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Expanding Roles for Organoboron Compounds – Versatile and Valuable Molecules for Synthetic, Biological, and Medicinal Chemistry

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The present essay offers an overview of the latest developments in the chemistry of organoboron compounds. The unique structural characteristics and the versatile reactivity profile of organoboron compounds continue to expand their roles in several areas of chemistry. A growing number of boron-mediated reactions have become vital tools for synthetic chemistry, particularly in asymmetric synthesis, metal-catalyzed processes, acid catalysis, and multicomponent reactions. As a result, boronic acids and related molecules have now evolved as major players in synthetic and medicinal chemistry. Moreover, their remnant electrophilic reactivity, even under physiological conditions, has allowed their incorporation in a growing number of bioactive molecules, including bortezomib, a clinically approved anticancer agent. Finally, the sensitive and selective binding of boronic acids to diols and carbohydrates has led to the development of a growing number of novel chemosensors for the detection, quantification, and imaging of glucose and other carbohydrates. There is no doubt that the chemistry of organoboron compounds will continue to expand into new discoveries and new applications in several fields of science.

Long History – Expanding Roles

Organic compounds containing boron have been known for over a century, and many aspects of their chemical properties and reactivity have been known for quite some time. Since the discovery and development of hydroboration, the resulting organoboranes are among the most widely used reagents and intermediates in organic synthesis including asymmetric reactions. Also, early investigations on the chemistry of boron hydrides and carboranes revealed new classes of compounds with unique structure and reactivity that continue to attract attention. Despite these early discoveries, however, the real potential of some of the more versatile and chemically stable organoboron compounds was not realized until recently.

Indeed, the growing list of valuable organoboron compounds in addition to organoboranes[1] now includes organoboronic acids and boronates,[2] and more recently organotrifluoroborates.[3–5] Many of these molecules have increasingly been used in a variety of newly discovered chemical processes, and as key functional components in other areas, including molecular receptors, molecular sensors, novel materials, as well as biological probes and pharmaceuticals.

Unique, Versatile and Tunable Reactivity

It is not surprising that organoboron compounds exhibit such a plethora of useful properties. The electronic structure of boron and its strategic position on the periodic table adjacent to carbon makes trivalent boron compounds behave as *electrophilic* molecules with trigonal planar structures that are neutral yet isoelectronic to carbocations. However, formation of an additional bond to boron generates anionic tetravalent boron compounds that have tetrahedral structures and behave as *nucleophilic* molecules. Most notably, both of these types of boron compounds can be stable while retaining significant reactivity that defines their unique, versatile, interconvertible, and tunable chemical behaviour.

Nearly every common type of boron bond (B–H, B–B, B–C, B–N, B–O, B–F, B–Cl, etc.) has distinctive reactivity features that can be exploited. Indeed, this broad spectrum of electronic, structural, and reactivity behaviour of organoboron compounds has led to a growing number of recent discoveries of useful chemical reactions, from metal-catalyzed processes to acid catalysis, asymmetric transformations, and multicomponent reactions. An added advantage of many of these processes is that

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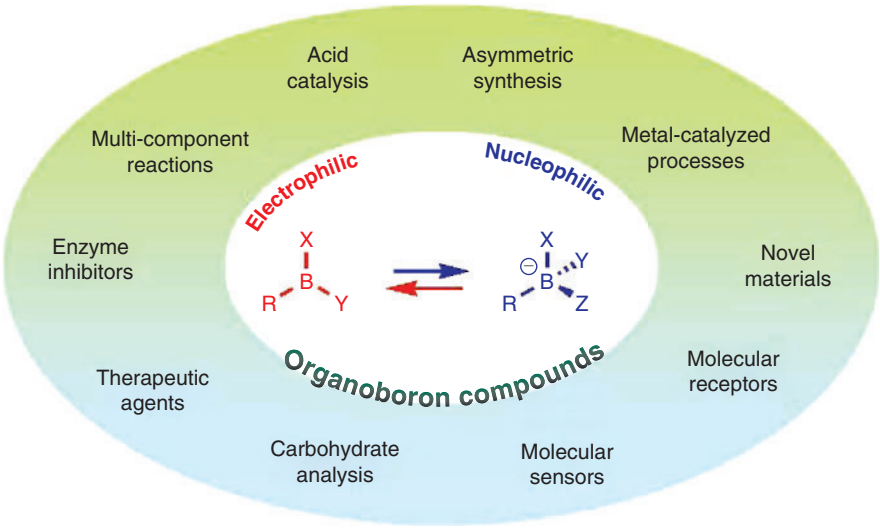

Fig. 1. Chemical applications of organoboron compounds.

their major boron by-product is boric acid, an environmentally friendly (green) substance.

As a result of their unique reactivity and other attractive features, organoboron compounds have provided the basis for the discovery of a growing number of new and novel reactions that have already been adopted in many areas of synthetic chemistry, from pharmaceuticals to materials. Most notable among these are processes in the areas of *asymmetric synthesis*, *metal-catalysis*, *acid-catalysis*, and *multicomponent reactions*.

Expanding the Scope of Boron-Mediated Organic Reactions

In addition to the growing use of organoboron compounds in organic synthesis, in recent years the scope of such processes has been expanded significantly, particularly in asymmetric synthesis and catalysis. Although asymmetric hydroboration,[6,7] asymmetric allylboration,[8–12] and asymmetric boron-hydride reduction[7,13] were among the first asymmetric processes to be developed, these reactions have evolved into very valuable transformations for the enantioselective and diastereoselective synthesis of many types of molecules, particularly alcohols and amines. Several recent improvements and new asymmetric and catalytic variations have expanded significantly the utility of these processes.

Metal-Catalyzed Processes

Among the most important advances in organoboron chemistry have been the discovery and development of the Pd-mediated cross-coupling reactions between organoboron compounds and organic halides or related derivatives (Suzuki–Miyaura coupling).[14] This chemistry has dramatically expanded the utility of organoboron compounds in synthetic and medicinal chemistry, and in the synthesis of new organic materials. In addition to many applications and new improvements in the Pd-catalyzed Suzuki coupling,[4,5,15–17] several additional metal-catalyzed processes involving organoboron compounds were also developed in recent years, including: the Heck-type Pd-catalyzed cross-coupling with alkenes,[18,19] the Rh-catalyzed 1,2 addition to aldehydes or imines and 1,4 addition to unsaturated carbonyl compounds,[4,20] the Rh-catalyzed addition to alkenes or alkynes,[20] the Ni-catalyzed coupling with alkynes and imines,[21] the Cu-catalyzed cross-coupling forming C–O and C–N bonds,[22] the Pd/Cu catalyzed cross-coupling with thioesters,[23] and various metal-catalyzed methods for the C–H borylation and further transformation of aromatic compounds.[24–26]

Acid Catalysis

Highly electrophilic boron compounds, such as BF_3 and related molecules, are well known Lewis acids that can mediate several chemical transformations. However, these molecules require anhydrous conditions because they react readily with water. In order to improve the synthetic utility of boron-based Lewis acids, several electrophilic arylboron compounds have been recently developed and were shown to be very effective as well as experimentally convenient catalysts.[27,28] In addition to promoting several important organic reactions including aldol reactions, carbonyl reductions, alcohol oxidation, cycloadditions, esterification and amide bond formation,[28] these organoboron compounds could also be produced in enantiomerically pure form and be used as novel chiral Lewis acids.[27,29] A special class of such chiral acids, known as Brønsted acid assisted Lewis acid catalysts (BLA), combines the Lewis acidity of the boron with a Brønsted acid to enhance their acidity and catalytic activity.[29] Molecules of this type, including chiral boronates and chiral oxazaborolidines were shown to be particularly effective catalysts for Diels–Alder and hetero-Diels–Alder reactions.[29,30]

Multicomponent Reactions

Another unique feature of certain organoboron compounds, such as boronic acids and trifluoroborates, is that they retain reactivity even in the presence of a variety of functional groups. Despite their chemical stability, however, it is also possible to activate these molecules in situ towards suitable reactive intermediates, enabling new types of transformations. Based on this concept, some time ago we introduced the use of organoboron compounds as key components in multicomponent reactions of amines and carbonyl compounds.[31–34] Several variations of this type of reaction were introduced, including the synthesis of amino acids,[31] amino alcohols,[32] and amino phenols.[33] Moreover, we and others have shown that this type of process can be used for the synthesis of a large variety of novel amine

derivatives, amino sugars, and heterocycles.[34] A notable feature of this chemistry is that it proceeds under mild conditions and can generate directly many types of novel drug-like molecules, making it especially useful for diversity-oriented synthesis[35] and applications in medicinal chemistry. Multicomponent reactions, especially those involving isocyanides,[36] have a long history and have attracted a renewed interest in recent times as a result of new developments in combinatorial chemistry and parallel synthesis. The use of organoboron compounds offers several advantages on the basis of their availability in a large variety of substitution patterns, and their tolerance of most common functional groups.

Biological and Medicinal Applications

The development of the above boron-mediated reactions and processes for synthetic chemistry has undoubtedly had a dramatic impact on the ability to design and synthesize many new and important types of drug leads as well as chemical probes and other chemical tools for biological research and drug discovery. However, the contributions of organoboron compounds in this area are not limited to their unique and versatile nature as synthetic intermediates. In fact, a growing number of boron-containing compounds have been shown to have important biological activities and are even suitable as pharmaceuticals agents for clinical use.[37]

Although boron-containing natural products are rare, several bioactive compounds containing boron have been identified, including the antibiotic boromycin and several bacterial quorum-sensing molecules, suggesting a role for boron in cell signalling and the immune function.[38,39] The potential role of boric acid as a cancer chemopreventing agent has been suggested by epidemiological and laboratory studies and it was recently documented in more detail for prostate cancer.[40]

Several synthetic boron-containing molecules were recently shown to exhibit important biological properties prompting their investigation as potential therapeutics.[37] The mild electrophilic nature of the boronic acid moiety has led to its use at the 'warhead' site of enzyme inhibitors, particularly for inhibiting proteases. Of particular interest in this area has been the development of α-aminoboronic acid derivatives[37,41,42] that serve as novel mimics of amino acids and allow their incorporation into designed and optimized enzyme inhibitors. One such compound, the novel proteasome inhibitor bortezomib (Velcade) has been recently approved for clinical use as an anticancer agent for the treatment of myeloma.[43]

Several other types of bioactive boron-containing molecules have been reported or are under investigation as therapeutic agents. These include certain boron analogues of biomolecules,[44] the antibacterial and antimalarial agent diazaborine,[45] various antibacterial oxazaborolidines,[46] the antibacterial diphenyl borinic esters that inhibit bacterial cell wall growth,[47] the antifungal agent benzoxaborole AN2690,[48] and an oestrogen receptor modulator containing a B–N bond.[49] Finally, boron-containing molecules, including boronic acids and carboranes,[50] have long been investigated as agents for boron-neutron capture therapy (BCNT) for the treatment of tumours.[37,50,51]

Molecular Receptors and Sensors

The ability of organoboronic acids to react reversibly with diols in a pH-sensitive manner even in aqueous media has led to another major application of these organoboron compounds as receptors and sensors for carbohydrates.[52–55] By combining the boronic acid moiety that binds selectively to a particular carbohydrate with a sensitive analytical technique, such as fluorescence, photoinduced electron transfer, colorimetry or electrochemistry, it has become possible to develop a large variety of highly sensitive sensors for the detection and quantification of glucose and other carbohydrates. Given the importance of glucose monitoring for patients with diabetes and for other applications, a great amount of effort has been directed towards the development of boronic acid-containing sensors that can operate under physiological conditions for routine monitoring.[56,57] Alternative applications of these boronic acid glucose sensors involve glucose imaging, and the use of novel polymeric materials that can be used for the controlled release of insulin on binding of glucose.[37] Finally, fluorescent boronic acid sensors can be used in a diagnostic manner for the detection and labelling of fucosylated oligosaccharides that occur in surface carbohydrates that are common in certain cancers.[58]

Expanding Research Front

Given the growing interest and the expanding new chemistry of organoboron compounds, it is quite timely that this field is highlighted as a *Research Front* in the *Australian Journal of Chemistry*. The list of included papers represents several currently active areas of research. Craig Hutton reviews the use of boron-based reagents and building blocks in the synthesis of amino acids and peptides,[59] while Todd Houston and coworkers highlight the use of boric and boronic acids to bind and catalyze various transformations of α-hydroxy acids.[60] Dennis Hall[61] and Peter Duggan[62] report new approaches for designing receptors to recognize biologically important oligosaccharides, while new aspects of carborane chemistry, boric acid catalysis, and asymmetric synthesis with boranes, are reported by Lou Rendina,[63] Todd Houston,[64] and Chandra D. Roy[65] respectively.

As new features of organoboron compounds continue to be uncovered, and as new applications continue to be developed, the interest in this area of research will continue to expand in several fields of science.

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