in a bromo-boronolactonization of olefins (Equation 89) [467].

1.6
Overview of other Applications of Boronic Acid Derivatives

1.6.1
Use as Reaction Promoters and Catalysts

By forming transient esters with alcohols, boronic acids can act as catalysts or templates for directed reactions. In the early 1960s, Letsinger demonstrated that a bifunctional boronic acid, 8-quinolineboronic acid, accelerates the hydrolysis of certain chloroalkanols (Equation 90, Figure 1.42) [468], and that boronoarylbenzimidazole serves as catalyst for the etherification of chloroethanol [469]. Mechanisms involving covalent hemiester formation between the boronic acid in the catalyst and the alcohol substrate, combined with a basic or nucleophilic participation of the nitrogen, were invoked. More recently, Yamamoto and co-workers found that several electron-poor arylboronic acids, in particular 3,4,5-trifluorobenzeneboronic acid, catalyze amidation reactions between carboxylic acids and amines [470]. Arylboronic acids catalyze the hydrolysis of salycylaldehyde imines [471], and affect the alkaline conversion of D-glucose into D-fructose [472]. Phenylboronic acid assists in the cyclodimerization of D-glucosamine into a pyrazine [473], and in the photocyclization of benzoin into 9,10-phenanthrenequinone [474].

Narasaka and co-workers demonstrated that phenylboronic acid can be employed to hold the diene and dienophile in such a way that the normal regiocontrol of a Diels–Alder reaction can even be inverted [475]. This templating strategy was elegantly exploited in the synthesis of a key intermediate in the total synthesis of taxol by Nicolaou and co-workers (Equation 91, Figure 1.42) [476]. By a similar trick, phenols are ortho-alkylated with aldehydes through a proposed six-membered transition state where phenylboronic acid, used stoichiometrically, holds the two reactants in place (Equation 92) [477]. Thermolysis of the resulting benzodioxaborinanes affords *ortho*-quinone methides that undergo a wide range of intermolecular cycloadditions and nucleophilic additions [478]. Molander and co-workers have demonstrated the existence of neighboring group participation from a chiral boronate in the reduction of ketones (Equation 93) [479]. A highly ordered cyclic transition structure with boron-carbonyl coordination was invoked to explain the high level of remote stereoinduction. The reduction of imine derivatives was also performed with high selectivity [480].

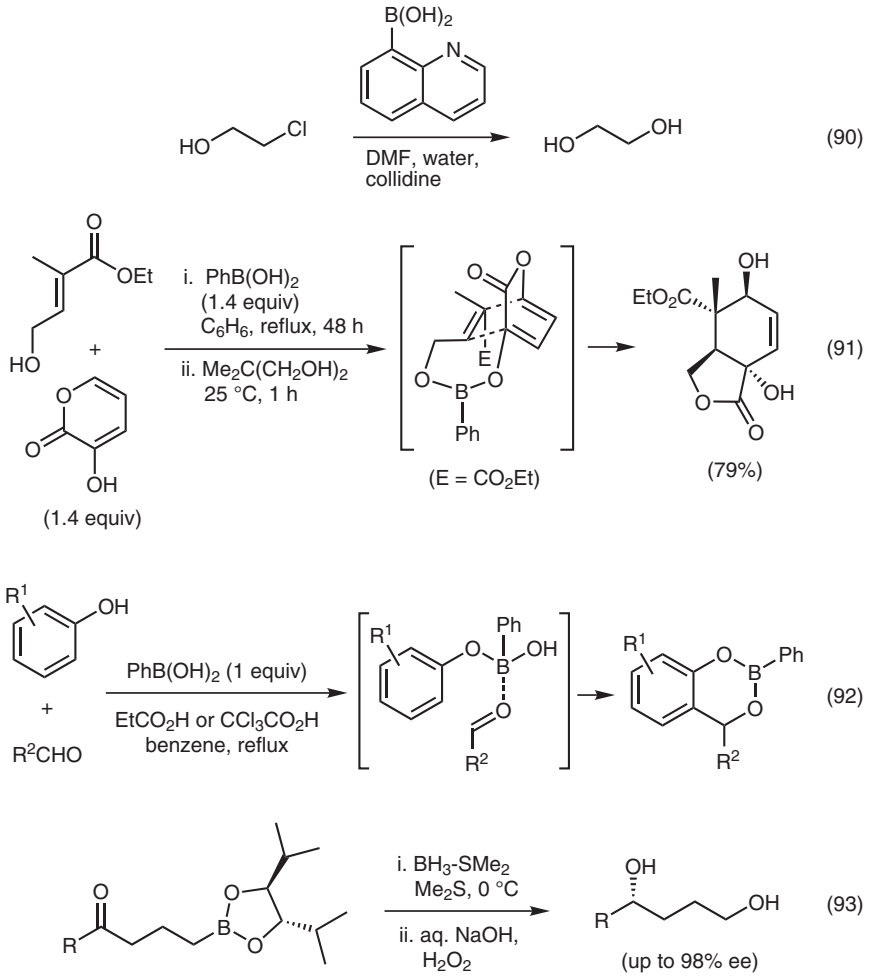


Figure 1.42 Selected examples of applications of boronic acids (esters) as reaction promoters and catalysts.

Boronic acids and their derivatives are very popular as components of chiral Lewis acids and promoters for various reaction processes [481]. Indeed, the chiral acyloxyboranes and the oxazaborolidines (Section 1.2.3.5) described in Chapter 11 made a mark in organic synthesis. Recently, Ryu and Corey extended the application of chiral oxaborolidinium catalysts to the cyanosilylation of aldehydes [482]. Chiral diazaborolidine salts were evaluated in the enantioselective protonation of enol ethers [145]. Likewise, a tartramide-derived dioxaborolane is key as a chiral promoter in the asymmetric cyclopropanation of allylic alcohols [483]. More examples and details on the applications of boronic acid derivatives as reaction promoters and catalysts are provided in Chapter 10.

1.6.2
Use as Protecting Groups for Diols and Diamines

The use of boronic acids to protect diol units in carbohydrate chemistry was demonstrated several decades ago, in particular by the work of Ferrier [484] and Köster [485]. For example, whereas an excess of ethylboronic acid (as the boroxine) leads to a bisboronate furanose derivative of D-lyxose, equimolar amounts provided 2,3-*O*-ethylboranediyl-D-lyxofuranose (Equation 94, Figure 1.43) [486]. From the latter, a regioselective diacetylation reaction followed by treatment with HBr led to the desired α-D-lyxofuranosyl bromide in a very high yield. An alternative method for the preparation of cyclic alkylboronic esters involves treatment of diols with lithium trialkylborohydrides [95]. Phenylboronic esters of carbohydrates have also been exploited in the regioselective sulfation of saccharides [487], and as a way to regioselectively alkylate diol units of pyranosides [488]. The reaction of phenylboronic acids with nucleosides and mononucleotides was described long ago [489]. The *ortho*-acetamidophenyl boronate group was employed to protect the vicinal 1,2-diol of adenosine [312]. It was found to be more resistant to hydrolysis than the corresponding phenylboronate, which was attributed to the beneficial coordination effect of the ortho substituent. Phenylboronic acid has also been used as a protecting group for 1,2- and 1,3-diol units of other natural products [481b], such as terpenes [490] macrolides [491], prostaglandins [492], quinic acid derivatives [493], anthracyclines [494], macrocyclic polyamines [495], and polyether antibiotics [496]. Typically, phenylboronates are made by a simple condensation with a diol, which can be eventually deprotected by exchange with another diol, or by a destructive oxidation with hydrogen peroxide. For example, Evans and co-workers used phenylboronic acid to selectively protect the 1,3-diol unit of a triol (Equation 95, Figure 1.43) [496]. Oxidation of the remaining hydroxyl and oxidative deprotection of the phenylboronate led to a concomitant cyclization to give a pyran product. In a key step to the synthesis of verbacine, the 1,3-diamine unit of a polyazamacrocycle was selectively protected with 3,5-$(CF_3)_2$-$C_6H_3B(OH)_2$ [495]. Recently, a high-yielding solid-state method for the protection of diols, polyols, and diamines with $PhB(OH)_2$ was described [497]. Phenylboronic acid was also employed as an in situ protective reagent in osmium tetraoxide promoted dihydroxylation of alkenes [498]. In this variant, it serves as a water replacement for cleavage of the osmate intermediate, while also providing a nonpolar cyclic boronate derivative that is easier to extract in organic solvents than is the free diol. Sharpless and co-workers applied this "boronate capture" procedure to the dihydroxylation of polyenes (Equation 96), and found several further advantages, such as faster reaction times, minimization of overoxidation, and a marked effect on the diastereoselectivity of these multiple dihydroxylations [499].

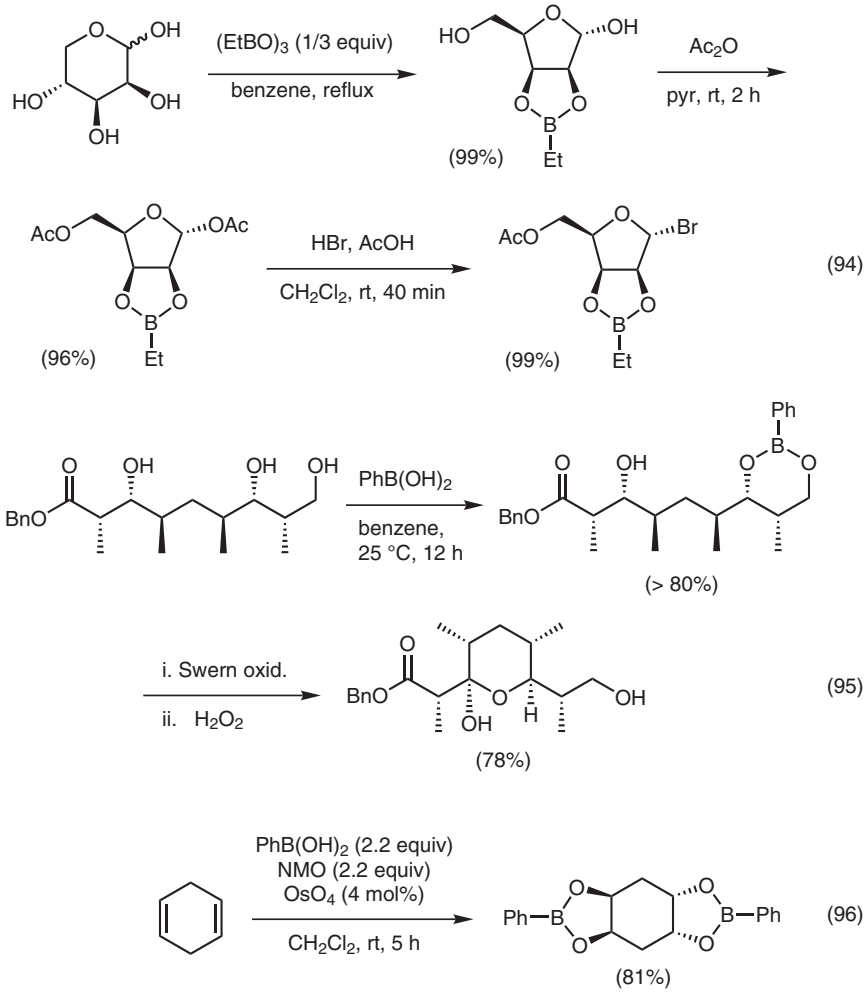


Figure 1.43 Examples of the use of boronic acids for the protection of diol compounds.

1.6.3
Use as Supports for Derivatization and Affinity Purification of Diols, Sugars, and Glycosylated Proteins

The concept of immobilizing diol compounds with a boronic acid conjugated support as a sort of heterogeneous protecting group strategy is the antipode of the diol-based supports described in Section 1.4.2. Examples of such boronic acid matrices include polystyryl boronic acid resins (**120**) [500–502], the cellulose-derived support **121** [503], the methacrylic polymer **122** [504], and the polyacrylamide-supported nitroarylben-

zene boronic acid **123** [505] (Figure 1.44). Applications of immobilized boronic acids have been reviewed, and include the purification or analysis of carbohydrates, diverse nucleic acid derivatives embedding rigid vicinal cis-diols, and catechols, including L-DOPA, catechol estrogens, and catecholamines from urine [506]. One of the most important biomedical uses of immobilized boronic acids is in the separation and quantification of glycosylated proteins [507], such as the level of glycosylated hemoglobin in red blood cells, which is an important indicator for the clinical analysis of diabetes. In one other application, a water-soluble polyacrylamide copolymer was tested as a mitogen for lymphocytes [508]. Other supports have also been considered as components of sensing systems for glucose [509] and nucleotides such as AMP [510]. With hydrogels, the extent of carbohydrate binding can be correlated with swelling (change in volume) [509c]. All of the above arylboronic acid supports demonstrate a selectivity profile similar to their homogeneous counterpart, and only cis-diols of a favorable

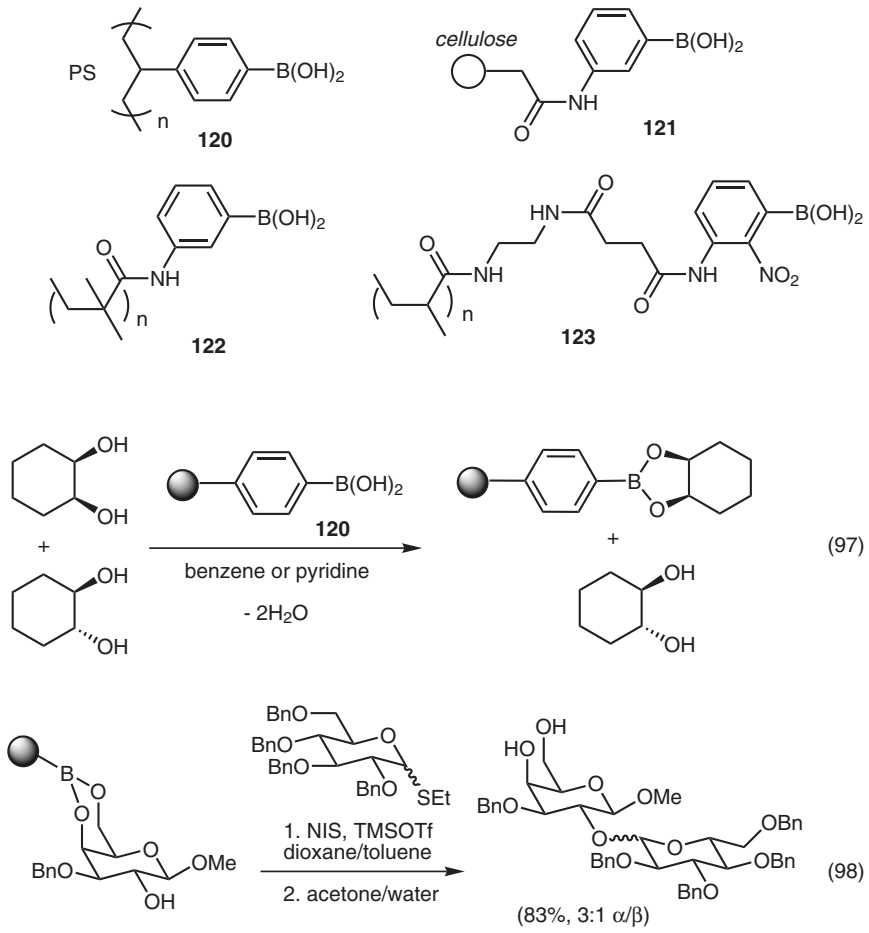


Figure 1.44 Boronic acid supports for diol compounds.

coplanar geometry can be immobilized efficiently. For example, polystyryl boronic acid (**120**) was put to use in the fractionation of carbohydrates and in the separation of isomeric diols [500, 511]. In agreement with the stereochemical arguments discussed in previous sections, of an isomeric mixture of *cis*- and *trans*-1,2-cyclohexenadiol, only the former bound to resin **120**, thereby allowing an effective separation of the two isomers (Equation 97, Figure 1.44) [511]. Among several other examples of applications to the purification of polyol compounds, the boronic acid substituted methacrylic polymer **122** was employed to separate ribonucleosides and deoxyribonucleoside mixtures [504]. The selectivity profile of support **121** in the binding of various nucleic acid and sugar derivatives was studied. Not surprisingly, the heterogeneous boronate formation process in a chromatography column was more efficient at a higher pH, with diols of favorable geometry, and also depended on the ionic strength and the nature of the cations in the eluent [503]. Polyacrylamide support **123** was employed in the purification of transfer ribonucleic acids [505]. Due to the low pK_a (ca. 7) of its electron-poor boronic acid unit, the immobilization process was performed efficiently at neutral pH, and the tRNA was recovered from the column at pH 4.5. In the hope of further increasing affinity and selectivity in carbohydrate binding, the technique of molecular imprinting polymerization was tested with boronic acid containing monomers [61a, 512, 513].

Fréchet and co-workers also demonstrated the utility of resin **120** in the selective immobilization and transformation of carbohydrate derivatives [501a, 514]. Inspired by this work, Boons and co-workers used the same resin as a reusable linker system for the solid-phase synthesis of oligosaccharides (Equation 98, Figure 1.44) [515].

1.6.4
Use as Receptors and Sensors for Carbohydrates and other Small Molecules

The ability of boronic acids to form esters reversibly with cis-diols (Section 1.2.3.2.3) has been a central theme in the intensive area of sensor and receptor development for oligosaccharides [516]. Such molecules can be used for various applications, such as derivatizing agents for the chromatographic detection of carbohydrates and, in particular, in the important global health issue of blood glucose monitoring for diabetes patients. The most recent advances in the field of carbohydrate sensing with boronic acids are reviewed in Chapter 12.

Mixed receptors containing boronic acids and charged functionalities were also developed for the recognition of sugar acids [517] and even for heparin [311], a polysulfated saccharide. Boronic acids also interact strongly with α-hydroxycarboxylic acids [518], and receptors selective for tartrate were reported [519].

1.6.5
Use as Antimicrobial Agents and Enzyme Inhibitors

Michaelis and Becker noted the toxicity of phenylboronic acid against microorganisms and its relative harmlessness against higher animals more than a century ago [198]. The antimicrobial properties of simple arylboronic acid derivatives were fur-

ther examined in the 1930s [176]. Interestingly, the activity of arylboronic acids in plants has been investigated thoroughly, and several were found to promote root growth [8, 55]. Several boronic acids and their benzodiaza- and benzodioxaborole derivatives were evaluated as sterilants of house flies [57]. Several boronic acids and esters display potent antifungal activity [520]. For instance, the diazaborine family, exemplified by the thienodiazaborine **124** (Figure 1.45), has long been known to possess potent activity against a wide range of Gram negative bacteria [521]. Initially, this biological effect was ascribed to the inhibition of lipopolysaccharide synthesis [522]. Recent evidence, however, point to a different molecular target, the NAD(P)H-dependent enoyl acyl carrier protein reductase [523]. This enzyme is involved in the last reductive step of fatty acid synthase in bacteria, and the structure of the inhibitory complex with diazaborines in the presence of the nucleotide cofactor was elucidated by X-ray crystallography [524]. Interestingly, the bisubstrate complex shows a covalent bond between boron, in a tetracoordinate geometry, and the 2′-hydroxyl of the nicotinamide ribose. In addition to their potential in the fight against microbial resistance in *Mycobacterium tuberculosis* and other strains, diazaborine compounds such as a recently reported estrogen mimic may find other medicinal applications [525]. A prostaglandin mimetic in which a boronyl group replaces the carboxylate, **125**, was found to be moderately active [526].

Boronic acids inhibit hydrolytic enzymes such as serine proteases [527], and the efficiency of a sepharose-based arylboronic acid sorbent in the chromatographic purification of this class of enzymes has been demonstrated [528]. In the development of boronic acid based enzyme inhibitors as pharmaceutical drugs, target specificity within a wide family is crucial to avoid side effects. The development of the α-aminoalkylboronic acid analogues of α-amino acids was key in the recent development of potent peptidylboronic acid analogues with improved specificity (Chapter n). The usual mechanism of inhibition is the formation of a tetracoordinate boronate complex (**126**, Figure 1.45) by coordination of the side chain hydroxyl nucleophile of the active serine residue, thus mimicking the tetrahedral intermediate for amidolysis [529]. Other modes of inhibition have been identified, however, like the formation of covalent adducts with the serine or histidine residues of the active site [530, 531]. This intensive area of medicinal chemistry research, reviewed in Chapter 13, has recently culminated in the commercialization of the peptidylboronic acid antineoplastic drug Velcade (**127**) [532, 533]. The latter has recently been approved by the United States FDA for treatment of relapsed and refractory multiple myeloma.

1.6.6
Use in Neutron Capture Therapy for Cancer

Several boronic acids such as 4-boronophenylalanine have been evaluated as sources of boron for their potential use in a form of brain cancer therapy based on the technology of soft neutron capture [534]. This topic is also reviewed in Chapter 13.

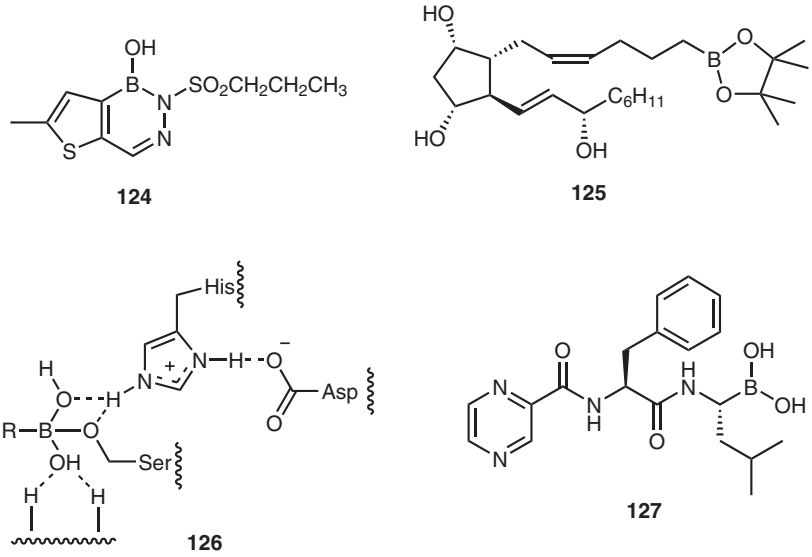


Figure 1.45 Examples of biologically active boronic acids. Note: **127** is the dipeptidyl boronic acid antineoplastic drug Velcade®, a selective proteasome inhibitor.

1.6.7
Use in Transmembrane Transport

As first demonstrated with monosaccharides by Shinbo and co-workers, the ability of boronic acids to complex diols can be exploited in the study of molecular transport across lipophilic membranes [535]. Compounds that possess such carrier properties have potential applications in drug delivery. For example, Mohler and Czarnik demonstrated the ability of a cholanyl 3-pyridiniumboronic acid derivative (**128**, Figure 1.46) to transport ribonucleosides across a dichloroethane liquid membrane [536]. Other examples of boronic acid based systems include a three-component amino acid transport system [537], the cathecholamine transporter **129** [538], and various carriers for monosaccharides such as fructose [54]. In fact, one of the most important potential applications of boronic acid carriers is in the area of development of selective fructose-permeable liquid membranes, which was reviewed recently [539]. D-Fructose is the sweetest and most valuable of all common natural sweeteners. Its current production as a "high fructose corn syrup", enriched from crudes containing other sugars, is an energy-intensive industrial process that involves the evaporation of large quantities of water. The use of membrane-based technology could be highly advantageous due to its potential amenability to a continuous automated process. Interested readers will find a more detailed account on the use of boronic acids in membrane transport in a review by Smith and Gardiner [540].

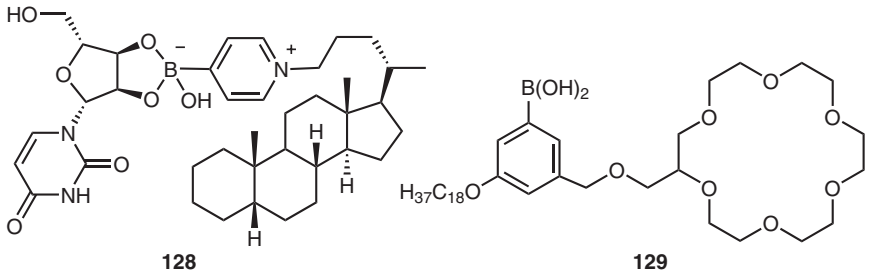


Figure 1.46 Examples of boronic acid based transporters.

1.6.8
Use in Bioconjugation and Labeling of Proteins and Cell Surface

Proteins and enzymes can be covalently linked to 3-aminophenylboronic acid, and the resulting conjugates were shown to bind to small cis-diol molecules and glycated hemoglobin [541]. Studies both in solution and using gel chromatography confirmed the low affinity of the boronate interaction. To address this problem, a conjugation method was developed based on the relatively stronger salicylhydroxamic acid–boronate interaction [150, 542]. As demonstrated with the diboronic acid–alkaline phosphatase conjugate **130** (Figure 1.47), higher affinity over a wider range of pH can be achieved by taking advantage of polyvalent interactions with the complexing sepharose support.

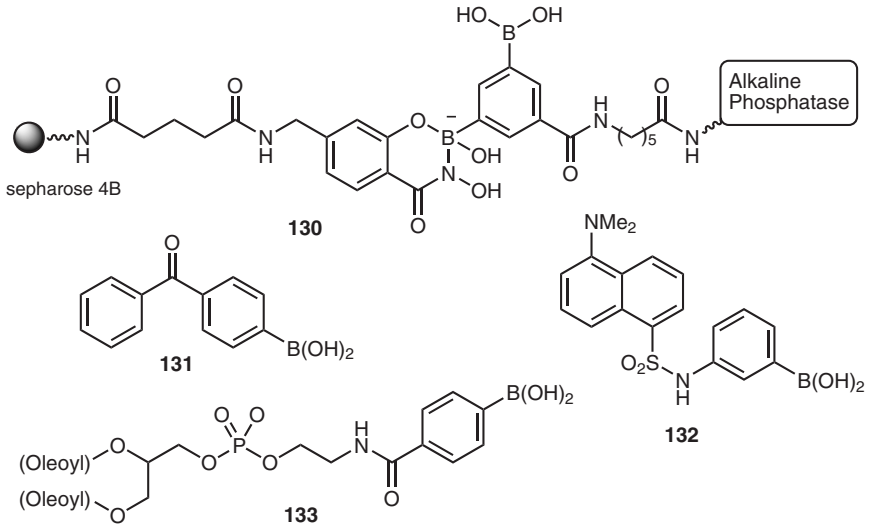


Figure 1.47 Boronic acid compounds used in protein labeling and conjugation.

A benzophenone boronic acid, **131**, was recently employed for probing altered specificity of chemically modified mutant subtilisin enzymes by photoaffinity labeling [543]. As discussed in Section 6.3, boronic acid supports can be employed to purify glycohemoglobin. A related soluble and colored arylboronic acid was reported for the quantification of these proteins [544]. More than two decades ago, a dansyl-labeled arylboronic acid (**132**) was reported to bind to the cell wall of the bacteria *B. subtilis*, presumably via boronate ester formation with the sugar coating [545]. In the same study, a diboronic acid was found to agglutinate erythrocytes. Recently, Smith and co-workers designed liposomes containing a phospholipid bearing an arylboronic acid (e.g., **133**), and demonstrated the binding of these liposomes to erythrocytes, presumably through interaction with the glycocalyx [546]. Likewise, diboronic acid sensors were reported to bind to tumor cells overexpressing the fucosylated sialyl Lewis X trisaccharide (Chapter 13) [547]. Recently, a fluorescein-based diboronate dye was shown to act as a selective, cell-permeable probe for hydrogen peroxide in living cells [548].

1.7 References

1 (a) E. Frankland, B. F. Duppa, *Justus Liebigs Ann. Chem.* **1860**, *115*, 319. (b) E. Frankland, B. Duppa, *Proc. Royal Soc. (London)* **1860**, *10*, 568. (c) E. Frankland, *J. Chem. Soc.* **1862**, *15*, 363.

2 H. C. Brown, *Organic Synthesis via Boranes*, Wiley, New York, **1975**.

3 D. S. Matteson, *Stereodirected Synthesis with Organoboranes*, Springer, Berlin, **1995**.

4 M. F. Lappert, *Chem. Rev.* **1956**, *56*, 959–1064.

5 A. Pelter, K. Smith, H. C. Brown, *Borane Reagents*, Academic Press, New York, **1988**.

6 B. M. Mikhailov, Y. N. Bubnov, *Organoboron Compounds in Organic Synthesis*, Harwood Academics, Glasgow, **1984**.

7 M. Vaultier, B. Carboni, in *Comprehensive Organometallic Chemistry II*, E. V. Abel, G. Wilkinson (Eds), Pergamon Press, Oxford, **1995**, Volume 11, Chapter 9, pp 191–276.

8 K. Torssell, in *Progress in Boron Chemistry*, H. Steinberg, A. L. McCloskey (Eds), Pergamon:New York, **1964**, Volume 1, pp 369–415.

9 M. Groziak, *Am. J. Therap.* **2001**, *8*, 321–328.

10 S. J. Rettig, J. Trotter, *Can. J. Chem.* **1977**, *55*, 3071–3075.

11 Cambridge Crystallographic Database Compound (CCDC) number 222652.

12 S. Soundararajan, E. N. Duesler, J. H. Hageman, *Acta Crystallogr., C*, **1993**, *49*, 690–693.

13 P. R. Parry, C. Wang, A. S. Batsanov, M. R. Bryce, B. Tarbit, *J. Org. Chem.* **2002**, *67*, 7541–7543. (CCDC numbers: bromide, 184781 and 184782; chloride, 184783)

14 J.-H. Fournier, T. Maris, J. D. Wuest, W. Guo, E. Galoppini, *J. Am. Chem. Soc.* **2003**, *125*, 1002–1006.

15 V. R. Pedireddi, N. Seethalekshmi, *Tetrahedron Lett.* **2004**, *45*, 1903–1906.

16 M. Sana, G. Leroy, C. Wilante, *Organometallics* **1991**, *10*, 264–270.

17 O. C. Ho, R. Soundararajan, J. Lu, D. S. Matteson, Z. Wang, X. Chen, M. Wei, R. D. Willett, *Organometallics* **1995**, *14*, 2855–2860.

18 V. V. Zhdankin, P. J. Persichini III, L. Zhang, S. Fix, P. Kiprof, *Tetrahedron Lett.* **1999**, *40*, 6705–6708.

19 S. J. Rettig, J. Trotter, *Can. J. Chem.* **1975**, *53*, 1393–1401.

20 R. Csuk, N. Müler, H. Sterk, *Z. Naturforsch., Teil B*, **1985**, *40*, 987–989.

21 T. Mancilla, R. Contreras, B. Wrackmeyer, *J. Organomet. Chem.* **1986**, *307*, 1–6.

22 J. T. Bien, M. J. Eschner, B. D. Smith, *J. Org. Chem.* **1995**, *60*, 4525–4529.
23 D. S. Matteson, T. J. Michnick, R. D. Willett, C. D. Patterson, *Organometallics* **1989**, *8*, 726–729.
24 Reference 3, pp 1–20.
25 M. Yamashita, Y. Yamamoto, K.-y. Akiba, S. Nagase, *Angew. Chem. Int. Ed.* **2000**, *39*, 4055–4058.
26 M. Yamashita, K. Kamura, Y. Yamamoto, K.-y. Akiba, *Chem. Eur. J.* **2002**, *8*, 2976–2979.
27 Y. Yamamoto, I. Moritani, *J. Org. Chem.* **1975**, *40*, 3434–3437.
28 D. S. Matteson, in *Progress in Boron Chemistry*, R. J. Brotherton, H. Steinberg (Eds), **1970**, Volume, pp 117–176.
29 C. D. Good, D. M. Ritter, *J. Am. Chem. Soc.* **1962**, *84*, 1162–1166.
30 L. W. Hall, J. D. Odom, P. D. Ellis, *J. Am. Chem. Soc.* **1975**, *97*, 4527–4531.
31 A. K. Holliday, W. Reade, R. A. W. Johnstone, A. F. Neville, *J. Chem. Soc., Chem. Commun.* **1971**, 51–52.
32 V. Bachler, N. Metzler-Nolte, *Eur. J. Inorg. Chem.* **1998**, 733–744.
33 H. C. Beachell, D. W. Beistel, *Inorg. Chem.* **1964**, *3*, 1028–1032.
34 D. S. Matteson, R. W. H. Mah, *J. Org. Chem.* **1963**, *28*, 2171–2174.
35 D. S. Matteson, *J. Org. Chem.* **1962**, *27*, 4293–4300.
36 (a) D. S. Matteson, K. Peacock, *J. Am. Chem. Soc.* **1960**, *82*, 5759–5760. (b) D. S. Matteson, J. O. Waldbillig, *J. Org. Chem.* **1963**, *28*, 366–369.
37 D. S. Matteson, M. L. Talbot, *J. Am. Chem. Soc.* **1967**, *89*, 1123–1126.
38 D. A. Evans, A. M. Golob, N. S. Mandel, G. S. Mandel, *J. Am. Chem. Soc.* **1978**, *100*, 8170–8174.
39 D. A. Singleton, *J. Am. Chem. Soc.* **1992**, *114*, 6563–6564.
40 H. R. Snyder, J. A. Kuck, J. R. Johnson, *J. Am. Chem. Soc.* **1938**, *60*, 105–111.
41 A. H. Soloway, B. Whitman, J. R. Messer, *J. Pharm. Exp. Ther.* **1960**, *129*, 310–314.
42 M. Benderdour, T. Bui-Van, A. Dicko, et al., *J. Trace Elem. Med. Biol.* **1998**, *12*, 2–7.
43 A. H. Soloway, B. Whitman, J. R. Messer, *J. Med. Pharm. Chem.* **1962**, *7*, 640.
44 A. H. Soloway, *Science* **1958**, *128*, 1572.
45 D. S. Matteson, A. H. Soloway, D. W. Tomlinson, J. D. Campbell, G. A. Nixon, *J. Med. Chem.* **1964**, *7*, 640–643.
46 R. J. Weir, Jr., R. S. Fisher, *Toxicol. Appl. Pharmacol.* **1972**, *23*, 351.
47 C. H. Linden, A. H. Hall, K. W. Kulig, *J. Toxicol. Clin. Toxicol.* **1986**, *24*, 269–279.
48 A. Restuccio, M. E. Mortensen, M. T. Kelley, *Am. J. Emerg. Med.* **1992**, *10*, 545–547.
49 J. P. Lorand, J. O. Edwards, *J. Org. Chem.* **1959**, *24*, 769–774.
50 G. E. K. Branch, D. L. Yabroff, B. Bettmann, *J. Am. Chem. Soc.* **1934**, *56*, 937–941.
51 D. L. Yabroff, G. E. K. Branch, B. Bettmann, *J. Am. Chem. Soc.* **1934**, *56*, 1850–1857.
52 B. Bettman, G. E. K. Branch, D. L. Yabroff, *J. Am. Chem. Soc.* **1934**, *56*, 1865–1870.
53 L. Babcock, R. Pizer, *Inorg. Chem.* **1980**, *19*, 56–61.
54 P. R. Westmark, S. J. Gardiner, B. D. Smith, *J. Am. Chem. Soc.* **1996**, *118*, 11093–11100.
55 K. Torssell, J. H. McLendon, G. F. Somers, *Acta Scand. Chem.* **1958**, *12*, 1373–1385.
56 S. Soundararajan, M. Badawi, C. M. Kohlrust, J. H. Hageman, *Anal. Biochem.* **1989**, *178*, 125–134.
57 J. A. Settepani, J. B. Stokes, A. B. Borkovek, *J. Med. Chem.* **1970**, *13*, 128–131.
58 H. R. Mulla, N. J. Agard, A. Basu, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 25–27.
59 F. C. Fisher, E. Havinga, *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 21–24.
60 W. Yang, J. Yan, G. Springsteen, S. Deeter, B. Wang, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1019–1022.
61 (a) G. Wulff, *Pure Appl. Chem.* **1982**, *54*, 2093–2102. (b) S. L. Wiskur, J. J. Lavigne, H. Ait-Haddou, V. Lynch, Y. H. Chiu, J. W. Canary, E. V. Anslyn, *Org. Lett.* **2001**, *3*, 1311–1314. (c) J. Juillard, N. Geuguen, *C. R. Acad. Paris* **1967**, *C264*, 259–261.
62 D. H. McDaniel, H. C. Brown, *J. Am. Chem. Soc.* **1955**, *77*, 3756–3763.
63 R. P. Singhal, B. Ramamurthy, N. Govindraj, Y. Sarwar, *J. Chromatogr.* **1991**, *543*, 17–38.
64 M. J. S. Dewar, R. Jones, *J. Am. Chem. Soc.* **1967**, *89*, 2408–2410.
65 M. J. S. Dewar, in *Progress in Boron Chemistry*, H. Steinberg, A. L. McCloskey (Eds),

Pergamon, New York, **1964**, Volume 1, pp 235–263.
66 B. Carboni, L. Monnier, *Tetrahedron* **1999**, *55*, 1197–1248.
67 D. L. Yabroff, G. E. K. Branch, *J. Am. Chem. Soc.* **1933**, *55*, 1663–1665.
68 H. R. Snyder, M. S. Konecky, W. J. Lennarz, *J. Am. Chem. Soc.* **1958**, *80*, 3611–3615.
69 M. T. Reetz, C. M. Niemeyer, K. Harms, *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1472–1474.
70 M. T. Reetz, C. M. Niemeyer, M. Hermes, R. Goddard, *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1017–1019.
71 M. T. Reetz, J. Huff, R. Goddard, *Tetrahedron Lett.* **1994**, *35*, 2521–2524.
72 K. Nozaki, M. Yoshida, H. Takaya, *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2452–2454.
73 K. Nozaki, T. Tsutsumi, H. Takaya, *J. Org. Chem.* **1995**, *60*, 6668–6669.
74 H. Sakurai, N. Iwasawa, K. Narasaka, *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2585–2594.
75 H. E. Katz, *J. Org. Chem.* **1989**, *54*, 2179–2183.
76 J. R. Johnson, M. G. Van Campen, Jr., O. Grummit, *J. Am. Chem. Soc.* **1938**, *60*, 111–115.
77 J. R. Johnson, M. G. Van Campen, Jr., *J. Am. Chem. Soc.* **1938**, *60*, 121–124.
78 F. Challenger, O. V. Richards, *J. Chem. Soc.* **1934**, 405–411.
79 H. R. Snyder, F. W. Wyman, *J. Am. Chem. Soc.* **1948**, *70*, 234–237.
80 H. G. Kuivila, K. V. Nahabedian, *J. Am. Chem. Soc.* **1961**, *83*, 2159–2163.
81 A. H. Soloway, *J. Am. Chem. Soc.* **1959**, *81*, 3017–3019.
82 (a) H. G. Kuivila, K. V. Nahabedian, *J. Am. Chem. Soc.* **1961**, *83*, 2164–2166. (b) K. V. Nahabedian, H. G. Kuivila, *J. Am. Chem. Soc.* **1961**, *83*, 2167–2174.
83 G. J. McKiernan, R. C. Hartley, *Org. Lett.* **2003**, *5*, 4389–4392.
84 M. A. Beckett, R. J. Gilmore, K. Idrees, *J. Organomet. Chem.* **1993**, *455*, 47–49.
85 (a) H. C. Brown, D. Basavaiah, S. U. Kulkarni, *J. Org. Chem.* **1982**, *47*, 3808–3810. (b) H. C. Brown, D. Basavaiah, S. U. Kulkarni, H. D. Lee, E.-i. Negishi, J.-J. Katz, *J. Org. Chem.* **1986**, *51*, 5270–5276.
86 R. F. Porter, S. K. Gupta, *J. Phys. Chem.* **1964**, *68*, 280–289.
87 S. K. Wason, R. F. Porter, *J. Phys. Chem.* **1964**, *68*, 1443–1447.
88 F. A. Grimm, L. Barton, R. F. Porter, *Inorg. Chem.* **1968**, *7*, 1309–1316.
89 C. H. Chang, R. F. Porter, S. H. Bauer, *Inorg. Chem.* **1969**, *8*, 1689–1693.
90 C. P. Brock, R. P. Minton, K. Niedenzu, *Acta Crystallogr., Sect. C*, **1987**, *43*, 1775–1779.
91 J. A. Torssell, P. Lazzeretti, *J. Phys. Chem.* **1990**, *94*, 1723–1724.
92 Y. Li, J. Ding, M. Day, Y. Tao, J. Lu, M. D'iorio, *Chem. Mater.* **2003**, *15*, 4936–4943.
93 Y. Tokunaga, H. Ueno, Y. Shimomura, T. Seo, *Heterocycles* **2002**, *57*, 787–790.
94 N. Farfan, H. Höpfl, V. Barba, Ma. E. Ochoa, R. Santillan, E. Gómez, a. Gutiérrez, *J. Organomet. Chem.* **1999**, *581*, 70–81, and references cited.
95 L. Garlaschelli, G. Mellerio, G. Vidari, *Tetrahedron Lett.* **1989**, *30*, 597–600.
96 W. V. Dahlhoff, R. Köster, *Heterocycles* **1982**, *18*, 421–449.
97 H. G. Kuivila, A. H. Keough, E. J. Soboczenski, *J. Org. Chem.* **1954**, *8*, 780–783.
98 J. M. Sugihara, C. M. Bowman, *J. Am. Chem. Soc.* **1958**, *80*, 2443–2446.
99 Y. H. Ahn, Y.-T. Chang, *J. Comb. Chem.* **2004**, *6*, 293–296.
100 (a) R. L. Letsinger, I. Skoog, *J. Am. Chem. Soc.* **1955**, *77*, 2491–2494. (b) O. C. Musgrave, T. O. Park, *Chem. Ind. (London)* **1955**, *48*, 1552–1552.
101 H. Weidman, H. K. Zimmerman, Jr., *Ann. Der Chemie, Justus Liebig* **1958**, *619*, 28–35.
102 (a) R. Haruta, M. Ishiguro, N. Ikeda, H. Yamamoto, *J. Am. Chem. Soc.* **1982**, *104*, 7667–7669. (b) W. R. Roush, A. G. Walts, L. K. Hoong, *J. Am. Chem. Soc.* **1985**, *107*, 8186–8190.
103 K. Ditrich, T. Bube, R. Stürmer, R. W. Hoffmann, *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1028–1030.
104 D. S. Matteson, A. A. Kandil, *Tetrahedron Lett.* **1986**, *27*, 3831–3834.
105 R. Ray, D. S. Matteson, *Tetrahedron Lett.* **1980**, *21*, 449–450.
106 T. Herold, U. Schrott, R. W. Hoffmann, *Chem. Ber.* **1981**, *111*, 359–374.
107 (a) J. E. A. Luithle, J. Pietruszka, *J. Org. Chem.* **1999**, *64*, 8287–8297. (b) J. E. A. Luithle, J. Pietruszka, *J. Org. Chem.* **2000**, *65*, 9194–9200.

108 D. S. Matteson, R. Ray, *J. Am. Chem. Soc.* **1980**, *102*, 7590–7591.

109 D. S. Matteson, K. M. Sadhu, G. E. Lienhard, *J. Am. Chem. Soc.* **1981**, *103*, 5241–5242.

110 D. S. Matteson, R. Ray, R. R. Rocks, D. J. S. Tsai, *Organometallics* **1983**, *2*, 1536–1543.

111 D. S. Matteson, K. M. Sadhu, *Organometallics* **1984**, *3*, 614–618.

112 V. Martichonok, J. B. Jones, *J. Am. Chem. Soc.* **1996**, *118*, 950–958.

113 H. C. Brown, M. V. Rangaishenvi, *J. Organomet. Chem.* **1988**, *358*, 15–30.

114 D. S. Matteson, G. Y. Kim, *Org. Lett.* **2002**, *4*, 2153–2155.

115 J. Wityak, R. A. Earl, M. M. Abelman, Y. B. Bethel, B. N. Fisher, G. S. Kauffman, C. A. Kettner, P. Ma, J. L. McMillan, L. J. Mersinger, J. Pesti, M. E. Pierce, F. W. Rankin, R. J. Chorvat, P. N. Confalone, *J. Org. Chem.* **1995**, *60*, 3717–3722.

116 S. J. Coutts, J. Adams, D. Krolikowski, R. J. Snow, *Tetrahedron Lett.* **1994**, *35*, 5109–5112.

117 R. A. Bowie, O. C. Musgrave, *J. Chem. Soc., Chem. Commun.* **1963**, 3945–3949.

118 W. G. Woods, I. S. Bengelsdorf, D. L. Hunter, *J. Org. Chem.* **1966**, *31*, 2766–2768.

119 D. S. Matteson, H.-W. Man, *J. Org. Chem.* **1996**, *61*, 6047–6051.

120 D. S. Matteson, R. Soundararajan, O. C. Ho, W. Gatzweiler, *Organometallics* **1996**, *15*, 152–163.

121 P. B. Tripathy, D. S. Matteson, *Synthesis* **1990**, 200–206.

122 C. A. Kettner, A. B. Shenvi, *J. Biol. Chem.* **1984**, *259*. 15106–15114.

123 G. Wulff, M. Lauer, H. Böhnke, *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 741–742.

124 J. O. Edwards, G. C. Morrison, V. Ross, J. W. Schultz, *J. Am. Chem. Soc.* **1955**, *77*, 266–268.

125 (a) G. Springsteen, B. Wang, *Tetrahedron* **2002**, *58*, 5291–5300. (b) J. Yan, G. Springsteen, S. Deeter, B. Wang, *Tetrahedron* **2004**, *60*, 11205–11209.

126 S. A. Barker, A. K. Chopra, B. W. Hatt, P. J. Somers, *Carbohydr. Res.* **1973**, *26*, 33–40.

127 R. Pizer, C. Tihal, *Inorg. Chem.* **1992**, *31*, 3243–3247.

128 M. Bielecki, H. Eggert, J. C. Norrild, *J. Chem. Soc., Perkin Trans. 2* **1999**, 449–455.

129 Y. Nagai, K. Kobayashi, H. Toi, Y. Aoyama, *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2965–2971.

130 D. Stones, S. Manku, X. Lu, D. G. Hall, *Chem. Eur. J.* **2004**, *10*, 92–100.

131 G. Springsteen, B. Wang, *Chem. Commun.* **2001**, 1608–1609.

132 W. G. Woods, P. L. Strong, *J. Am. Chem. Soc.* **1966**, *88*, 4667–4671.

133 H. C. Brown, S. K. Gupta, *J. Am. Chem. Soc.* **1971**, *93*, 1816–1818.

134 C. E. Tucker, J. Davidson, P. Knochel, *J. Org. Chem.* **1992**, *57*, 3482–3485.

135 J. S. Panek, F. Xu, *J. Org. Chem.* **1992**, *57*, 5288–5290.

136 S. Thaisrivongs, J. D. Wuest, *J. Org. Chem.* **1977**, *42*, 3243–3246.

137 (a) K. Furuta, Y. Miwa, K. Iwanaga, H. Yamamoto, *J. Am. Chem. Soc.* **1988**, *110*, 6254–6255. (b) K. Furuta, T. Maruyama, H. Yamamoto, *J. Am. Chem. Soc.* **1991**, *113*, 1041–1042.

138 (a) M. Takasu, H. Yamamoto, *Synlett* **1990**, 194–196. (b) D. Sartor, J. Saffrich, G. Helmchen, *Synlett* **1990**, 197–198. (c) S.-i. Kiyooka, Y. Kaneko, M. Komura, H. Matsuo, M. Nakano, *J. Org. Chem.* **1991**, *56*, 2276–2278.

139 (a) T. B. Marder, N. C. Norman, *Topics Catal.* **1998**, *5*, 63–73. (b) T. Ishiyama, N. Miyaura, *J. Organomet. Chem.* **2000**, *611*, 392–402.

140 T. Ishiyama, M. Murata, T.-a. Ahiko, N. Miyaura, *Org. Synth.* **2000**, *77*, 176–182.

141 N. R. Anastasi, K. M. Waltz, W. L. Weerakoon, J. F. Hartwig, *Organometallics* **2003**, *22*, 365–369.

142 R. L. Letsinger, S. B. Hamilton, *J. Am. Chem. Soc.* **1958**, *80*, 5411–5413.

143 M. J. S. Dewar, V. P. Kubba, R. Pettit, *J. Chem. Soc.* **1958**, 3076–3079.

144 R. T. Hawkins, H. R. Snyder, *J. Am. Chem. Soc.* **1960**, *82*, 3863–3866.

145 A. Yanagisawa, H. Inanami, H. Yamamoto, *Chem. Commun.* **1998**, 1573–1574.

146 L. K. Mohler, A. W. Czarnik, *J. Am. Chem. Soc.* **1993**, *115*, 7037–7038.

147 B. K. Shull, D. E. Spielvogel, R. Gopalaswamy, S. Sankar, P. D. Boyle, G. Head, K. Devito, *J. Chem. Soc., Perkin Trans. 2*, **2000**, 557–561.

148 (a) S. S. Chissick, M. J. S. Dewar, P. M. Maitlis, *J. Am. Chem. Soc.* **1959**, *81*, 6329–6330. (b) S. S. Chissick, M. J. S. De-

war, P. M. Maitlis, *J. Am. Chem. Soc.* **1961**, *83*, 2708–2711.
149 M. Pailer, W. Fenzl, *Monatsh. Chem.* **1961**, *92*, 1294–1299.
150 M. L. Stolowitz, C. Ahlem, K. A. Hughes, R. J. Kaiser, E. A. Kesicki, G. Li, K. P. Lund, S. M. Torkelson, J. P. Wiley, *Bioconj. Chem.* **2001**, *12*, 229–239.
151 (a) E. J. Corey, T.-P. Loh, *J. Am. Chem. Soc.* **1991**, *113*, 8966–8967. (b) E. J. Corey, C. L. Cywin, T. D. Roper, *Tetrahedron Lett.* **1992**, *33*, 6907–6010. (c) K. Ishihara, S. Kondo, H. Yamamoto, *J. Org. Chem.* **2000**, *65*, 9125–9128. (d) M. Kinugasa, T. Harada, A. Oku, *J. Am. Chem. Soc.* **1997**, *119*, 9067–9068.
152 E. Vedejs, R. W. Chapman, S. Lin, M. Müller, D. R. Powell, *J. Am. Chem. Soc.* **2000**, *122*, 3047–3052.
153 E. J. Corey, *Angew. Chem., Int. Ed.* **2002**, *41*, 1650–1667.
154 E. J. Corey, C. J. Helal, *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012.
155 H. R. Snyder, A. J. Reedy, W. J. Lennarz, *J. Am. Chem. Soc.* **1958**, *80*, 835–838.
156 W. J. Lennarz, H. R. Snyder, *J. Am. Chem. Soc.* **1960**, *82*, 2172–2175.
157 (a) A. H. Soloway, *J. Am. Chem. Soc.* **1960**, *82*, 2442–2444. (b) M. J. S. Dewar, R. C. Dougherty, *J. Am. Chem. Soc.* **1964**, *86*, 433–436. (c) P. Tschampel, H. R. Snyder, *J. Org. Chem.* **1964**, *29*, 2168–2172. (d) D. S. Matteson, M. S. Biernbaum, R. A. Bechtold, J. D. Campbell, R. J. Wilcsek, *J. Org. Chem.* **1978**, *43*, 950–954. (e) O. Boldyreva, V. A. Dorokhov, B. M. Mikhailov, *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1985**, 428–430. (f) M. P. Hughes, B. D. Smith, *J. Org. Chem.* **1997**, *62*, 4492–4499. (g) J.-C. Zhuo, A. H. Soloway, J. C. Beeson, W. Ji, B. A. Barnum, F.-G. Rong, W. Tjarks, G. T. Jordan, IV, J. Liu, S. G. Shore, *J. Org. Chem.* **1999**, *64*, 9566–9574.
158 M. P. Groziak, A. D. Ganguly, P. D. Robinson, *J. Am. Chem. Soc.* **1994**, *116*, 7597–7605. 159. P. D. Robinson, M. P. Groziak, L. Yi, *Acta Crystallogr., Sect. C* **1996**, *52*, 2826–2830.
160 D. S. Matteson, T.-C. Cheng, *J. Org. Chem.* **1968**, *33*, 3055–3060.
161 H. C. Brown, A. M. Salunkhe, A. B. Argade, *Organometallics* **1992**, *11*, 3094–3097.
162 H. C. Brown, T. E. Cole, R. K. Bakshi, M. Srebnik, B. Singaram, *Organometallics* **1986**, *5*, 2303–2307.
163 H. C. Brown, A. M. Salunkhe, B. Singaram, *J. Org. Chem.* **1991**, *56*, 1170–1175.
164 H. C. Brown, T. E. Cole, B. Singaram, *Organometallics* **1984**, *3*, 774–777.
165 (a) E. Vedejs, R. W. Chapman, S. C. Fields, S. Lin, M. R. Schrimpf, *J. Org. Chem.* **1995**, *60*, 3020–3027. (b) E. Vedejs, S. C. Fields, R. Hayashi, S. R. Hitchcock, D. R. Powell, M. R. Schrimpf, *J. Am. Chem. Soc.* **1999**, *121*, 2460–2470.
166 S. Darses, J.-P. Genêt, *Eur. J. Org. Chem.* **2003**, 4313–4327.
167 (a) S. Darses, J.-P. Genêt, J.-L. Brayer, J.-P. Demoute, *Tetrahedron Lett.* **1997**, *38*, 4393–4396. (b) S. Darses, G. Michaud, J.-P. Genêt, *Tetrahedron Lett.* **1998**, *39*, 5045–5048. (c) M. Xia, Z.-C. Chen, *Synth. Commun*, **1999**, *29*, 2457–2465. (d) R. A. Batey, T. D. Quach, *Tetrahedron Lett.* **2001**, *42*, 9099–9103. (e) G. A. Molander, T. Ito, *Org. Lett.* **2001**, *3*, 393–396. (f) G. A. Molander, M. Rodriguez Rivero, *Org. Lett.* **2002**, *4*, 107–109. (g) G. A. Molander, C. R. Bernardi, *J. Org. Chem.* **2002**, *67*, 8424–8429. (h) G. A. Molander, B. W. Katona, F. Machrouhi, *J. Org. Chem.* **2002**, *67*, 8416–8423. (i) G. A. Molander, B. Biolatto, *Org. Lett.* **2002**, *4*, 1867–1870. (j) G. A. Molander, B. Biolatto, *J. Org. Chem.* **2003**, *68*, 4302–4314. (k) G. H. Fang, Z.-J. Yan, M.-Z. Deng, *Org. Lett.* **2004**, *6*, 357–360.
168 (a) R. A. Batey, A. N. Thadani, *Org. Lett.* **1999**, *1*, 1683–1686. (b) M. Pucheault, S. Darses, J.-P. Genêt, *Eur. J. Org. Chem.* **2002**, 3552–3557. (c) M. Pucheault, V. Michaut, S. Darses, J.-P. Genêt, *Tetrahedron Lett.* **2004**, *45*, 4729–4732. (d) L. Navarre, S. Darses, J.-P. Genêt, *Eur. J. Org. Chem.* **2004**, 69–73.
169 (a) T. D. Quach, R. A. Batey, *Org. Lett.* **2003**, *5*, 1381–1384. (b) T. D. Quach, R. A. Batey, *Org. Lett.* **2003**, *5*, 4397–4400.
170 (a) A. N. Thadani, R. A. Batey, *Org. Lett.* **2002**, *4*, 3827–3830. (b) A. N. Thadani, R. A. Batey, *Tetrahedron Lett.* **2003**, *44*, 8051–8055.
171 B. J. Kim, D. S. Matteson, *Angew. Chem., Int. Ed.* **2004**, *43*, 3056–3058.
172 G. A. Molander, M. Ribagorda, *J. Am. Chem. Soc.* **2003**, *125*, 11148–11149.

173 H. Gilman, L. O. Moore, *J. Am. Chem. Soc.* **1958**, *80*, 3609–3611.

174 (a) E. Khotinsky, M. Melamed, *Ber.* **1909**, *54*, 2784. (b) E. Khotinsky, M. Melamed, *Chem. Ber.* **1909**, *42*, 3090.

175 E. Krause, R. Nitsche, *Ber.* **1921**, *55*, 1261–1265.

176 W. Seaman, J. R. Johnson, *J. Am. Chem. Soc.* **1931**, *53*, 711–723.

177 F. R. Bean, J. R. Johnson, *J. Am. Chem. Soc.* **1932**, *54*, 4415–4425.

178 D. E. Cladingboel, *Org. Proc. Res. Devel.* **2000**, *4*, 153–155.

179 R. Zenk, S. Partzsch, *Chim. Oggi* **2003**, 70–73.

180 H. C. Brown, T. E. Cole, *Organometallics* **1983**, *2*, 1316–1319.

181 H. C. Brown, M. Srebnik, T. E. Cole, *Organometallics* **1986**, *5*, 2300–2303.

182 W. Li, D. P. Nelson, M. S. Jensen, R. S. Hoerrner, D. Cai, R. D. Larsen, P. J. Reider, *J. Org. Chem.* **2002**, *67*, 5394–5397.

183 S. Das, V. L. Alexeev, A. C. Sharma, S. J. Geib, S. A. Asher, *Tetrahedron Lett.* **2003**, *44*, 7719–7722.

184 D. A. Evans, J. L. Katz, G. S. Peterson, T. Hintermann, *J. Am. Chem. Soc.* **2001**, *123*, 12411–12413.

185 H. Gilman, L. Santucci, D. R. Swayampati, R. D. Ranck, *J. Am. Chem. Soc.* **1957**, *79*, 3077–3081.

186 K.-T. Wong, Y.-Y. Chien, Y.-L. Liao, C.-C. Lin, M.-Y. Chou, M.-K. Leung, *J. Org. Chem.* **2002**, *67*, 1041–1044.

187 N. K. Garg, R. Sarpong, B. M. Stoltz, *J. Am. Chem. Soc.* **2002**, *124*, 13179–13184.

188 P. Y. Chavant, M. Vaultier, *J. Organomet. Chem.* **1993**, *455*, 37–46.

189 G. Marr, R. E. Moore, B. W. Rockett, *J. Organomet. Chem.* **1967**, *7*, P11–P13.

190 R. T. Hawkins, D. B. Stroup, *J. Org. Chem.* **1969**, *34*, 1173–1174.

191 M. Lauer, G. Wulff, *J. Organomet. Chem.* **1983**, *256*, 1–9.

192 M. J. Sharp, V. Snieckus, *Tetrahedron Lett.* **1985**, *49*, 5997–6000.

193 M. J. Sharp, W. Cheng, V. Snieckus, *Tetrahedron Lett.* **1987**, *28*, 5093–5096.

194 B. I. Alo, A. Kandil, P. A. Patil, M. J. Sharp, M. A. Siddiqui, V. Snieckus, *J. Org. Chem.* **1991**, *96*, 3763–3768.

195 R. D. Larsen, A. O. King, C. Y. Chen, E. G. Corley, B. S. Foster, F. E. Roberts, C. Yang, D. R. Lieberman, R. A. Reamer, D. M. Tschaen, T. R. Verhoeven, P. J. Reider, Y. S. Lo, L. T. Rossano, A. S. Brookes, D. Meloni, J. R. Moore, J. F. Arnett, *J. Org. Chem.* **1994**, *59*, 6391–6394.

196 S. Caron, J. M. Hawkins, *J. Org. Chem.* **1998**, *63*, 2054–2055.

197 J. Kristensen, M. Lysén, P. Vedso, M. Begtrup, *Org. Lett.* **2001**, *3*, 1435–1437.

198 (a) A. Michaelis, P. Becker, *Ber.* **1880**, *13*, 58. (b) A. Michaelis, P. Becker, *Ber.* **1882**, *15*, 180–185.

199 W. Haubold, J. Herdtle, W. Gollinger, W. Einholz, *J. Organomet. Chem.* **1986**, *315*, 1–8.

200 T. Ishiyama, M. Murata, N. Miyaura, *J. Org. Chem.* **1995**, *60*, 7508–7510.

201 (a) M. Murata, S. Watanabe, Y. Masuda, *J. Org. Chem.* **1997**, *62*, 6458–6459. (b) M. Murata, T. Oyama, S. Watanabe, Y. Masuda, *J. Org. Chem.* **2000**, *65*, 164–168. (c) O. Baudoin, D. Guénard, F. Guéritte, *J. Org. Chem.* **2000**, *65*, 9268–9271.

202 O. Baudoin, A. Décor, M. Cesario, F. Guéritte, *Synlett* **2003**, 2009–2012.

203 Y.-L. Song, C. Morin, *Synlett* **2001**, 266–268.

204 J. C. Yoburn, D. L. Van Vranken, *Org. Lett.* **2003**, *5*, 2817–2820.

205 S. Lin, S. J. Danishefsky, *Angew. Chem., Int. Ed.* **2001**, *40*, 1967–1970.

206 H. Nakamura, M. Fujiawara, Y. Yamamoto, *J. Org. Chem.* **1998**, *63*, 7529–7530.

207 T. Ishiyama, K. Ishida, N. Miyaura, *Tetrahedron* **2001**, *57*, 9813–9816.

208 A. Fürstner, G. Seidel, *Org. Lett.* **2002**, *4*, 541–543.

209 Y. Ma, C. Song, W. Jiang, G. Xue, J. F. Cannon, X. Wang, M. B. Andrus, *Org. Lett.* **2003**, *5*, 4635–4638.

210 (a) K. M. Waltz, J. F. Hartwig, *Science* **1997**, *277*, 211–213. (b) H. Chen, J. F. Hartwig, *Angew. Chem., Int. Ed.* **1999**, *38*, 3391–3393.

211 (a) C. N. Iverson, M. R. Smith, III, *J. Am. Chem. Soc.* **1999**, *121*, 7696–7697. (b) J.-Y. Cho, C. N. Iverson, M. R. Smith, III, *J. Am. Chem. Soc.* **2000**, *122*, 12868–12869.

212 H. Chen, S. Schlecht, T. C. Temple, J. F. Hartwig, *Science* **2000**, *287*, 1995–1997.

213 T. Ishiyama, J. Takagi, K. Ishida, N. Miyaura, N. R. Anastasi, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 390–391.

214 S. Shimada, A. S. Batsanov, J. A. K. Howard, T. B. Marder, *Angew. Chem., Int. Ed.* **2001**, *40*, 2168–2171.

215 H. Tamura, H. Yamazaki, H. Sato, S. Sakaki, *J. Am. Chem. Soc.* **2003**, *125*, 16114–16126.

216 T. Ishiyama, N. Miyaura, *J. Organomet. Chem.* **2003**, *680*, 3–11.

217 M. W. Davies, C. N. Johnson, J. P. A. Harrity, *J. Org. Chem.* **2001**, *66*, 3525–3532.

218 D. R. Nielsen, W. E. McEwen, *J. Am. Chem. Soc.* **1957**, *79*, 3081–3084.

219 D. Kaufman, *Chem. Ber.* **1987**, *120*, 901–905.

220 E. G. IJpeij, F. H. Beijer, H. J. Arts, C. Newton, J. G. de Vries, G.-J. M. Gruter, *J. Org. Chem.* **2002**, *67*, 169–176.

221 R. L. Letsinger, J. R. Nazy, *J. Am. Chem. Soc.* **1959**, *81*, 3013–3017.

222 E. Tyrrell, P. Brookes, *Synthesis* **2004**, 469–483.

223 A. A Fuller, H. R. Hester, E. V. Salo, E. P. Stevens, *Tetrahedron Lett.* **2003**, *44*, 2935–2938.

224 H. A. Dieck, R. F. Heck, *J. Org. Chem.* **1975**, *40*, 1083–1090.

225 H. C. Brown, N. G. Bhat, *Tetrahedron Lett.* **1988**, *29*, 21–24.

226 J. Uenishi, K. Matsui, A. Wada, *Tetrahedron Lett.* **2003**, *44*, 3093–3096.

227 D. S. Matteson, *J. Am. Chem. Soc.* **1960**, *82*, 4228–4233.

228 P. B. Tivola, A. Deagostino, C. Prandi, P. Venturello, *Org. Lett.* **2002**, *4*, 1275–1277.

229 (a) G. M. Farinola, V. Fiandanese, L. Mazzone, F. Naso, *J. Chem. Soc., Chem. Commun.* 1995, 2523–2524. (b) F. Babudri, G. M. Farinola, V. Fiandanesse, L. Mazzone, F. Naso, *Tetrahedron* **1998**, *54*, 1085–1094.

230 I. Mikhail, D. Kaufmann, *J. Organomet. Chem.* **1990**, *398*, 53–57.

231 K. Itami, T. Kamei, J.-i. Yoshida, *J. Am. Chem. Soc.* **2003**, *125*, 14670–14671.

232 T. E. Cole, R. Quintanilla, S. Rodewald, *Organometallics* **1991**, *10*, 3777–3781.

233 K. Takahashi, J. Takagi, T. Ishiyama, N. Miyaura, *Chem. Lett.* **2000**, 126–127.

234 J. Takagi, K. Takahashi, T. Ishiyama, N. Miyaura, *J. Am. Chem. Soc.* **2002**, *124*, 8001–8006.

235 T. Ishiyama, J. Takagi, A. Kamon, N. Miyaura, *J. Organomet. Chem.* **2003**, *687*, 284–290.

236 M. Murata, T. Oyama, S. Watanabe, Y. Masuda, *Synthesis* **2000**, *6*, 778–780.

237 H. C. Brown, B. C. Subba Rao, *J. Am. Chem. Soc.* **1956**, *78*, 5694–5695.

238 H. C. Brown, *Hydroboration*, Benjamin/Cummings, Reading MA, **1962**.

239 H. C. Brown, G. Zweifel, *J. Am. Chem. Soc.* **1961**, *83*, 3834–3840.

240 G. Zweifel, H. C. Brown, *J. Am. Chem. Soc.* **1963**, *85*, 2066–2072.

241 G. Zweifel, G. M. Clark, N. L. Polston, *J. Am. Chem. Soc.* **1971**, *93*, 3395–3399.

242 H. C. Brown, C. G. Scouten, R. Liotta, *J. Am. Chem. Soc.* **1979**, *101*, 96–99.

243 N. Miyaura, A. Suzuki, *Chem. Lett.* **1981**, 879–882.

244 R. W. Hoffmann, S. Dresely, *Synthesis* **1988**, 103–106.

245 H. C. Brown, A. K. Mandal, S. U. Kulkarni, *J. Org. Chem.* **1977**, *42*, 1392–1398.

246 P. Martinez-Fresneda, M. Vaultier, *Tetrahedron Lett.* **1989**, *30*, 2929–2932.

247 A. Kamabuchi, T. Moriya, N. Miyaura, A. Suzuki, *Synth. Commun.* **1993**, *23*, 2851–2859.

248 A. V. Kalinin, S. Scherer, V. Snieckus, *Angew. Chem., Int. Ed.* **2003**, *42*, 3399–3404.

249 (a) H. C. Brown, S. K. Gupta, *J. Am. Chem. Soc.* **1972**, *94*, 4370–4371. (b) H. C. Brown, S. K. Gupta, *J. Am. Chem. Soc.* **1975**, *97*, 5249–5255. (c) C. F. Lane, G. W. Kabalka, *Tetrahedron* **1976**, *32*, 981–990.

250 A. Arase, M. Hoshi, A. Mijin, K. Nishi, *Synth. Commun.* **1995**, *25*, 1957–1962.

251 K. A. Scheidt, A. Tasaka, T. D. Bannister, M. D. Wendt, W. R. Roush, *Angew. Chem., Int. Ed.* **1999**, *38*, 1652–1655.

252 H. C. Brown, J. B. Campbell, *J. Org. Chem.* **1980**, *45*, 389–395.

253 A. Hassner, J. A. Soderquist, *J. Organomet. Chem.* **1977**, *131*, C1–C4.

254 R. Soundararajan, D. S. Matteson, *J. Org. Chem.* **1990**, *55*, 2274–2275.

255 K. V. B. Josyula, P. Gao, C. Hewitt, *Tetrahedron Lett.* **2003**, *44*, 7789–7792.

256 H. C. Brown, T. Imai, *Organometallics* **1984**, *3*, 1392–1395.

257 H. C. Brown, D. Basavaiah, S. U. Kulkarni, *J. Org. Chem.* **1982**, 47, 3808–3810.

258 H. C. Brown, T. Imai, N. G. Bhat, *J. Org. Chem.* **1986**, *51*, 5277–5282.

259 T. Hata, H., Kitagawa, H. Masai, T. Kurahashi, M. Shimizu, T. Hiyama, *Angew. Chem., Int. Ed*. **2001**, *40*, 790–792.

260 D. Männig, H. Nöth, *Angew. Chem., Int. Ed. Engl*. **1985**, *24*, 878–879.

261 (a) K. Burgess, M. J. Ohlmeyer, *Chem. Rev.* **1991**, *91*, 1179–1191. (b) I. Beletskaya, A. Pelter, *Tetrahedron* **1997**, *53*, 4957–5026.

262 X. He, J. F. Hartwig, *J. Am. Chem. Soc.* **1996**, *118*, 1696–1702.

263 S. Pereira, M. Srebnik, *Organometallics* **1995**, *14*, 3127–3128.

264 S. Pereira, M. Srebnik, *Tetrahedron Lett.* **1996**, *37*, 3283–3286.

265 I. D. Gridnev, N. Miyaura, A. Suzuki, *Organometallics* **1993**, *12*, 589–592.

266 M. Satoh, Y. Nomoto, N. Miyaura, A. Suzuki, *Tetrahedron Lett*. **1989**, *30*, 3789–3792.

267 Y. Yamamoto, R. Fujikawa, A. Yamada, N. Miyaura, *Chem. Lett*. **1999**, 1069–1070.

268 T. Ohmura, Y. Yamamoto, N. Miyaura, *J. Am. Chem. Soc*. **2000**, *122*, 4990–4991.

269 J. Renaud, S. G. Ouellet, *J. Am. Chem. Soc.* **1998**, *120*, 7995–7996.

270 S. J. Connon, S. Blechert, *Angew. Chem., Int. Ed*. **2003**, *42*, 1900–1923.

271 H. E. Blackwell, D. J. O'Leary, A. K. Chatterjee, R. A. Washenfelder, D. A. Bussmann, R. H. Grubbs, *J. Am. Chem. Soc.* **2000**, *122*, 58–71.

272 C. Morrill, R. H. Grubbs, *J. Org. Chem.* **2003**, *68*, 6031–6034.

273 J. T. Njardarson, K. Biswas, S. J. Danishefsky, *Chem. Commun*. **2002**, 2759–2761.

274 J. Renaud, C.-D. Graf, L. Oberer, *Angew. Chem., Int. Ed*. **2000**, *39*, 3101–3104.

275 G. C. Micalizio, S. L. Schreiber, *Angew. Chem., Int. Ed*. **2002**, *41*, 3272–3276.

276 M. Srebnik, N. G. Bhat, H. C. Brown, *Tetrahedron Lett*. **1988**, *29*, 2635–2638.

277 L. Deloux, M. Srebnik, *J. Org. Chem.* **1994**, *59*, 6871–6873.

278 D. S. Matteson, D. Majumdar, *Organometallics* **1983**, *2*, 230–236.

279 D. S. Matteson, R. J. Moody, P. K. Jesthi, *J. Am. Chem. Soc*. **1975**, *97*, 5608–5609.

280 D. S. Matteson. R. J. Moody, *Organometallics* **1982**, *1*, 20–28.

281 J.-i. Uenishi, J.-M. Beau, R. W. Armstrong, Y. Kishi, *J. Am. Chem. Soc*. **1987**, *109*, 4756–4758.

282 D. A. Evans, H. P. Ng, D. L. Rieger, *J. Am. Chem. Soc*. **1993**, *115*, 11446–11459.

283 K. Takai, N. Shinomiya, H. Kaihara, N. Yoshida, T. Moriwake, *Synlett* **1995**, 963–964.

284 I. T. Raheem, S. N. Goodman, E. N. Jacobsen, *J. Am. Chem. Soc*. **2003**, *126*, 706–707.

285 (a) A. P. Lightfoot, G. Maw, C. Thirsk, S. J. R. Twiddle, A. Whiting, *Tetrahedron Lett*. **2003**, *44*, 7645–7648. (b) K. Itami, K. Tonogaki, Y. Ohashi, J.-I. Yoshida, *Org. Lett*. **2004**, *6*, 4093–4096.

286 R. Benjamin Coapes, F. E. S. Souza, R. Ll. Thomas, J. J. Hall, T. B. Marder, *Chem. Commun*. **2003**, 614–615.

287 (a) Y. Satoh, H. Serizawa, N. Miyaura, S. Hara, A. Suzuki, *Tetrahedron Lett*. **1988**, *29*, 1811–1814. (b) M. Sato, Y. Yamamoto, S. Hara, A. Suzuki, *Tetrahedron Lett*. **1993**, *34*, 7071–7074.

288 (a) T. Ishiyama, N. Matsuda, N. Miyaura, A. Suzuki, *J. Am. Chem. Soc*. **1993**, *115*, 11018–11019. (b) T. Ishiyama, N. Matsuda, M. Murata, F. Ozawa, A. Suzuki, N. Miyaura, *Organometallics* **1996**, *15*, 713–720.

289 (a) C. N. Iverson, M. R. Smith, *Organometallics* **1996**, *15*, 5155–5165. (b) M. J. G. Lesley, P. Nguyen, N. J. Taylor, T. B. Marder, A. J. Scott, W. Clegg, N. C. Norman, *Organometallics* **1996**, *15*, 5137–5154. (c) K. M. Anderson, M. J. G. Lesley, N. C. Norman, A. G. Orpen, J. Starbuck, *New. J. Chem*. **1999**, *23*, 1053–1055.

290 (a) T. Ishiyama, M. Yamamoto, N. Miyaura, *Chem. Commun*. **1996**, 2073–2074. (b) T. Ishiyama, T. Kitano, N. Miyaura, *Tetrahedron Lett*. **1998**, *39*, 2357–2360.

291 K. Takahashi, T. Ishiyama, N. Miyaura, *J. Organometallic Chem*. **2001**, *625*, 47–53.

292 (a) M. Suginome, T. Ohmura Y. Miyake, S. Mitani, Y. Ito, M. Murakami, *J. Am. Chem. Soc*. **2003**, *125*, 11174–11175. (b) M. Suginome, Y. Ito, *J. Organomet. Chem*. **2003**, *680*, 43–50.

293 M. Suginome, A. Yamamoto, M. Murakami, *J. Am. Chem. Soc*. **2003**, *125*, 6358–6359.

294 D. S. Matteson, K. Peacock, *J. Org. Chem.* **1963**, *28*, 369–371.

295 H. C. Brown, N. G. Bhat, M. Srebnik, *Tetrahedron Lett*. **1988**, *29*, 2631–2634.

296 M. Sato, N. Miyaura, A. Suzuki, *Chem. Lett*. **1989**, 1405–1408.

297 (a) M. W. Rathke, E. Chao, G. Wu, *J. Organomet. Chem*. **1976**, *122*, 145–149. (b)

P. G. M. Wuts, P. A. Thompson, *J. Organomet. Chem.* **1982**, *234*, 137–141. (c) K. M. Sadhu, D. S. Matteson, *Organometallics* **1985**, *4*, 1687–1689.

298 T. J. Michnick, D. S. Matteson, *Synlett* **1991**, 631–632.

299 (a) D. S. Matteson, D. Majumdar, *J. Organomet. Chem.* **1979**, *170*, 259–264. (b) D. P. Phillion, R. Neubauer, S. S. Andrew, *J. Org. Chem.* **1986**, *51*, 1610–1612.

300 H. C. Brown, B. Singaram, *Acc. Chem. Res.* **1988**, *21*, 287–293.

301 H. C. Brown, B. Singaram, *J. Am. Chem. Soc.* **1984**, *106*, 1797–1800.

302 (a) C. M. Crudden, D. Edwards, *Eur. J. Org. Chem.* **2003**, 4695–4712. (b) C. M. Crudden, Y. B. Hleba, A. C. Chen, *J. Am. Chem. Soc.* **2004**, *126*, 9200–9201.

303 M. Rubina, M. Rubin, V. Gevorgyan, *J. Am. Chem. Soc.* **2003**, *125*, 7198–7199.

304 E. Hupe, I. Marek, P. Knochel, *Org. Lett.* **2002**, *4*, 2861–2863.

305 M. Ueda, A. Satoh, N. Miyaura, *J. Organomet. Chem.* **2002**, *642*, 145–147.

306 (a) C. Morin, *Tetrahedron* **1994**, *50*, 12521–12569. (b) M. Srebnik, *Tetrahedron* **2003**, *59*, 579–593.

307 C. Laplante, D. G. Hall, *Org. Lett.* **2001**, *3*, 1487–1490.

308 D. S. Matteson, J. D. Liedtke, *J. Am. Chem. Soc.* **1965**, *87*, 1526–1531.

309 D. S. Matteson, *J. Organomet. Chem.* **1999**, *581*, 51–65.

310 A. Michaelis, *Ann.* **1901**, *315*, 19.

311 Z. Zhong, E. V. Anslyn, *J. Am. Chem. Soc.* **2002**, *124*, 9014–9015.

312 S. X. Cai, J. F. W. Keana, *Bioconj. Chem.* **1991**, *2*, 317–322.

313 (a) D. S. Matteson, K. H. Arne, *J. Am. Chem. Soc.* **1978**, *100*, 1325–1326. (b) D. S. Matteson, K. H. Arne, *Organometallics* **1982**, *1*, 280–288.

314 D. S. Matteson, D. Majumdar, *J. Chem. Soc., Chem. Commun.* **1980**, 39–40.

315 S. Jagannathan, T. P. Forsyth, C. A. Kettner, *J. Org. Chem.* **2001**, *66*, 6375–6380.

316 D. S. Matteson, R. J. Moody, *J. Org. Chem.* **1980**, *45*, 1091–1095.

317 D. S. Matteson, *Synthesis* **1975**, 147–158.

318 D. S. Matteson, J. W. Wilson, *Organometallics* **1985**, *4*, 1690–1692.

319 P. Knochel, *J. Am. Chem. Soc.* **1990**, *112*, 7431–7433.

320 J. R. Waas, A. Sidduri, P. Knochel, *Tetrahedron Lett.* **1992**, *33*, 3717–3720.

321 H. C. Brown, T. Imai, *J. Am. Chem. Soc.* **1983**, *105*, 6285–6289.

322 D. S. Matteson, *Tetrahedron* **1998**, *54*, 10555–10607.

323 J. Wityak, R. A. Earl, M. M. Abelman, Y. B. Bethel, B. N. Fisher, G. K. Kauffman, C. A. Kettner, P. Ma, J. L. McMillan, L. J. Mersinger, J. Pesti, M. E. Pierce, F. W. Rankin, R. J. Chorvat, P. N. Confalone, *J. Org. Chem.* **1995**, *60*, 3717–3722.

324 A. D. Ainley, F. Challenger, *J. Chem. Soc.* **1930**, 2171–2180.

325 W. Ni, H. Fang, G. Springsteen, B. Wang, *J. Org. Chem.* **2004**, *69*, 1999–2007.

326 T. Moriya, A. Suzuki, N. Miyaura, *Tetrahedron Lett.* **1995**, *36*, 1887–1888.

327 H. Lopes-Ruiz, S. Z. Zard, *Chem. Commun.* **2001**, 2618–2619.

328 (a) C. Rasset-Deloge, P. Martinez-Fresneda, M. Vaultier, *Bull. Soc. Chim. Fr.* **1992**, *129*, 285–290. (b) E. Jehanno, M. Vaultier, *Tetrahedron Lett.* **1995**, *36*, 4439–4442.

329 D. H. Kinder, M. M. Ames, *J. Org. Chem.* **1987**, *52*, 2452–2454.

330 H. Gilman, D. R. Swayampati, R. O. Ranck, *J. Am. Chem. Soc.* **1958**, *80*, 1355–1357.

331 P. Vedsø, P. H. Olesen, T. Hoeg-Jensen, *Synlett* **2004**, 892–894.

332 L. Santucci, H. Gilman, *J. Am. Chem. Soc.* **1958**, *80*, 193–196.

333 H. Cao, T. McGill, M. D. Heagy, J. *Org. Chem.* **2004**, *69*, 2959–2966.

334 (a) D. G. Hall, J. Tailor, M. Gravel, *Angew. Chem., Int. Ed.* **1999**, *38*, 3064–3067. (b) S. Arimori, J. H. Hartley, M. L. Bell, C. S. Oh, T. D. James, *Tetrahedron Lett.* **2000**, *41*, 10291–10294.

335 M. Gravel, K. A. Thompson, M. Zak, C. Bérubé, D. G. Hall, *J. Org. Chem.* **2002**, *67*, 3–15.

336 M. Gravel, C. Bérubé, D. G. Hall, *J. Comb. Chem.* **2000**, *2*, 228–231.

337 K. A. Thompson, D. G. Hall, *Chem. Commun.* **2000**, 2379–2380.

338 B. Carboni, C. Pourbaix, F. Carreaux, H. Deleuze, B. Maillard, *Tetrahedron Lett.* **1999**, *40*, 7979–7983.

339 C. Pourbaix, F. Carreaux, B. Carboni, *Org. Lett.* **2001**, *3*, 803–805.

340 C. Pourbaix, F. Carreaux, B. Carboni, H. Deleuze, *Chem. Commun.* **2000**, 1275–1276.

341 W. Li, K. Burgess, *Tetrahedron Lett.* **1999**, *40*, 6527–6530.

342 R. M. Dunsdon, J. R. Greening, P. S. Jones, S. Jordan, F. X. Wilson, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1577–1579.

343 T. Arnauld, A. G. M. Barrett, R. Seifried, *Tetrahedron Lett.* **2001**, *42*, 7889–7901.

344 W. Q. Wang, X. M. Gao, G. Springsteen, B. Wang, *Tetrahedron Lett.* **2002**, *43*, 6339–6342.

345 (a) D. Chen, F.-l. Qing, Y. Huang, *Org. Lett.* **2002**, *4*, 1003-1006. (b) Y. Huang, D. Chen, F.-L. Qing, *Tetrahedron* **2003**, *59*, 7879–7886.

346 A. Hebel, R. Haag, *J. Org. Chem.* **2002**, *67*, 9452–9455.

347 L. M. Dennis, R. S. Shelton, *J. Am. Chem. Soc.* **1930**, *52*, 3128–3132.

348 H. Gilman, L. Santucci, D. R. Swayampati, R. O. Ranck, *J. Am. Chem. Soc.* **1957**, *79*, 2898–2901.

349 C. Longstaff, M. E. Rose, *Org. Mass Spectrom.* **1982**, *17*, 508–518.

350 J. J. Kaminski, R. E. Lyle, *Org. Mass Spectrom.* **1978**, *13*, 425–428.

351 M. J. Haas, K. F. Blom, C. H. Schwarz, III, *Anal. Chem.* **1999**, *71*, 1574–1578.

352 S. Hermánek, *Chem. Rev.* **1992**, *92*, 325–362.

353 H. Nöth, B. Wrackmeyer, in *Nuclear Magnetic Resonance Spectroscopy of Boron Compounds*, P. Diehl, E. Fluck, R. Kosfeld (Eds), NMR Basic Principles and Progress Series 14, Springer-Verlag, Berlin, **1978**.

354 D. S. Matteson, E. Krämer, *J. Am. Chem. Soc.* **1968**, *90*, 7261–7267.

355 R. C. Larock, S. K. Gupta, H. C. Brown, *J. Am. Chem. Soc.* **1972**, *94*, 4371–4373.

356 M. J. Rozema, D. Rajagopal, C. E. Tucker, P. Knochel, *J. Organomet. Chem.* **1992**, *438*, 11–27.

357 F. Challenger, Parker, *J. Chem. Soc.* **1931**, 1462.

358 H. G. Kuivila, J. F. Reuwer, J. A. Mangravite, *J. Am. Chem. Soc.* **1964**, *86*, 2666–2670.

359 H. C. Brown, G. Zweifel, *J. Am. Chem. Soc.* **1961**, *83*, 2544–2551.

360 R. E. Maleczka, Jr., F. Shi, D. Holmes, M. R. Smith, III, *J. Am. Chem. Soc.* **2003**, *125*, 7792–7793.

361 (a) H. G. Kuivila, *J. Am. Chem. Soc.* **1954**, *76*, 870–874. (b) H. G. Kuivila, A. G. Armour, *J. Am. Chem. Soc.* **1957**, *79*, 5659–5662.

362 G. W. Kabalka, H. C. Hedgecock, Jr., *J. Org. Chem.* **1975**, *40*, 1776–1779.

363 K. S. Webb, D. Levy, *Tetrahedron Lett.* **1995**, *36*, 5117–5118.

364 D. S. Matteson, R. Ray, *J. Am. Chem. Soc.* **1980**, *102*, 7591–7593.

365 P. Fontani, B. Carboni, M. Vaultier, G. Maas, *Synthesis* **1991**, 605–609.

366 M. Murata, K. Satoh, S. Watanabe, Y. Masuda, *J. Chem. Soc., Perkin Trans. 1* **1998**, 1465–1466.

367 M.-L. Huber, J. T. Pinhey, *J. Chem. Soc., Perkin Trans. 1* **1990**, 721–722.

368 (a) S. Stefan, S. Jurgen, G. K. S. Prakash, N. A. Petasis, G. A. Olah, *Synlett* **2000**, 1845–1847. (b) G. K. S. Prakash, C. Panja, T. Mathew, V. Surampudi, N. A. Petasis, G. A. Olah, *Org. Lett.* **2004**, *6*, 2205–2207.

369 H. C. Brown, K.-W. Kim, T. E. Cole, B. Singaram, *J. Am. Chem. Soc.* **1986**, *108*, 6761–6764.

370 P.-Y. Chavant, F. Lhermitte, M. Vaultier, *Synlett* **1993**, 519–521.

371 (a) J.-M. Jego, B. Carboni, M. Vaultier, R. Carrié, *J. Chem. Soc., Chem. Commun.* **1989**, 142–143. (b) J.-M. Jego, B. Carboni, M. Vaultier, *Bull. Soc. Chim. Fr.* **1992**, *129*, 554–565.

372 H. G. Kuivila, E. K. Easterbrook, *J. Am. Chem. Soc.* **1951**, *73*, 4629.

373 H. G. Kuivila, A. R. Hendrickson, *J. Am. Chem. Soc.* **1952**, *74*, 5068–5070.

374 C. Thiebes, G. K. S. Prakash, N. A. Petasis, G. A. Olah, *Synlett* **1998**, 141–142.

375 R. H. Szumigala, Jr., P. N. Devine, D. R. Gauthier, Jr., R. P. Volante, *J. Org. Chem.* **2004**, *69*, 566–569.

376 (a) L. J. Diorazio, D. A. Widdowson, J. M. Clough, *Tetrahedron* **1992**, *48*, 8073–8088. (b) J. M. Clough, L. J. Diorazio, D. A. Widdowson, *Synlett* **1990**, 761–762.

377 M. A. Carroll, V. W. Pike, D. A. Widdowson, *Tetrahedron Lett.* **2000**, *41*, 5393–5396.

378 H. C. Brown, T. Hamaoka, N. Ravindran, *J. Am. Chem. Soc.* **1973**, *95*, 6456–6457.

379 H. C. Brown, N. G. Bhat, S. Rajagopalan, *Synthesis* **1986**, 480–482.

380 H. C. Brown, C. Subrahmanyam, T. Hamaoka, N. Ravindran, D. H. Bowman,

S. Misumi, M. K. Unni, V. Somayaji, N. G. Bhat, *J. Org. Chem.* **1989**, *54*, 6068–6075.
381 H. C. Brown, T. Hamaoka, N. Ravindran, *J. Am. Chem. Soc.* **1973**, *95*, 5786–5788.
382 H. C. Brown, V. Somayaji, *Synthesis* **1984**, 919–920.
383 H. C. Brown, T. Hamaoka, N. Ravindran, C. Subrahmanyam, V. Somayaji, N. G. Bhat, *J. Org. Chem.* **1989**, *54*, 6075–6079.
384 G. W. Kabalka, E. E. Gooch, H. C. Hsu, *Synth. Commun.* **1981**, *11*, 247–251.
385 S. K. Stewart, A. Whiting, *Tetrahedron Lett.* **1995**, *36*, 3929–3932.
386 N. A. Petasis, I. A. Zavialov, *Tetrahedron Lett.* **1996**, *37*, 567–570.
387 S. A. Kunda, T. L. Smith, M. D. Hylarides, G. W. Kabalka, *Tetrahedron Lett.* **1985**, *26*, 279–280.
388 N. Miyaura, A. Suzuki, *J. Chem. Soc., Chem. Commun.* **1979**, 866–867.
389 N. Miyaura, T. Yanagi, A. Suzuki, *Synth. Commun.* **1981**, *11*, 513–519.
390 (a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483. (b) A. Suzuki, in *Metal-Catalyzed Cross-Coupling Reactions*, F. Diederich, P. J. Stang (Eds), Wiley-VCH, Weinheim, **1998**, Chapter 2, pp 49–98. (c) A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147–168. (d) N. Miyaura, *Top. Curr. Chem.* **2002**, *219*, 11–59. (e) S. Kotha, K. Lahiri, D. Kashinath, *Tetrahedron* **2002**, *58*, 9633–9695. (f) J. Hassan, M. Sévignon. C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359–1469.
391 N. Miyaura, K. Yamada, H. Suginome, A. Suzuki, *J. Am. Chem. Soc.* **1985**, *107*, 972–980.
392 G. B. Smith, G. C. Dezeny, D. L. Hughes, A. O. King, T. R. Verhoeven, *J. Org. Chem.* **1994**, *59*, 8151–8156.
393 M. Moreno-Manas, M. Pérez, R. Pleixats, *J. Org. Chem.* **1996**, *61*, 2346–2351.
394 A. O. Aliprantis, J. W. Canary, *J. Am. Chem. Soc.* **1994**, *116*, 6985–6986.
395 N. Miyaura, *J. Organometallic Chem.* **2002**, *653*, 54–57.
396 A. R. Martin, Y. Yang, *Acta Chem. Scand.* **1993**, *47*, 221–230.
397 (a) T. Ishiyama, H. Kizaki, N. Miyaura, A. Suzuki, *Tetrahedron Lett.* **1993**, *34*, 7595–7598. (b) T. Ishiyama, H. Kizaki, T. Hayashi, A. Suzuki, N. Miyaura, *J. Org. Chem.* **1998**, *63*, 4726–4731.
398 (a) N. A. Bumagin, D. N. Korolev, *Tetrahedron Lett.* **1999**, *40*, 3057–3060. (b) M. Haddach, J. R. McCarthy, *Tetrahedron Lett.* **1999**, *40*, 3109–3112.
399 L. J. Goossen, K. Ghosh, *Angew. Chem., Int. Ed.* **2001**, *40*, 3458–3460.
400 (a) S. Gronowitz, A.-B. Hörnfeldt, Y.-H. Yang, *Chem. Scr.* **1986**, *26*, 383–386. (b) H. Chaumeil, S. Signorella, C. Le Drian, *Tetrahedron* **2000**, *56*, 9655–9662.
401 S. W. Wright, D. L. Hageman, L. D. McClure, *J. Org. Chem.* **1994**, *59*, 6095–6097.
402 T. Watanabe, N. Miyaura, A. Suzuki, *Synlett* **1992**, 207–209.
403 H. Yoshida, Y. Yamaryo, J. Ohshita, A. Kunai, *Tetrahedron Lett.* **2003**, *44*, 1541–1544.
404 X. Cai, V. Snieckus, *Org. Lett.* **2004**, *6*, 2293–2295.
405 W. R. Roush, M. L. Reilly, K. Koyama, B. B. Brown, *J. Org. Chem.* **1997**, *62*, 8708–8721.
406 (a) N. Miyaura, H. Suginome, A. Suzuki, *Tetrahedron* **1983**, *39*, 3271–3277. (b) N. Miyaura, A. Suzuki, *Org. Synth.* **1990**, *68*, 130–136.
407 H. Tsukamoto, M. Sato, Y. Kondo, *Chem. Commun.* **2004**, 1200–1201.
408 (a) S. R. Chemler, D. Trauner, S. J. Danishefsky, *Angew. Chem., Int. Ed.* **2001**, *40*, 4544–4568; and references cited. (b) G. Zou, Y. K. Reddy, J. R. Falck, *Tetrahedron Lett.* **2001**, *42*, 7213–7215. (c) N. Kataoka, Q. Shelby, J. P. Stambuli, J. F. Hartwig, *J. Org. Chem.* **2002**, *67*, 5553–5566.
409 S.-M. Zhou, M.-Z. Deng, L.-J. Xia, M.-H. Tang, *Angew. Chem., Int. Ed.* **1998**, *37*, 2845–2847.
410 J. H. Kirchhoff, M. R. Netherton, I. D. Hills, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 13662–13663.
411 (a) R. Franzen, *Can. J. Chem.* **2000**, *78*, 957–962. (b) S. Brase, J. H. Kirchhoff, J. Kobberling, *Tetrahedron* **2003**, *59*, 885–939.
412 (a) Y. Urawa, H. Naka, M. Miyasawa, S. Souda, K. Ogura, *J. Organomet. Chem.* **2002**, *653*, 269–278. (b) N. Yasuda, *J. Organomet. Chem.* **2002**, *653*, 279–287.
413 A. F. Littke, G. C. Fu, *Angew. Chem., Int. Ed.* **2002**, *41*, 4176–4211.
414 (a) A. F. Littke, G. C. Fu, *Angew. Chem., Int. Ed.* **1998**, *37*, 3387–3388. (b) A. F. Littke, C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028.

415 D. W. Old, J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 9722–9723. (b) J. P. Wolfe, R. A. Singer, B. H. Yang, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 9550–9561. (c) J. Yin, M. P. Rainka, X.-X. Zhang, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 1162–1163.

416 (a) C. W. K. Gstottmayr, V. P. M. Bohn, E. Herdtweck, M. Grosche, W. A. Hermann, *Angew. Chem., Int. Ed.* **2002**, *41*, 1363–1365. (b) J. P. Stambuli, R. Kuwano, J. F. Hartwig, *Angew. Chem., Int. Ed.* **2002**, *41*, 4746–4748.

417 S. D. Walker, T. E. Barder, J. R. Martinelli, S. L. Buchwald, *Angew. Chem., Int. Ed.* **2004**, *43*, 1871–1876.

418 O. Navarro, R. A. Kelly, III, S. P. Nolan, *J. Am. Chem. Soc.* **2003**, *125*, 16194–16195.

419 V. Percec, J.-Y. Bae, D. H. Hill, *J. Org. Chem.* **1995**, *60*, 1060–1065.

420 Y. Na, S. Park, S. B. Han, H. Han, S. Ko, S. Chang, *J. Am. Chem. Soc.* **2004**, *126*, 250–258.

421 H. Sakurai, T. Tsukuda, T. Hirao, *J. Org. Chem.* **2002**, *67*, 2721–2722; and references cited therein.

422 N. E. Leadbeater, M. Marco, *J. Org. Chem.* **2003**, *68*, 5660–5667. This claim has recently been retracted: see *J. Org. Chem.* **2005**, *70*, 161–168.

423 (a) H. N. Nguyen, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 11818–11819. (b) V. Percec, G. M. Golding, J. Smidrkal, O. Weichold, *J. Org. Chem.* **2004**, *69*, 3447–3452. (c) Z.-Y. Ang, Q.-S. Hu, *J. Am. Chem. Soc.* **2004**, 126, 3058–3059.

424 S. B. Blakey, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 6046–6047.

425 J. Srogl, G. D. Allred, L. S. Liebeskind, *J. Am. Chem. Soc.* **1997**, *119*, 12376–12377.

426 (a) C. Savarin, J. Srogl, L. S. Liebeskind, *Org. Lett.* **2000**, *2*, 3229–3231. (b) L. S. Liebeskind, J. Srogl, *J. Am. Chem. Soc.* **2000**, *122*, 11260–11261.

427 (a) C. Savarin, J. Srogl, L. S. Liebeskind, *Org. Lett.* **2001**, *3*, 91–93. (b) L. S. Liebeskind, J. Srogl, *Org. Lett.* **2002**, *4*, 979–981. (c) C. L. Kusturin, L. S. Liebeskind, *Org. Lett.* **2002**, *4*, 983–985.

428 C. Kusturin, L. S. Liebeskind, H. Rahman, K. Sample, B. Schweitzer, J. Srogl, W. L. Neumann, *Org. Lett.* **2003**, *5*, 4349–4352.

429 J. Blais, A. L'Honoré, J. Soulié, P. Cadiot, *J. Organomet. Chem.* **1974**, *78*, 323–337.

430 (a) S. E. Denmark, N. G. Almstead, in *Modern Carbonyl Chemistry*, J. Otera (Ed), Wiley-VCH, Weinheim, **2000**, Chapter 10, pp 299–402. (b) S. R. Chemler, W. R. Roush, in *Modern Carbonyl Chemistry*, J. Otera (Ed), Wiley-VCH, Weinheim, **2000**, Chapter 11, pp 403–490.

431 (a) J. W. J. Kennedy, D. G. Hall, *J. Am. Chem. Soc.* **2002**, *124*, 11586–11587. (b) T. Ishiyama, T. -a. Ahiko, N. Miyaura, *J. Am. Chem. Soc.* **2002**, *124*, 12414–12415. (c) V. Rauniyar, D. G. Hall, *J. Am. Chem. Soc.* **2004**, *126*, 4518–4519.

432 (a) H. Lachance, X. Lu, M. Gravel, D. G. Hall, *J. Am. Chem. Soc.* **2003**, *125*, 10160–10161. (b) M. Gravel, H. Lachance, X. Lu, D. G. Hall, *Synthesis* **2004**, 1290–1302.

433 N. A. Petasis, I. A. Zavialov, *J. Am. Chem. Soc.* **1997**, *119*, 445–446.

434 N. A. Petasis, I. A. Zavialov, *J. Am. Chem. Soc.* **1998**, *120*, 11798–11799.

435 M. Sakai, M. Ueda, N. Miyaura, *Angew. Chem., Int. Ed.* **1998**, *37*, 3279–3281.

436 M. Sakai, H. Hayashi, N. Miyaura, *Organometallics* **1997**, *16*, 4229–4231.

437 T. Hayashi, K. Yamasaki, *Chem. Rev.* **2003**, *103*, 2829–2844.

438 Z. Wang, G. Zou, J. Tang, *Chem. Commun.* **2004**, 1192–1193.

439 M. Kuriyama, T. Soeta, X. Hao, Q. Chen, K. Tomioka, *J. Am. Chem. Soc.* **2004**, *126*, 8128–8129.

440 C. H. Oh, H. H. Jung, K. S. Kim, N. Kim, *Angew. Chem., Int. Ed.* **2003**, *42*, 805–808.

441 (a) S. Ma, N. Jiao, L. Ye, *Chem. Eur. J.* **2003**, *9*, 6049–6056. (b) C. H. Oh, T. W. Ahn, R. Reddy V. *Chem. Commun.* **2003**, 2622–2623.

442 E. Shirakawa, G. Takahashi, T. Tsuchimoto, Y. Kawakami, *Chem. Commun.* **2002**, 2210–2211.

443 G. Zou, Z. Wang, J. Zhu, J. Tang, *Chem. Commun.* **2003**, 2438–2439.

444 E. J. Farrington, J. M. Brown, C. F. J. Barnard, E. Rowsell, *Angew. Chem., Int. Ed.* **2002** *41*, 169–171.

445 T. Koike, X. Du, T. Sanada, Y. Danda, A. Mori, *Angew. Chem., Int. Ed.* **2003**, *42*, 89–92.

446 (a) C. S. Cho, S. Uemura, *J. Organomet. Chem.* **1994**, *465*, 85–92. (b) X. Du, M.

Suguro, K. Hirabayashi, A. Mori, T. Nishikata, N. Hagiwara, K. Kawata, T. Okeda, H. F. Wang, K. Fugami, M. Kosugi, *Org. Lett.* **2001**, *3*, 3313–3316. (c) Y. C. Jung, R. K. Mishra, C. H. Yoon, K. W. Jung, *Org. Lett.* **2003**, *5*, 2231–2234.

447 G. Zou, J. Zhu, J. Tang, *Tetrahedron Lett.* **2003**, *44*, 8709–9711.

448 D. M. T. Chan, K. L. Monaco, R.-P. Wang, M. P. Winters, *Tetrahedron Lett.* **1998**, *39*, 2933–2936.

449 D. A. Evans, J. L. Katz, T. R. West, *Tetrahedron Lett.* **1998**, *39*, 2937–2940.

450 P. Y. S. Lam, C. G. Clark, S. Saubern, J. Adams, M. P. Winters, D. M. T. Chan, A. Combs, *Tetrahedron Lett.* **1998**, *39*, 2941–2944.

451 (a) A. P. Combs, S. Saubern, M. Rafalski, P. Y. S. Lam, *Tetrahedron Lett.* **1999**, *40*, 1623–1626. (b) A. P. Combs, S. Tadesse, M. Rafalski, T. S. Haque, P. Y. S. Lam, *J. Comb. Chem.* **2002**, *4*, 179–182.

452 J. M. Chong, L. Shen, N. J. Taylor, *J. Am. Chem. Soc.* **2000**, *122*, 1822–1823.

453 J. Morgan, J. T. Pinhey, *J. Chem. Soc., Perkin Trans. 1* **1990**, 715–722.

454 R. Mizojiri, Y. Kobayashi, *J. Chem. Soc., Perkin Trans. 1* **1995**, 2073–2075.

455 B. M. Trost, M. D. Spagnol, *J. Chem. Soc., Perkin Trans. 1* **1995**, 2083–2096.

456 M. Retbøll, A. J. Edwards, A. D. Rae, A. C. Willis, M. A. Bennett, E. Wenger, *J. Am. Chem. Soc.* **2002**, *124*, 8348–8360.

457 C. Bolm, J. Rudolph, *J. Am. Chem. Soc.* **2003**, *125*, 14850–14851.

458 F. Kakiuchi, S. Kan, K. Igi, N. Chatani, S. Murai, *J. Am. Chem. Soc.* **2003**, *125*, 1698–1699.

459 F. Kakiuchi, M. Usui, S. Ueno, N. Chatani, S. Murai, *J. Am. Chem. Soc.* **2004**, *126*, 2706–2707.

460 T. Matsuda, M. Makino, M. Murakami, *Org. Lett.* **2004**, *6*, 1257–1259.

461 F. Minutolo, J. A. Katzenellenbogen, *J. Am. Chem. Soc.* **1998**, *120*, 13264–13625.

462 S. J. Patel, T. F. Jamison, *Angew. Chem., Int. Ed.* **2003**, *42*, 1364–1367.

463 T.-H. Huang, H.-M. Chang, M.-Y. Wu, C.-H. Cheng, *J. Org. Chem.* **2002**, *67*, 99–105.

464 Y. Yamamoto, J.-i. Ishii, H. Nishiyama, K. Itoh, *J. Am. Chem. Soc.* **2004**, *126*, 3712–3713.

465 H. Hayakawa, N. Okada, M. Miyashita, *Tetrahedron Lett.* **1999**, *40*, 3191–3194.

466 A. Hirai, X.-Q. Yu, T. Tonooka, M. Miyashita, *Chem. Commun.* **2003**, 2482–2483.

467 J. R. Falck, M. Bondlela, S. K. Venkataraman, D. Srinivas, *J. Org. Chem.* **2001**, *66*, 7148–7150.

468 (a) R. L. Letsinger, S. Dandegaonker, W. J. Vullo, J. D. Morrison, *J. Am. Chem. Soc.* **1963**, *85*, 2223–2227. (b) R. L. Letsinger, J. D. Morrison, *J. Am. Chem. Soc.* **1963**, *85*, 2227–2229.

469 R. L. Letsinger, D. B. MacLean, *J. Am. Chem. Soc.* **1963**, *85*, 2230–2236.

470 K. Ishihara, S. Ohara, H. Yamamoto, *J. Org. Chem.* **1996**, *61*, 4196–4197.

471 G. Rao, M. Philipp, *J. Org. Chem.* **1991**, *56*, 505–512.

472 S. A. Barker, B. W. Hatt, P. J. Somers, *Carbohydr. Res.* **1973**, *26*, 41–53.

473 J. Rohovec, J. Kotek, J. A. Peters, T. Maschmeyer, *Eur. J. Org. Chem.* **2001**, 3899–3901.

474 J. G. de Vries, S. A. Hubbard, *J. Chem. Soc., Chem. Commun.* **1988**, 1172–1173.

475 K. Narasaka, G. Shimada, K. Osoda, N. Iwasawa, *Synthesis* **1991**, 1171–1172.

476 K. C. Nicolaou, J.-J. Liu, Z. Yang, H. Ueno, E. J. Sorensen, C. F. Claiborne, R. K. Guy, C.-K. Hwang, M. Nakada, P. G. Nantermet, *J. Am. Chem. Soc.* **1995**, *117*, 634–644.

477 (a) W. Nagata, K. Okada, T. Aoki, *Synthesis* **1979**, 365–368. (b) W. S. Murphy, S. M. Tuladhar, B. Duffy, *J. Chem. Soc., Perkin Trans. 1* **1992**, 605–609.

478 J. D. Chambers, J. Crawford, H. W. R. Williams, C. Dufresne, J. Scheigetz, M. A. Bernstein, C. K. Lau, *Can. J. Chem.* **1992**, *70*, 1717–1732.

479 (a) G. A. Molander, K. L. Bobbitt, C. K. Murry, *J. Am. Chem. Soc.* **1992**, *114*, 2759–2760. (b) G. A. Molander, K. L. Bobbitt, *J. Am. Chem. Soc.* **1993**, *115*, 7517–7518.

480 H. E. Sailes, J. P. Watts, A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, **2000**, 3362–3374.

481 (a) K. Ishihara, H. Yamamoto, *Eur. J. Org. Chem.* **1999**, 527–538. (b) P. J. Duggan, E. M. Tyndall, *J. Chem. Soc., Perkin Trans 1,* **2002**, 1325–1339.

482 D. H. Ryu, E. J. Corey, *J. Am. Chem. Soc.* **2004**, *126*, 8106–8107.

483 A. B. Charette, H. Juteau, H. Lebel, C. Molinaro, *J. Am. Chem. Soc.* **1998**, *120*, 11943–11952.

484 R. J. Ferrier, *Adv. Carbohydr. Chem. Biochem.* **1978**, *35*, 31–80.

485 (a) W. V. Dahlhoff, R. Köster, *Heterocycles* **1982**, *18*, 421–449. (b) W. V. Dahlhoff, W. Fenzl, R. Köster, *Liebigs Ann. Chem.* **1990**, 807–810.

486 W. V. Dahlhoff, R. Köster, *Synthesis* **1980**, 936–937.

487 S. Langston, B. Bernet, A. Vasella, *Helv. Chim. Acta* **1994**, *77*, 2341–2353.

488 K. Oshima, E.-i. Kitazono, Y. Aoyama, *Tetrahedron Lett.* **1997**, *38*, 5001–5004.

489 A. M. Yurkevich, I. I. Kolodkina, L. S. Varshavskaya, V. I. Borodulina-Shvetz, I. P. Rudakova, N. A. Preobrazhenski, *Tetrahedron* **1969**, *25*, 477–484.

490 J. E. McMurry, M. D. Erion, *J. Am. Chem. Soc.* **1985**, *107*, 2712–2720.

491 T. J. Perun, J. R. Martin, R. S. Egan, *J. Org. Chem.* **1974**, *39*, 1490–1493.

492 C. Liljebris, B. M. Nilsson, B. Resul, U. Hacksell, *J. Org. Chem.* **1996**, *61*, 4028–4034.

493 A. Flores-Parra, C. Paredes-Tepox, P. Joseph-Nathan, R. Contreras, *Tetrahedron* **1990**, *46*, 4137–4148.

494 E. Bertounesque, J.-C. Florent, C. Monneret, *Synthesis* **1991**, 270–272.

495 (a) K. Ishihara, Y. Kuroki, N. Hanaki, S. Ohara, H. Yamamoto, *J. Am. Chem. Soc.* **1996**, *118*, 1569–1570. (b) Y. Kuroki, K. Ishihara, N. Hanaki, S. Ohara, H. Yamamoto, *Bull. Chem. Soc. Jpn* **1998**, *71*, 1221–1230.

496 (a) D. A. Evans, R. P. Polniaszek, *Tetrahedron Lett.* **1986**, *27*, 5683–5686. (b) D. A. Evans, R. P. Polniaszek, K. M. DeVries, D. E. Guinn, D. J. Mathre, *J. Am. Chem. Soc.* **1991**, *113*, 7613–7630.

497 G. Kaupp, M. R. Naimi-Jamal, V. Stepanenko, *Chem. Eur. J.* **2003**, *9*, 4156–4160.

498 N. Iwasawa, T. Kato, K. Narasaka, *Chem. Lett.* **1988**, 1721–1724.

499 A. Gypser, D. Michel, D. S. Nirschl, K. B. Sharpless, *J. Org. Chem.* **1998**, *63*, 7322–7327.

500 S. A. Barker, B. W. Hatt, P. J. Somers, R. R. Woodbury, *Carbohydr. Res.* **1973**, *26*, 55–64.

501 (a) E. Seymour, J. M. J. Fréchet, *Tetrahedron Lett.* **1976**, 1149–1152. (b) M. J. Farrall, J. M. J. Frechet, *J. Org. Chem.* **1976**, *41*, 3877–3882.

502 N. P. Bullen, P. Hodge, F. G. Thorpe, *J. Chem. Soc., Perkin 1* **1981**, 1863–1867.

503 (a) H. L. Weith, J. L. Wiebers, P. T. Gilham, *Biochemistry* **1970**, *9*, 4396–4401. (b) M. Rosenberg, J. L. Wiebers, P. T. Gilham, *Biochemistry* **1972**, *11*, 3623–3628.

504 (a) H. Schott, *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 824–825. (b) H. Schott, E. Rudloff, P. Schmidt, R. Roychoudhury, H. Kössel, *Biochemistry* **1973**, *12*, 932–938.

505 B. J. B. Johnson, *Biochemistry* **1981**, *20*, 6103–6108.

506 (a) J. R. Mazzeo, I. S. Krull, *BioChromatography* **1989**, *4*, 124–130. (b) R. P. Singhal, S. S. M. DeSilva, *Adv. Chromatogr.* **1992**, *31*, 293–335.

507 (a) A. K. Mallia, G. T. Hermanson, R. I. Krohn, E. K. Fujimoto, P. K. Smith, *Anal. Lett.* **1981**, *14(B8)*, 649–661. (b) F. A. Middle, A. Bannister, A. J. Bellingham, P. D. G. Dean, *Biochem. J.* **1983**, *209*, 771–779.

508 H. Miyazaki, A. Kikuchi, Y. Koyama, T. Okano, Y. Sakurai, K. Kataoka, *Biochem. Biophys. Res. Commun.* **1993**, *195*, 829–836.

509 (a) K. Kataoka, H. Miyazaki, T. Okano, Y. Sakurai, *Macromolecules* **1994**, *27*, 1061–1062. (b) A. Kikuchi, K. Suzuki, O. Okabayashi, H. Hoshino, K. Kataoka, Y. Sakurai, T. Okano, *Anal. Chem.* **1996**, *68*, 823–828. (c) R. Gabai, N. Sallacan, V. Chegel, T. Bourenko, E. Katz, I. Willner, *J. Phys. Chem. B* **2001**, *105*, 8196–8202.

510 Y. Kanekiyo, M. Sano, R. Iguchi, S. Shinkai, *J. Pol. Sci. A: Pol. Chem.* **2000**, *38*, 1302–1310.

511 E. Seymour, J. M. J. Fréchet, *Tetrahedron Lett.* **1976**, 3669–3672.

512 M. Glad, O. Norrlöw, B. Sellergren, N. Siegbahn, K. Mosbach, *J. Chromatogr.* **1985**, *347*, 11–23.

513 G. Wulff, S. Schauhoff, *J. Org. Chem.* **1991**, *56*, 395–400.

514 J. M. J. Frechet, L. J. Nuyens, E. Seymour, *J. Am. Chem. Soc.* **1979**, *101*, 432–436.

515 (a) G. Belogi, T. Zhu, G.-J. Boons, *Tetrahedron Lett.* **2000**, *41*, 6965–6968. (b) G. Belogi, T. Zhu, G.-J. Boons, *Tetrahedron Lett.* **2000**, *41*, 6969–6972.

516 (a) T. D. James, K. R. A. S. Sandanayake, S. Shinkai, *Angew. Chem., Int. Ed.* **1996**, *35*, 1910–1922. (b) T. D. James, S. Shinkai, *Topp. Curr. Chem.* **2002**, *218*, 159–200. (c)

W. Wang, X. Gao, B. Wang, *Curr. Org. Chem.* **2002**, *6*, 1285–1317.

517 J. Zhao, T. M. Fyles, T. D. James, *Angew. Chem., Int. Ed.* **2004**, *43*, 3461–3464.

518 C. W. Gray, Jr., T. A. Houston, *J. Org. Chem.* **2002**, *67*, 5426–5428.

519 (a) J. J. Lavigne, E. V. Anslyn, *Angew. Chem., Int. Ed.* **1999**, *38*, 3666–3669. (b) B. T. Nguyen, S. L. Wiskur, E. V. Anslyn, *Org. Lett.* **2004**, *6*, 2499–2501.

520 (a) C. M. Vogels, L. G. Nikolcheva, H. A. Spinney, D. W. Norman, M. O. Baerlocher, F. J. Baerlocher, S. A. Westcott, *Can. J. Chem.* **2001**, *79*, 1115–1123. (b) A. S. King, L. G. Nikolcheva, C. R. Graves, A. Kaminski, C. M. Vogels, R. H. E. Hudson, R. J. Ireland, S. J. Duffy, S. A. Westcott, *Can. J. Chem.* **2002**, *80*, 1217–1222. (c) A. M. Irving, C. M. Vogels, L. G. Nikolcheva, J. P. Edwards, X.-F. He, M. G. Hamilton, M. O. Baerlocher, F. J. Baerlocher, A. Decken, S. A. Westcott, *New. J. Chem.* **2003**, *27*, 1419–1424. (d) A. Jabbour, D. Steinberg, V. M. Dembitsky, A. Moussaieff, B. Zaks, M. Srebnik, *J. Med. Chem.* **2004**, 47, 2409–2410.

521 S. Gronowitz, T. Dalgren, J. Namtvedt, C. Roos, B. Sjöberg, U. Forsgren, *Acta Pharm. Suecica*. **1971**, *8*, 377–390.

522 G. Högenauer, M. Woisetschläger, *Nature* **1981**, *293*, 662–664.

523 C. Baldock, G.-J. de Boer, J. B. Rafferty, A. R. Stuitje, D. W. Rice, *Biochem. Pharmacol.* **1998**, *55*, 1541–1549.

524 C. Baldock, J. B. Rafferty, S. E. Sedelnikova, P. J. Baker, A. R. Stuitje, A. R. Slabas, T. R. Hawkes, D. W. Rice, *Science* **1996**, *274*, 2107–2110.

525 P. D. Robinson, M. P. Groziak, *Acta. Crystallogr., Sect. C* **1999**, *55*, 1701–1704.

526 Z. Feng, M. Hellberg, *Tetrahedron Lett.* **2000**, *41*, 5813–5814.

527 W. Yang, X. Gao, B. Wang, *Med. Res. Rev.* **2003**, *23*, 346–368.

528 (a) V. K. Akparov, V. M. Stepanov, *J. Chromatogr.* **1978**, *155*, 329–336. (b) S. Cartwright, S. Waley, *Biochem. J.* **1984**, *221*, 505–512.

529 E. Tsilikounas, C. A Kettner, W. W. Bachovkin, *Biochemistry* **1992**, *31*, 12839–12846.

530 E. Tsilikounas, C. A Kettner, W. W. Bachovkin, *Biochemistry* **1993**, *32*, 12651–12655.

531 V. S. Stoll, B. T. Eger, R. C. Hynes, V. Martichonok, J. B. Jones, E. F. Pai, *Biochemistry* **1998**, *37*, 451–462.

532 J. A. Adams, M. Behnke, S. Chen, A. A. Cruickshank, L. R. Dick, L. Grenier, J. M. Klunder, Y.-T. Ma, L. Plamondon, R. L. Stein, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 333–338.

533 A. Paramore, S. Frantz, *Nat. Rev.* **2003** (Drug Discovery), *2*, 611–612.

534 A. H. Soloway, W. Tjarks, B. A Barnum, F.-G. Rong, R. F. Barth, I. M. Codogni, J. G. Wilson, *Chem. Rev.* **1998**, *98*, 1515–1562.

535 T. Shinbo, K. Nishimura, T. Yamaguchi, M. Sugiura, *J. Chem. Soc., Chem. Commun.* **1986**, 349–351.

536 L. K. Mohler, A. W. Csarnik, *J. Am. Chem. Soc.* **1993**, *115*, 2998–2999.

537 M. T. Reetz, J. Huff, J. Rudolph, K. Töllner, A. Deege, R. Goddard, *J. Am. Chem. Soc.* **1994**, *116*, 11588–11589.

538 M.-F. Paugam, J. T. Bien, B. D. Smith, L. A. J. Chrisstoffels, F. de Jong, D. N. Reinhoudt, *J. Am. Chem. Soc.* **1996**, *118*, 9820–9825.

539 P. J. Duggan, *Aust. J. Chem.* **2004**, *57*, 291–299.

540 B. D. Smith, S. J. Gardiner, in *Advances in Supramolecular Chemistry*, G. W. Gokel (Ed), JAI Press, **1999**, Volume 5, pp 157–202.

541 F. Frantzen, K. Grimsrud, D.-E. Heggli, E. Sundrehagen, *J. Chromatogr. B* **1995**, *670*, 37–45.

542 J. P. Wiley, K. A. Hughes, R. J. Kaiser, E. A. Kesicki, K. P. Lund, M. L. Stolowitz, *Bioconjug. Chem.* **2001**, *12*, 240–250.

543 G. DeSantis, C. Paech, J. B. Jones, *Bioorg. Med. Chem.* **2000**, *8*, 563–570.

544 F. Frantzen, K. Grimsrud, D.-E. Heggli, E. Sundrehagen, *Clin. Chim. Acta* **1997**, *263*, 207–224.

545 T. J. Burnett, H. C. Peebles, J. H. Hageman, *Biochem. Biophys. Res. Commun.* **1980**, *96*, 157–162.

546 Y. R. Vandenburg, Z.-Y. Zhang, D. J. Fishkind, B. D. Smith, *Chem. Commun.* **2000**, 149–150.

547 (a) W. Yang, S. Gao, X. Gao, V. V. R. Karnati, W. Ni, B. Wang, W. B. Hooks, J. Carson, B. Weston, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2175–2177. (b) W. Yang, H. Fan, X. Gao, S. Gao, V. V. R. Karnati, W. Ni, W. B. Hooks, J. Carson, B. Weston, B. Wang, *Chem. Biol.* **2004**, *11*, 439–448.

548 M. C. Y. Chang, A. Pralle, E. Y. Isacoff, C. J. Chang, *J. Am. Chem. Soc.* **2004**, *126*, 15392–15393.