Recent Advances in the Synthesis of Acylboranes and Their Widening Applicability

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ABSTRACT: The most common types of acylboranes are acyltrifluoroborates, acyl MIDA-boronates, and monofluoroacylboronates. Because of the increasing importance of these compounds in the past decade, we highlight the recently reported synthetic strategies to access acylboranes. In addition, an expanding array of their applications has been discovered, based on either the ability of acylboranes to enter rapid amide-forming ligations or the retained ketone-like character of the carbonyl group. Therefore, we also describe ground-breaking achievements where acylboranes were successfully put to use, such as their utility in biochemical, material, and medicinal sciences.

INTRODUCTION

Organoboron chemistry comprises a structurally and chemically diverse set of compounds, such as boranes, boronic acids and their derivatives, and aminoboronic acids.1 While these compounds have found broad use in various fields of chemistry, ranging from organic synthesis to pharmaceuticals,2 acylboranes have long remained unexplored. The term acylboranes covers compounds in which a boron-containing moiety is covalently bound to a carbonyl C atom. The most notable representatives of this group, due to their marked stability and chemical reactivity, are potassium acyltrifluoroborates (KATs). They were shown to be easily interconvertible with other most common subclasses of acylboranes, that is, the N-methyliminodiacetic acid (MIDA) protected analogues3 and monofluoroacylboronates4 (Scheme 1).

Acylboranes have become increasingly important in the past decade, as exciting possibilities for their use were discovered in parallel to the first synthetic procedures to provide them. While the methods to access acylboranes are relatively limited, their most important asset lies in the ability to rapidly form amide bonds with hydroxylamines in aqueous media, giving rise to immense opportunities especially in the field of peptide chemistry. The aspects of their synthesis and use were thoroughly covered in a previous review by Marder et al.5 However, a number of important synthetic strategies have arisen since, along with further applications, and are described herein. In order to avoid repetition, the reader is referred to Marder’s review for a deeper insight into the origins of this chemistry. Nevertheless, we will briefly remark on the early achievements in this field as a means of introduction to the more recent findings, which in some cases importantly complement the previous ones.

EARLY ACHIEVEMENTS

Acylboranes were suggested as reactive intermediates in organoboron chemistry as early as the 1960s,6 and the hypothesis of their existence was later corroborated by experimental and DFT studies.7 However, it was not until 2007 when Nozaki and co-workers were the first to isolate and fully characterize an acylborane compound,8 in which the boron atom was protected by a cyclic diamino moiety, the structure being isoelectronic to N-heterocyclic carbenes (NHC) (Scheme 2, entry 1). The synthesis of the first KAT was reported by Molander et al. in 2010, also showing its remarkable ability to form amides with azides while being inert to Suzuki–Miyaura conditions (Scheme 2, entry 2).9a However, only one KAT was synthesized and the scope of azides, with which it was coupled successfully, was not broad.
The next leap forward was achieved by Bode’s group in 2012, who discovered a more general method to provide KATs from benzotriazole-based \( N,O \)-acetals (Scheme 2, entry 3), or in several alternative examples, from dihydropyrans or an \( N \)-protected tetrahydropyridine.\(^9\) Concurrently, they demonstrated the use of these compounds in rapid ligations with \( O \)-benzoyl hydroxylamines to yield amides.\(^9\) This reaction proceeded in water/\( t \)-BuOH without any additives. Using \( N,N \)-diethylcarbamates instead of hydroxylamines as ligation partners, the same group was later able to significantly broaden the scope of this reaction and use it to perform ligations of KATs with unprotected peptides.\(^9\) In addition to this procedure, Bode and co-workers disclosed a novel synthetic strategy in 2014, starting from a specially designed zwitterionic reagent—an internal salt of the trifluoroborate anion and dimethyliminium cation (Scheme 2, entry 4).\(^9\) This method began with the lithiation of aryl- and heteroaryl halides, which successfully attacked the zwitterionic precursor, yielding a number of KATs bearing structurally and electronically diverse side groups.

In regard to other acylboranes, Yudin et al. were the first to synthesize acyl MIDA-boronates in 2012, converting \( \alpha \)-boryl carboxylic acids to \( \alpha \)-borylalcohols, followed by oxidation with Dess–Martin periodinane (Scheme 3, entry 1).\(^{10}\) These were later synthesized also directly from KATs by Noda and Bode (see Scheme 1),\(^3\) who disclosed a method to convert KATs to monofluoroacylboronates as well (Scheme 3, entry 2).\(^4\) Both classes were shown to be good ligation partners with hydroxylamines, and acyl MIDA-boronates exhibited high reactivity with \( O \)-alkylhydroxylamines as opposed to KATs, while being less stable in aqueous media. The experiments on ligation of different acylboranes conducted by the Bode group allowed direct comparison of their reactivity, which can be tuned by using different substituents at the boron atom.\(^3,4\)

It is also important to mention the work of Campos and Aldridge, who synthesized a series of acylboranes bearing the NHC-like protecting group on boron (Scheme 3, entry 3),\(^{11}\) which was previously also used by Nozaki et al. This was the first catalytic method to provide acylboranes and can be viewed as a boron version of the Negishi coupling. A stable bis(boryl) zinc reagent was prepared and reacted with acyl chlorides under palladium catalysis. The acylboranes were found to be chemically inert, probably due to the bulky heterocyclic protecting group on boron, but one example was easily transformed into KAT.

**RECENT ADVANCES IN SYNTHESIS OF ACYLBORANES**

**Synthesis of KATs.** A significant progress in this field has been achieved lately, with some fascinating methods emerging in the last three to four years. Bode and co-workers disclosed two procedures based on their previous ground-breaking discovery of a zwitterionic trifluoroborate precursor (see Scheme 2, entry 4). In 2018, the scope of their original method was broadened to allow the synthesis of alkyl-substituted KATs (Scheme 4, entry 1).\(^{12}\) If following the same procedure as published for aryllithiums, double addition to the precursor was observed with their alkyl...
The problem was circumvented by transmetalating alkyl Grignards or alkyllithiums to copper(I), thus reducing the nucleophilicity of the alkyl chain to avoid double addition. As in the previously described approach, the synthesis proceeded through an iminium intermediate, which was hydrolyzed with saturated aqueous solution of KF. The method furnished a range of primary, secondary, and tertiary aliphatic KATs in yields from 58 to 95%.

Later, a further aspect of this reaction was explored. The original method required the use of butyllithium, meaning that the presence of protic or electrophilic moieties on the aryl halide was not possible. Bode et al. therefore modified the trifluoroborate precursor to include the tributylstannane moiety instead of the EtS- leaving group. This allowed the precursor to enter palladium-catalyzed Stille coupling with aryl halides or triflates, giving rise to the first catalytic method to access KATs directly (Scheme 4, entry 2). Interestingly, it appeared that in some cases, the iminium intermediate, at least partially, hydrolyzed to KAT during the coupling, thus complicating the isolation. It should be stressed that KATs are salts and as such cannot be separated from inorganic or organic impurities by chromatography. To confront this problem, the authors in situ converted the KAT back to the "intermediate" iminium using dimethylamine and acetic acid, according to a procedure previously described by the same group. The iminium-trifluoroborate zwitterion could then be isolated and subjected to hydrolysis to provide the desired KAT. While this approach was limited to aryl- and α,β-unsaturated KATs, the scope of these was broad and the method tolerated carbonyl- and amino-substituents as well as heterocycles with protic nitrogen atoms. The yields ranged from 44 to 92%, while the KATs already synthesized using the previously published method (see Scheme 2, entry 4) were provided in higher yields by this approach.

In 2019, Ito and co-workers presented their procedure to afford KATs in two steps from commercially available aldehydes (Scheme 4, entry 3). The aldehydes were subjected to copper-catalyzed borylation with B$_2$pin$_2$ followed by treatment with KHF$_2$ to provide α-hydroxy trifluoroborates in the first step (26–90% yields). While this transformation had been described before, the Ito group was the first to accomplish the oxidation of such substrates, thus synthesizing KATs. The oxidation proceeded either under Albright–Goldman oxidation conditions using DMSO/Ac$_2$O, or alternatively required catalytic amounts of nor-AZADO as stoichiometric co-oxidant. The yields of the oxidation step ranged from 30 to 93%, and the scope covered various aromatic and aliphatic KATs, as well as an aromatic example bearing a carbohydrate substituent. Importantly, several amino-acid-derived KATs were synthesized with complete retention of configuration at the stereogenic center.

**Synthesis of Acyl MIDA-boronates.** Bode, Ito, and co-workers also disclosed a strategy to access acyl MIDA-boronates from alkyl MIDA-boronates by ozonolysis with the addition of Me$_2$S or pyridine (Scheme 5, entry 1). One example with an aryl substituent was shown, while the others possessed various alkyl chains, including protected amines and

**Scheme 4. Recent Methods to Provide KATs**

1. Bode, 2018

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MeNiMe
EtS$_2$BF$_3$ + R$^1$Li\rightarrow Cu\rightarrow Cu
1. R$^1$MgX\rightarrow CuCN
2. KF (aq)
R$^1$BF$_3$K
R$^1$ = alkyl
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2. Bode, 2019

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MeNiMe + Bu$_3$SnBF$_3$ + R$^1$X\rightarrow Cu\rightarrow Cu
1. Pd(PPh$_3$)$_4$\rightarrow CuL(CF$_3$CF$_2$F)$_2$
2. HNMe$_2$AcOH
3. KHCO$_3$ (aq)
R$^1$BF$_3$K
X = I, OTf
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3. Ito, 2019

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MeNiMe
Bu$_3$SnBF$_3$

1. B$_2$pin$_2$\rightarrow (ICy)CuCl
2. KH$_2$F (aq)
R$^1$H\rightarrow OH
R$^1$BF$_3$K
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nor-AZADO = 9-azanoradamantane N-oxide.

**Scheme 5. Recent Advances in the Synthesis of Acyl MIDA-boronates**

1. Ito & Bode, 2017

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R$^2$BHMDA
1. O$_3$, 2. Me$_3$S
or O$_3$, pyridine
R$^1$BHMDA
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2. Perrin, 2017

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R$^1$BHMDA\rightarrow OsO$_4$, NMO
OH
R$^1$BHMDA\rightarrow NaO$_2$
R$^1$BHMDA
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3. Sharma, 2019

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R$^1$BHMDA\rightarrow BpinMIDA
HC(OEt)$_2$
Bpin\rightarrow NaBO$_2$+H$_2$O
OH
R$^1$BHMDA\rightarrow DMP
R$^1$BHMDA
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4. Yudin, 2017

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R$^1$BHMDA\rightarrow OsO$_4$, NMO
OH
R$^1$BHMDA\rightarrow DMP
R$^1$BHMDA
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5. Wang, 2019

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R$^1$BHMDA\rightarrow X = Cl if HFIP
X = I if Nal
(both one-pot)
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**NMO = N-methylmorpholine N-oxide. DMP = Dess–Martin periodinane. HFIP = hexafluoropropionan. Nu = nucleophile.**
alcohols. An l-alanine derivative was also synthesized and completely retained the configuration at the stereogenic center. The yields for the first step (i.e., to provide the acyl MIDA-boronate) were 65–94%, but it has to be noted that these yields also comprise a minor part of the side product acyloxyboronate, typically in quantities around 10%. One example was also transformed into KAT, as previously also shown by Noda and Bode.3

Concurrently, a complementary procedure also starting from alkenyl MIDA-boronates, which were subjected to Upjohn dihydroxylation with OsO₄ and N-methylmorpholine N-oxide, was published (Scheme 5, entry 2).16b This reaction proceeded in a mixture of acetone and phosphate buffer (pH = 7), as the BMIDA group is known to be labile in basic conditions. The resulting dihydroxy MIDA-boronates were then treated with NaIO₄ to afford the desired acyl MIDA-boronates by oxidative cleavage. The yields for the first step were 56–90% and ranged from 17 to 93% for the second step. Notably, amine, ester, carbonyl and halogen functionalities were tolerated and both steps were conducted in the presence of water, which is remarkable in this field where dry solvents and Schlenk techniques are often required. Interestingly, the second step did not require buffered conditions.

In 2019, a novel methodology starting from geminal diborylalkanes with boron in the form of its pinacolate ester was presented by Sharma and co-workers (Scheme 5, entry 3).17 These were in turn derived from terminal alkynes, alkenes, or vinyl boronic esters. One of the pinacolatoboron moieties could then be selectively transformed into its MIDA-counterpart, yielding unsymmetrical geminal diborons. The presence of two different boronate moieties then allowed the authors to selectively oxidize only one of them. This was achieved by treating these compounds with sodium perborate—the aqueous solution of which is basic, so the reaction proceeded in phosphate buffer for the same reason as described above. This reaction gave α-hydroxy MIDA-boronates, which were then further oxidized. Of all the oxidants that were screened, Dess–Martin periodinane proved to be the best choice in this case and provided the desired compounds in 40–83% yields. This reaction was analogous to the oxidation of α-hydroxytrifluoroborates described above (see Scheme 4, entry 3). Interestingly, while Ito et al. conducted experiments with the same oxidant, it proved inactive in the oxidation of α-hydroxytrifluoroborates.

Lastly, two methods furnishing α-functionalized acyl MIDA-boronates should be described as these compounds have great synthetic value, especially in the synthesis of borylated heterocycles.18 In 2017, the Yudin group reported a procedure to provide oxalyl boronates, which can also be viewed as α-keto functionalized acyl boronates (Scheme 5, entry 4).18a Similar to the Perrin group above, they made use of the Upjohn dihydroxylation, but they used vinyl MIDA-boronates, so the reaction yielded boryl-substituted vicinal diols. These could be oxidized with Dess–Martin periodinane to provide diketo-compounds (i.e., oxalyl MIDA-boronates).

Wang and co-workers also disclosed a method to access α-functionalized acyl MIDA-boronates through nucleophilic ring opening of α-chloroepoxyboronates (Scheme 5, entry 5).18b Aryl-substituted epoxides opened readily in hexafluoroisopropanol, while their alkyl counterparts required treatment with NaI as the nucleophile, furnishing α-iodo acyl MIDA-boronates. Furthermore, the authors discovered that a wide range of nucleophiles could be used to provide various α-functionalized acyl MIDA-boronates in a one-pot fashion in 55–94% yields. The synthetic utility of α-functionalized acylboranes is further discussed in a dedicated section below.

### NEW APPLICATIONS OF ACYLBORANES

**Amide-Forming Ligations.** In the last years, the scientific community has witnessed further development of acylborane use, these compounds being in the spotlight especially for their ability to enter amide-forming ligation. Various applications of this reaction are shown in Scheme 6, along with a proposed mechanism as first put forward in 2012, showing the two
(possibly interconnected) pathways which were to some extent supported by experimental studies.26 An important improvement of the amide-forming ligation of KATs was disclosed by the Bode group in 2017. This new procedure did not require hydroxylamines as ligation partners but proceeded chemoselectively with primary amines or primary amides in the presence of unprotected moieties such as carboxylic acids, alcohols, ketones, and even secondary amines.19 The key step was in situ N-chlorination of the amine with 1,3-dichloro-5,5-dimethylhydantoin (DCH) as chlorinating agent, which allowed the reaction to proceed rapidly in THF/citrate buffer (pH = 3). For electron-poor heteroarylamines, 1,3,5-trichloroisocyanuric acid proved to be the best chlorinating agent and could also be used with primary amines, which gave imides with KATs.

This methodology was then used to rapidly form hydrogels from KAT-bearing polyethylene glycol (PEG) chains and multidentate amines.20 These authors had previously already disclosed a procedure to form hydrogels by KAT ligation, but using O-carbamoyl hydroxylamines, which take several steps to prepare. The main advantage of the improved procedure was that only the addition of an inexpensive chlorinating agent (N-chlorosuccinimide) to the aqueous reaction mixture was needed to form the hydrogel in seconds at pH = 3. This property allowed the authors to store a premixed solution of reagents for weeks and form the hydrogel at will by adding the chlorinating agent. The reaction rate could be tuned by changing the pH, while the hydrogel properties could be tuned by changing the properties of the amine cross-linker. In addition, monodentate amines, such as dyes, sensors or bio tags, could be immobilized in the hydrogel by amide bonds if they were added to the gelation mixture in the beginning.20

The previously described method using hydroxylamines could nevertheless be used by the same group to PEGylate and dimerize expressed and already folded proteins.21 Hydroxylamine-equipped proteins were readily ligated with 2-pyridyl KATs bearing a PEG-linker.21a The use of 2-pyridyl KATs was essential as they were shown to be significantly more susceptible toward ligation than other aryl KATs. If the KAT possessed a PEG-chain, the protein in question was readily PEGylated, and two KATs connected by a PEG-linker enabled the homodimerization of the given protein. The Bode group used a similar procedure to derivatize a folded synthetic insulin, introducing dyes, lipids, and PEGs or forming homodimers.21b

The ease of protein derivatization by KAT ligation means that this reaction can also be used to radiolabel proteins. This was achieved by Bode, Ametamey, and co-workers, who introduced an $^{18}$F-atom to the 6-position of 6-bromo-3-pyridyl KAT by nucleophilic substitution.22 The reaction proceeded without competitive substitution of fluorine atoms in the trifluoroborate moiety. This compound served as a prosthetic group for radiolabeling of peptides and proteins. The authors showed the remarkable utility of their discovery by radiolabeling a hydroxylamine-derivatized protein (superfolder green fluorescent protein) and using it to perform a PET/CT scan in a mouse.

The utility of amide ligations using acylboranes and hydroxylamines was driven even further and shown to work remarkably in the field of traceless reactions.23 KATs and hydroxylamines were reacted by Bode, Johnson et al., who were able to form polymer networks by means of this reaction and influence their topological features through the choice of alkyl chains of the hydroxylamine.23a Bis-KAT oligomers were reacted with four-arm PEG polymers bearing either O-diethylcarbamoyl- or O-dioctylcarbamoyl hydroxylamines, and the resulting two hydrogels types exhibited different topological features although their chemical structures were identical. The leaving groups could thus directly template the network topology in a traceless manner, a phenomenon previously unobserved in this field.

Later, the use of acylboronate ligation in traceless templated reactions was demonstrated.23b A monofluorocarbonylboronate and a hydroxylamine, both equipped with desthiobiotin, were reacted in a dilute medium with streptavidin serving as a template (Scheme 7). Upon the formation of the amide bond, the template was readily detached, meaning that the reaction proceeded in a traceless manner (i.e., no part of the template remained on the formed product). This was again a novelty in the field of templated organic reactions and another proof of the utility of acylboronates.

In addition, the KAT ligation reaction was used for on-surface functionalization of lipid nanoparticles by Yamakoshi and co-workers.24 To a mixture of lipids standardly used for this purpose, a KAT bearing an oleil chain was added. The lipid nanoparticles which were then produced contained the oleil chains with hydrophilic KAT heads on the outside. These readily entered KAT ligation with an N-hydroxylamine derivative of fluorescein, meaning that the authors obtained fluorescently labeled nanoparticles.

**Formation of Imines and Amines.** While acylboranes are now well-known for their ability to undergo chemoselective ligation reactions, it was already in 2012 when Dumas and Bode showed that KATs retain their carbonyl character and react as ketones.20 However, this venue remained unexplored until 2016, when Yudin et al. performed reductive amination of acyl MIDA-borates to provide aminoboronic acid derivatives.25 They were able to prove the formation of the imine intermediate through NMR experiments, but could not isolate it due to C–N migration of the boryl moiety. In 2018, the Bode group made a significant contribution to the field of acylborane chemistry by reacting KATs with amines to yield a new class of compounds, namely trifluoroborate-iminiums (TIMs) (Scheme 8, entry 1a).24b These zwitterionic salts are highly stable and can be easily handled. It was shown that in anhydrous conditions, an amine salt reacts with KATs to give an imine, while aqueous conditions are a prerequisite for the amide-forming ligation. The authors were able to reduce TIMs to aminoboronic acids with borohydride, or alkylate them with Grignard reagents to give tertiary aminoboronic acids.
Acylboranes were for decades regarded as scientific curiosities, the mere existence of which was a matter of theoretical studies and for a long time not absolutely confirmed. However, they have now become a recognized and highly useful compound class. Their potential as reagents for amide-forming ligation is immense, as proven by the research highlighted here. The sheer ubiquity of the amide bond in nature means that this reaction could be used in almost every setting. Formation of hydrogels, protein labeling, and traceless templated reactions are only several fields where acylboranes were successfully used in the last years. In addition, their retained ketone-like character allows for dual, or in the case of additional functionalization (see Scheme 5, entries 4 and 5), triple reactivity. This property will in our opinion give acylboranes a unique role as synthons in organic chemistry, as recently exemplified by the work of Wang and Yudin groups described above. However, in spite of these decisive advances, the synthesis of acylboranes remains the main challenge in this field. The quest to discover a general, mild, and inexpensive method to convert acylboranes further into aldehydes and ammonium acetate to provide 2,5-disubstituted 4-borylimidazoles. Such complex substitution pattern is highly relevant in the field of medicinal chemistry, albeit difficult to achieve. The borylimidazoles were further subjected to Suzuki–Miyaura coupling to afford nanomolar inhibitors of the serine/threonine-protein kinase STK10.

Even more complex and diverse motifs were accessed from α-chloroepoxyboronates disclosed by Wang and co-workers (Scheme 5, entry 5). If dinucleophiles were used to cleave the epoxide, various borylated heterocycles were provided in a one-pot reaction. This included borylated thiazoles, quinolines, imidazo[1,2-a]pyridines, and many others, notably also an interesting four-membered diaza-heterocycle accessed from phenylhydrazine. One example was shown to readily enter Suzuki–Miyaura coupling to give a fully substituted thiazole.

Lastly, the Yudin group recently discovered carboxy-MIDA-boronate, a small but highly useful molecule consisting only of the COOH functional group bound to the BMIDA moiety. It was shown that this compound can undergo HATU- or DIC-mediated coupling with nucleophiles to afford carbamoyl-, oxycarbo- and thio-carboxoboranes. Similar to the above, coupling with dinucleophiles and subsequent cyclization was shown to give rise to borylated heterocycles, such as oxadiazoles, triazoles, and thiadiazoles. These were in turn again used in Suzuki–Miyaura reactions and allowed the linkage of different heterocycles.

### SUMMARY AND OUTLOOK

Acylboranes were for decades regarded as scientific curiosities, the mere existence of which was a matter of theoretical studies and for a long time not absolutely confirmed. However, they have now become a recognized and highly useful compound class. Their potential as reagents for amide-forming ligation is immense, as proven by the research highlighted here. The sheer ubiquity of the amide bond in nature means that this reaction could be used in almost every setting. Formation of hydrogels, protein labeling, and traceless templated reactions are only several fields where acylboranes were successfully used in the last years. In addition, their retained ketone-like character allows for dual, or in the case of additional α-functionalization (see Scheme 5, entries 4 and 5), triple reactivity. This property will in our opinion give acylboranes a unique role as synthons in organic chemistry, as recently exemplified by the work of Wang and Yudin groups described above. However, in spite of these decisive advances, the synthesis of acylboranes remains the main challenge in this field. The quest to discover a general, mild, and inexpensive approach to acylboranes will certainly prove to be a challenge for synthetic chemists in the future. Nevertheless, only 10 years ago, the current number and scope of reactions yielding acylboranes, along with their general utility, would have seemed impossible. This gives us hope that the challenges, which we might now deem insurmountable, will be swept aside by innovative discoveries in the years to come.
Aminoboronic Acid Derivatives: An Update on Recent Advances.

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Development, Global Drug Development, Novartis, Basel, Chemical & Analytical Development, Technical Research &

DEDICATION

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DEDICATION

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