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* Colour graphic: maximum size 8 cm x 4 cm

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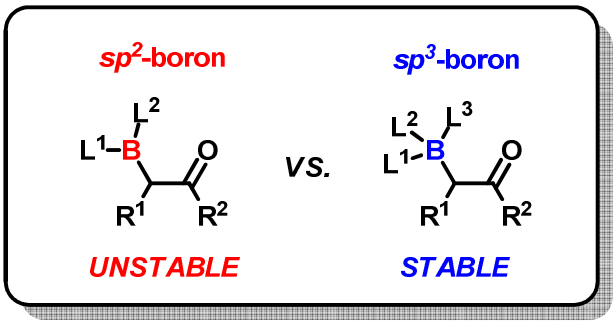
Various aspects of α-borylcarbonyl chemistry are discussed including transient intermediate detection, stable molecule preparation, and their applications in organic synthesis.



α-Borylcarbonyl Compounds: from Transient Intermediates to Robust Building Blocks

*Zhi He, Adam Zajdlik, and Andrei K. Yudin**

Davenport Research Laboratories, Department of Chemistry,

University of Toronto, 80 St. George Street, Toronto M5S 3H6, Canada

1. Introduction

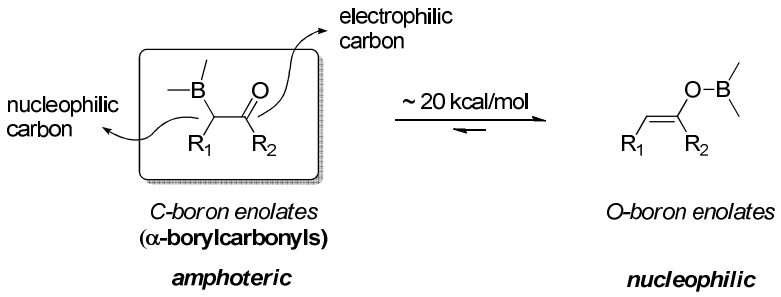
Organoboron compounds are widely used in modern organic synthesis, materials science, medicine, and other fields.[1] Of particular importance is their utility in the development of new methodologies for carbon-carbon bond construction. Boron's relatively low electronegativity tends to enhance the nucleophilicity of the carbon-based substituents to which it is attached. Compared to other organometallic nucleophiles, chemical transformations involving organoboron compounds produce environmentally benign boric acid ($B(OH)_3$) as the primary inorganic byproduct after aqueous workup, which makes them an attractive class of reagents and intermediates in synthetic chemistry.

O-boron enolates are one of the most widely utilized organoboron species for carbon-carbon bond formation.[2] They have been employed as intermediates in aldol additions and condensations, coupling reactions and many other useful transformations. Unlike *O*-boron enolates, which react primarily as nucleophiles, their *C*-bound tautomers (α-borylcarbonyl species) contain an electrophilic carbonyl group adjacent to the nucleophilic α-carbon and are therefore classified as *kinetically amphoteric* (Scheme 1).[3] Compounds which exhibit kinetic amphoterism are of significant value in chemical synthesis as they exhibit multiple modes of reactivity. As such, α-borylcarbonyl species are also expected to be indispensable reagents in modern organic synthesis.

However, compared to *O*-boron enolates, α-borylcarbonyls are typically much less thermodynamically stable due to the increased strength of boron–oxygen bonds over boron–carbon bonds (Scheme 1). The typical difference in thermodynamic stability

between *O*- and *C*-bound boron enolates is estimated to be ~20 kcal/mol and rearrangement between the two species occurs rapidly via a 1,3-boron shift.[4]

Scheme 1. Equilibrium between *C*- and *O*-boron enolates



The instability and short life-time of α-borylcarbonyl species complicates their study. Trapping of transient α-borylcarbonyl intermediates and preparation of stable α-borylcarbonyl building blocks for use in synthesis remain significant challenges for chemists. In the past several decades, many efforts have been made in developing new chemistry related to this species. Direct evidence for the formation of α-borylcarbonyl compounds with sp^2-boron centers is sparse despite their proposed involvement as reactive intermediates in many transformations. Encouragingly, a few examples of direct identification of reactive α-borylcarbonyl intermediates using spectroscopic methods have emerged recently. In other cases, stable compounds containing α-borylcarbonyl structures, although rare, have been reported.[5] Installation of electron-rich tetracoordinated sp^3-boron centers, which impose a barrier to the rapid carbon-to-oxygen 1,3-boron shift of a *C*-boron enolate, is a viable strategy to render α-borylcarbonyl systems stable. In this *Perspective*, various aspects of α-borylcarbonyl chemistry are discussed including synthetic examples through proposed α-borylcarbonyl intermediates, detection of intermediary α-borylcarbonyl species, strategies toward isolable α-borylcarbonyl compounds, and the factors underpinning their stability. We further showcase synthetic applications of a class of isolable α-boryl aldehydes recently discovered in our group, the stability of which is enabled by the tetracoordinated *N*-methyliminodiacetyl (MIDA) boryl group, from which a wide range of functionalized

organoboron compounds, which are difficult to access from other methods, have been obtained.

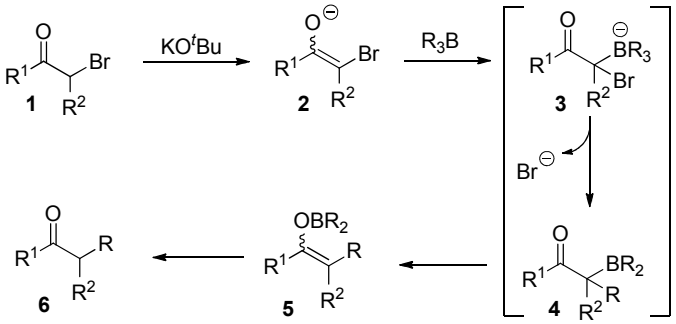
2. α-Borylcarbonyl species as intermediates in organic synthesis

2.1. Proposed α-borylcarbonyl intermediates in reactions

2.1.1. Generation of α-borylcarbonyls via carbon-boron bond formation

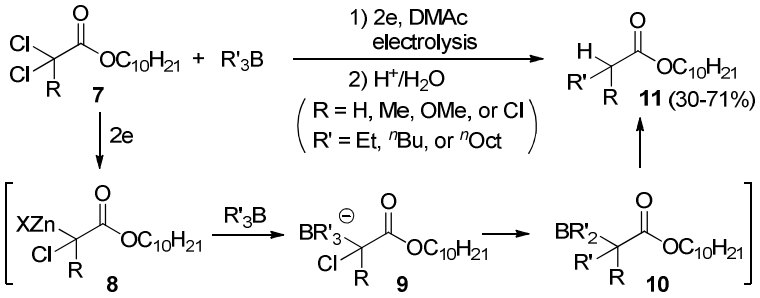
Brown reported a fast and efficient alkylation procedure for the preparation of α-alkyl ketones using α-bromo esters or ketones and organoborane reagents in the presence of strong base.[6] α-Borylcarbonyl intermediates were proposed to form during the interaction of trialkylboranes with pre-formed α-bromo enolates (Scheme 2). The rearrangement of the borate anion **3** via an intramolecular nucleophilic displacement of the α-bromine generated an unstable α-borylcarbonyl intermediate **4**, which quickly isomerized to an *O*-boron enolate **5** and hydrolyzed to the final alkylated ester or ketone product **6**. This procedure avoids the concurrent formation of polyalkyl derivatives, which is a common side reaction in α-alkylation of esters or ketones via conventional S_N2 approaches using strong bases and alkyl halides. In addition, dialkylation of α,α-dibromo or dichloroacetate can be achieved in two successive manipulations using different organoborane reagents, permitting the introduction of two different organic groups into the acetic acid moiety. These reactions thus provide an alternative approach to the commonly used malonic ester synthesis[7] for the preparation of disubstituted acetic acids.

Scheme 2. α-Alkylation of esters and ketones with trialkylboranes



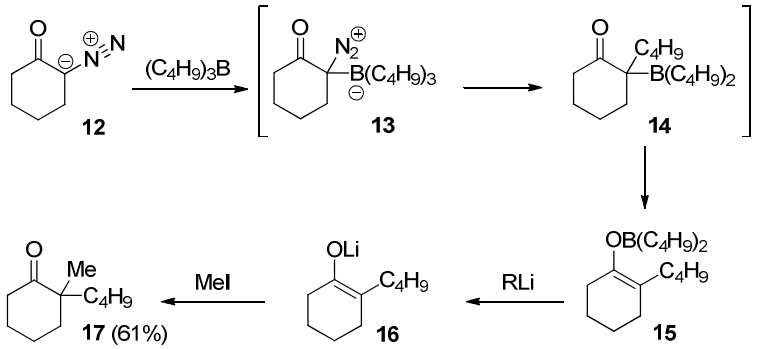
The generation of α-haloenolate anions can also be achieved via electrochemical methods. Condon and co-workers reported an electrochemical alkyl transfer reaction from trialkylboranes to polyhalo compounds (Scheme 3).[8] The reaction was exemplified by reduction of decyl dichloro and trichloroacetate **7** under mild electrolysis conditions using an undivided cell fitted with a consumable zinc rod anode. The *in situ* formed zinc α-chloroenolate **8** readily reacted with trialkylboranes to give alkylated products in a one-pot fashion. Similarly, the α-borylcarbonyl species **9** and **10** were the key intermediates resulting in the final alkyl substitution. This methodology, in which the use of strong base is avoided, provides a complementary method to Brown's conditions described above.

Scheme 3. Elelectrochemical alkylation of polyhalo esters



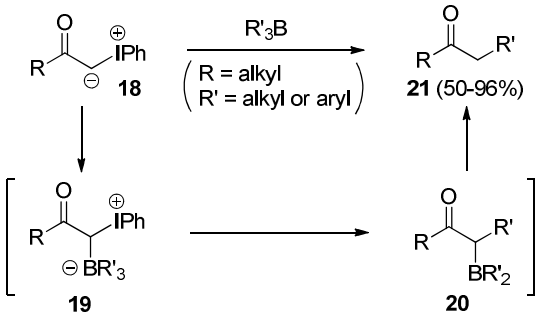
Another elegant reaction involving a regiospecific α,α-dialkylation of diazo ketones using organoboranes and alkyl halides further highlights the postulated formation of intermediary α-borylcarbonyl species (Scheme 4).[9, 10] During treatment with trialkylboranes in THF, the starting diazo ketone **12** generated a vinyloxyborane **15** (*O*-boron enolate) via the formation of an α-diazonium borate complex **13** and subsequent extrusion of molecular N_2 by nucleophilic migration of an alkyl group from the boron center. It is postulated that an unstable neutral α-borylcarbonyl species **14** is formed, which quickly isomerizes to the stable vinyloxyborane intermediate **15**. The corresponding lithium enolate **16** can be generated via metal exchange by treating the *O*-boron enolate THF solution with an alkyllithium reagent. Treatment of the newly formed lithium enolate with alkyl iodides ultimately results in the installation of a second alkyl group at the same α-position. The overall procedure thus leads to a facile position-specific preparation of α,α-dialkyl ketones **17**, which are difficult to prepare from unsymmetrical ketones through conventional enolization-alkylation process.

Scheme 4. Regiospecific α,α-dialkylation of diazo ketones



In a similar case, the exposure of monocarbonyl iodonium ylides **18** to organoboranes likely furnishes a transient α-borylcarbonyl species **20** through an initial Lewis acid-base interaction between the ylide and organoborane and a concomitant 1,2-shift of the carbon ligand (Scheme 5).[11] The unstable α-boryl ketone intermediate **20** rapidly decomposes to the final α-alkylated or arylated ketone product **21**. Interestingly, when stabilized dicarbonyl iodonium ylides are used, no such α-substitution is observed. This is presumably due to the weak nucleophilicity of the stabilized ylide which renders it unreactive towards organoboranes.

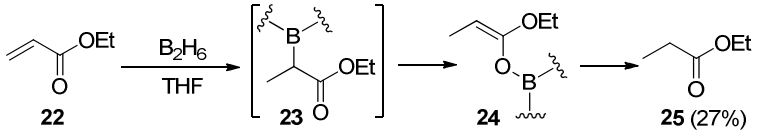
Scheme 5. Reaction of monocarbonyl iodonium ylides with organoboranes



Besides initial Lewis acid-base interaction between organoboranes and carbanions, borylation at the α-position of a carbonyl group can be achieved by regioselective hydroboration of α,β-unsaturated carbonyl systems. In 1964, Brown first described the chemoselective reduction of acrylates to propionates using diboranes.[12] The first step is

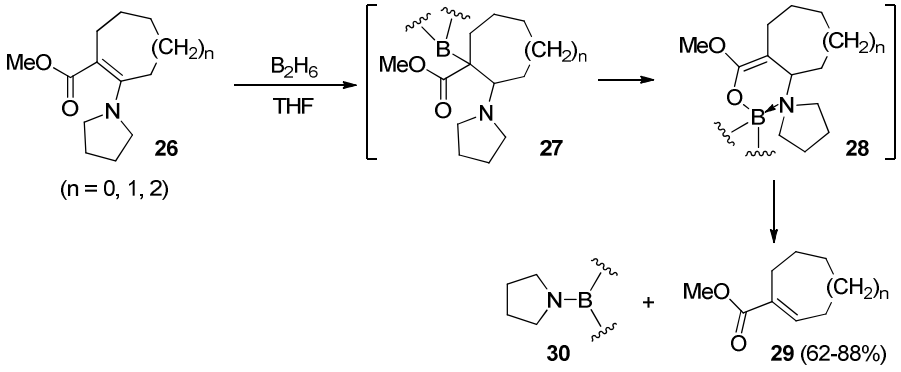
believed to involve a selective 1,2-addition of borane to the alkene rather than the carbonyl group. The powerful directing influence of the carbonyl group favors installation of the boron atom predominantly in the α-position to form α-boryl carbonyl **23** (Scheme 6). The following rapid transfer of boron from carbon to the neighboring oxygen and subsequent hydrolysis results in the final 1,2-reduction products **25**.

Scheme 6. Selective reduction of α,β-unsaturated esters with diboranes



In a similar strategy, a formal hydrogenation of cyclic β-enamine methyl esters (6-8 membered rings) leading to the removal of amine groups can be achieved by treatment with diborane (B_2H_6) in THF (Scheme 7).[13] The reaction is also believed to proceed via a regioselective 1,2-addition of diborane to the carbon-carbon double bond of the conjugated system. The initially formed α-boryl ester intermediate **27** rearranges to a more stable *O*-boron enolate **28**, which is characteristic of a six-membered complex due to the coordination between the boron and amino groups. Elimination of an aminoborane equivalent **30** from the organoborane complex ultimately affords the final unsaturated ester product **29**. Surprisingly, substrates with a five-membered ring system do not undergo this transformation. This is presumably due to the rigidity of the five-membered ring preventing any accommodation to strain in the transition state.

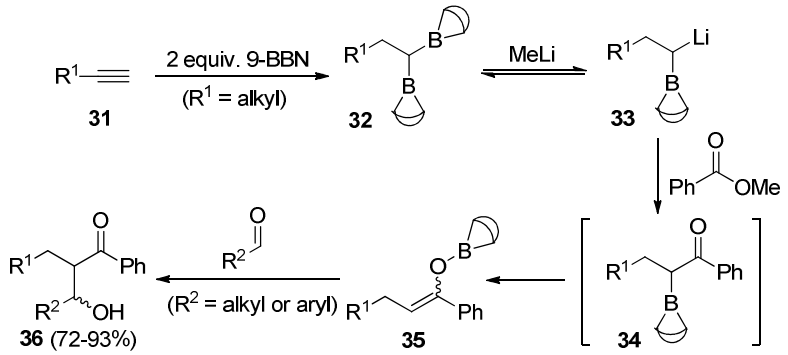
Scheme 7. Regioelective hydroboration of β-enamine methyl esters



2.1.2. Generation of α-boryl carbonyls via carbon-carbon bond formation

Besides reactions involving an initial carbon-boron bond formation, transient α-boryl carbonyl intermediates can also be created via a carbon-carbon interaction between α-boryl carbanions and acylating reagents. Mukaiyama and co-workers reported a procedure for the preparation of phenyl-substituted vinyloxyboranes (*O*-boron enolates) via acylation of boron-stabilized carbanions with methyl benzoate (Scheme 8).[14] The starting α-boryl carbanion reagents **33** were obtained from terminal alkynes **31** via double hydroboration with 9-BBN and subsequent lithiation with methyllithium. The lithiation step involves a ligand exchange process resulting in the displacement of one of the 9-BBN boryl groups with lithium. Subsequent nucleophilic addition of the newly formed 1-boryl organolithium intermediate **33** to the benzoate thus creates an unstable α-boryl ketone **34**, which in turn rapidly isomerizes to the desired vinyloxyborane **35**. The *O*-boron enolates further react with aldehydes to give the corresponding cross-aldol condensation products **36** in good yields. It is noteworthy that the possible formation of tertiary alcohol byproducts from the addition of organolithium nucleophiles to the α-boryl ketone intermediates is not observed, which could be attributed to the fast rearrangement of *C*-boron enolates to their stable *O*-bound tautomers.

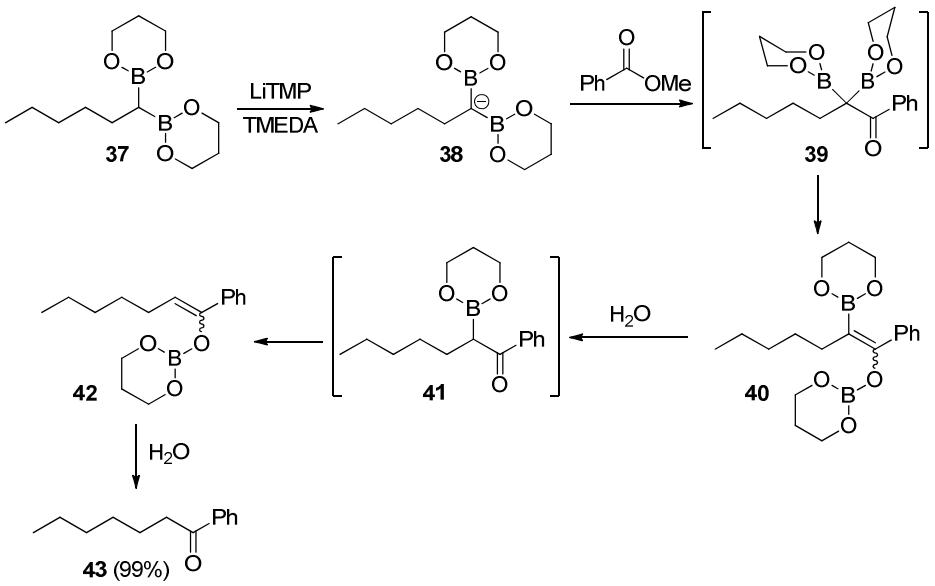
Scheme 8. The generation of phenyl-substituted vinyloxyboranes (*O*-boron enolates) via acylation of boron-stabilized carbanions with methyl benzoate



In sharp contrast to Mukaiyama's results, in which a boryl group was replaced by lithium, Matteson has since accomplished an efficient generation of 1,1-bis(dioxaborinyl)

alkyllithium reagents **38** through the α-deprotonation of 1,1-diboronic esters **37** with the geminal boryl groups intact (Scheme 9).[15] Rather than using a simple alkyllithium reagent, the reaction utilizes lithium 2,2,6,6-tetramethylpiperidide (LiTMP) as the base in the presence of tetramethylethylenediamine (TMEDA) as an activator. The *gem*-diboryl carbanionic intermediates **38** are in turn condensed with methyl benzoate to ultimately yield a class of l-phenyl ketone products **43**. Two different unstable α-boryl ketones **39** and **41** are presumably involved in a sequence of consecutive rearrangement-hydrolysis processes.

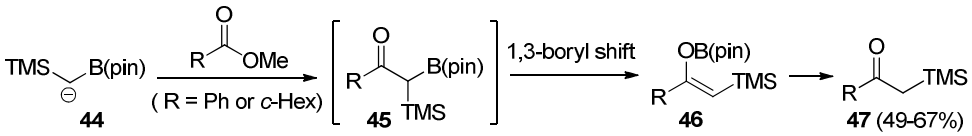
Scheme 9. Deprotonation of 1,1-diboronic esters and the acylation of 1,1-diboryl alkyllithium intermediates



Matteson further extended the above α-lithiation chemistry to a new class of α-substituted boronic esters, α-(silyl)alkaneboronates (Scheme 10).[16] Upon reaction with LiTMP in the presence of TMEDA, pinacol (trimethylsily1)methaneboronate was transformed to the corresponding lithio(trimethylsilyl)methaneboronate **44**. Treatment of the resulting organolithium solution with carboxylic esters smoothly afforded the corresponding α-silyl ketones **47** with concomitant elimination of the boryl group. The reaction is also postulated to proceed via a transient α-boryl-α-silyl ketone species **45** that in turn rearranges to the more stable *O*-boron enolate **46** and hydrolyzes to the final

ketone product **47**. It is noteworthy that this reaction unambiguously illustrates the much higher tendency of the 1,3-shift of boryl groups from carbon to the neighboring oxygen than that of silyl groups. While the vacant and acidic *p* orbital of the boron atom makes this 1,3-shift Woodward-Hoffmann allowed, the much less acidic *d* orbital of silicon leaves the corresponding 1,3-shift with partially forbidden character despite the increased strength of oxygen-silicon bonds over oxygen-boron bonds.

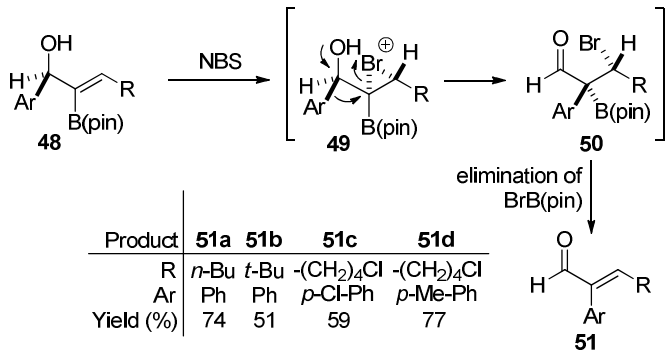
Scheme 10. α-Silyl ketone preparation from α-(silyl)alkaneboronates



2.1.3. Generation of α-boryl carbonyls via rearrangement

Another potential approach to achieve transient α-boryl carbonyl intermediates is via the rearrangement of pre-formed organoboron compounds. Walsh *et al*. reported an interesting skeletal rearrangement of boryl-substituted allylic arylcarbinols **48** in the presence of NBS resulting in stereospecific formation of (*E*)-trisubstituted enals **51** (Scheme 11).[17] Compounds **48** can be obtained from alkynyl boronates through a sequence of transformations involving hydroboration, zinc/boron transmetallation, and nucleophilic addition to aldehydes. In the reaction between **48** and NBS, a possible reaction pathway for the formation of the enals involves attack of NBS by the carbon-carbon double bond forming a bromonium ion intermediate **49**. A semipinacol-type rearrangement consisting of migration of the aryl group, opening of the bromonium ion, and generation of the carbonyl group after deprotonation leads to the formation of an α-boryl aldehyde intermediate **50**. Rather than the thermodynamically favored carbon-to-oxygen 1,3-shift of the boryl group to generate the more stable *O*-boron enolate, the α-boryl aldehyde presumably undergoes a faster bond rotation leading to a *syn* elimination of the boryl group and the vicinal bromine atom to give the observed (*E*)-enal product **51** with exclusive stereoselectivity. As α,β-unsaturated aldehydes are usually difficult to prepare with high selectivity due to the ease of double bond isomerization by nucleophiles, the present reaction provides an attractive solution to this challenge.

Scheme 11. NBS-promoted rearrangement of boryl-substituted allylic alcohols



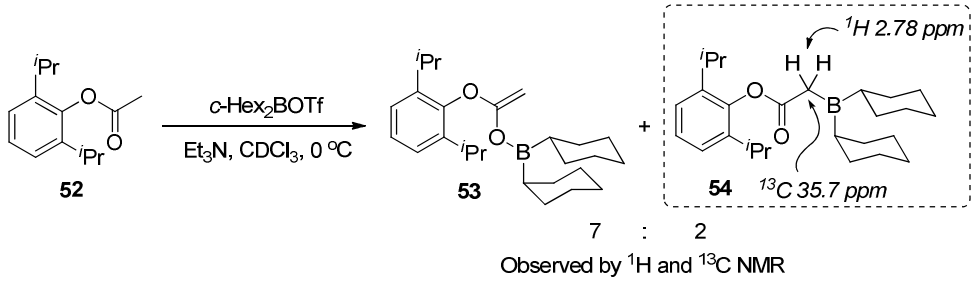
Product	51a	51b	51c	51d
R	*n*-Bu	*t*-Bu	-$(CH_2)_4$Cl	-$(CH_2)_4$Cl
Ar	Ph	Ph	*p*-Cl-Ph	*p*-Me-Ph
Yield (%)	74	51	59	77

2.2. α-Borylcarbonyl Intermediates detected via spectroscopic methods

Despite the fact that reactive α-boryl carbonyl intermediates have been proposed in many transformations, direct evidence in support of these transient species is sparse. With the advancement of analytical technology, a few examples of direct identification of reactive α-borylcarbonyl intermediates using spectroscopic methods have recently emerged.

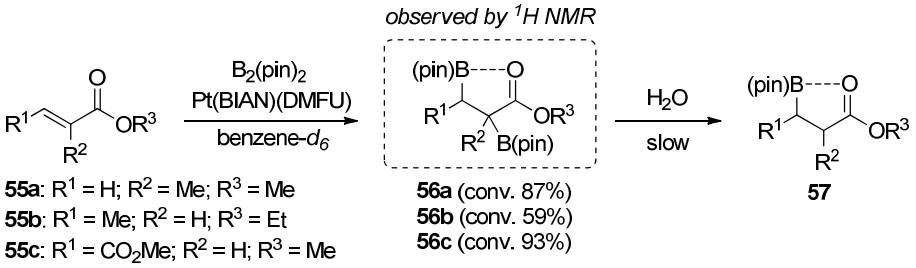
Abiko and co-workers were the first to report the NMR characterization of a class of *C*-boron enolates of 2,6-disubstituted phenyl acetates during treatment of the acetates with *c*-Hex_2BOTf and triethylamine in deuterated chloroform at 0 °C (Scheme 12).[18] For instance, the ^1H NMR spectrum of the enolization mixture using bulky 2,6-diisopropylphenyl acetate **52** showed the formation of the two boron enolate species **53** and **54** in a 7:2 ratio (the *O*- and *C*-boron enolate, respectively) with 90% conversion. The *C*-boron enolate **54** exhibited a broad singlet at 2.78 ppm in ^1H NMR and a ^{13}C signal at 35.7 ppm, characteristic of the methylene (CO***CH₂***B) equipped with an α-boryl group. The structures of these enolates were also confirmed using two-dimensional NMR techniques. The degree of formation of the *C*-boron enolate is highly dependent on the steric factor of the acetate. In general, formation of *C*-boron enolates becomes more favorable with more sterically demanding substituents *ortho* to the phenoxyl group, which could be attributed to the decreased stability of *O*-enolates due to steric interactions with *ortho*-substituents.

Scheme 12. Formation of a *C*-boron enolate from 2,6-diisopropylphenyl acetate



Another example of direct observation of α-borylcarbonyl intermediates was described by Marder in a 3,4-diboration of α,β-unsaturated esters using Pt(BIAN)(DMFU) (BIAN = *bis*(phenylimino)acenaphthene, DMFU = dimethylfumarate), and a platinum(0)diimine species as the precatalyst (Scheme 13).[19] A series of primary 3,4-diboration intermediates **56** possessing two pinacolylboryl groups at both the α- and β-positions of the ester groups were identified with *in situ* ^{1}H NMR spectroscopic analysis of reaction mixtures in benzene-d_6 at room temperature. For instance, compound **56a** was identified by the presence of an AB doublet of doublets at 1.55 ppm (^{1}H NMR). This is consistent with a CH_2 group adjacent to a chiral center and thus the structure is that of the 3,4-diborated product. While internally conjugated alkenes were used, the diboration products usually consisted of a mixture of two diastereomers. It is interesting that, while the primary diborated products **56** hydrolyzed slowly in the presence of moisture to yield the final β-borylcarboxylic esters, the carbon-boron bond α to the carbonyl group was stable when exposed to dry air. The exceptional stability of this class of α-borylcarbonyl compounds presumably arises from an efficient coordination of the β-boryl group to the carbonyl oxygen in a five-membered-ring fashion,[20] thus eliminating the possibility of interaction between α-boryl groups and the same oxygen atom and weakening the tendency of the carbon-to-oxygen 1,3-boryl shift that could result in the formation of *O*-boron enolates.

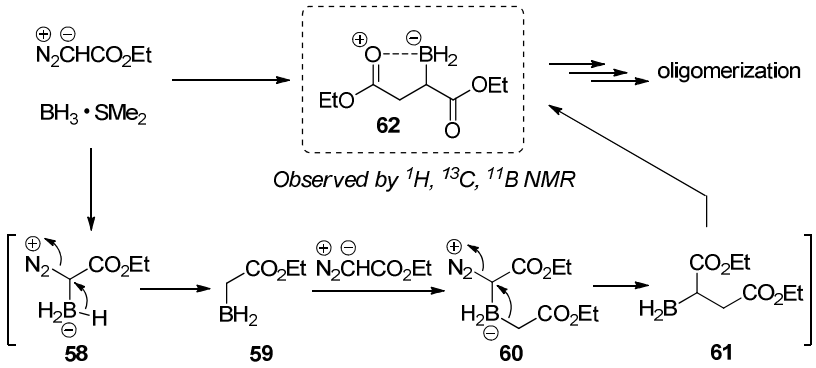
Scheme 13. Pt-catalyzed 3,4-diboration of α,β-unsaturated esters



In a study of BH_3-catalyzed oligomerization of ethyl diazoacetate, Shea *et al.* identified a *C*-boron enolate intermediate by spectroscopic analysis. To establish the mechanism of the oligomerization, ethyl diazoacetate was treated with 1.2 equiv. of $BH_3 \cdot SMe_2$ in CD_2Cl_2 at -78°C followed by warming to room temperature. ^{1}H NMR studies indicated that a diethyl 2-borylsuccinate **62** was the dominant species present in the crude reaction mixture (Scheme 14).[21] The structure of the *C*-boron enolate **62** was further characterized with ^{13}C, ^{11}B, and 2D NMR. The considerable downfield ^{13}C NMR shift of one of the ester carbonyl groups (190.6 ppm) and upfield ^{11}B NMR shift of the boron center (11.7 ppm) indicated a strong coordination between the carbonyl oxygen and the boron atom in a five-membered-ring geometry. DFT calculations indicated that this intramolecular dative bonding contributes to the stabilization of the *C*-boron enolate.

A pathway to generate the *C*-boron enolate **62** was proposed. Lewis acidic $BH_3 \cdot SMe_2$ reacts first with the nucleophilic ethyl diazoacetate to form a zwitterionic borate complex **58**. It supposedly undergoes loss of N_2 and rapid 1,2-hydride migration to afford *C*-boron enolate **59**. The enolate can subsequently react with a second molecule of ethyl diazoacetate followed by 1,2-migration of the CH_2CO_2Et group to generate enolate **60.** Intermediate **60** then collapses into the cyclic borane **8**, the "resting" species in the oligomerization.

Scheme 14. Diethyl 2-borylsuccinate intermediates in the BH_3-catalyzed oligomerization of ethyl diazoacetate

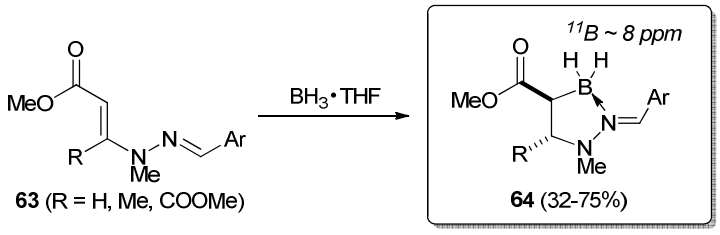


3. Preparation of stable α-boryl carbonyl compounds and their synthetic applications

The vacant *p* orbital of an sp^2-hybridized boron atom is believed to be the key factor that destabilizes the α-borylcarbonyl species. It makes the carbon-to-oxygen 1,3-boron shift not only kinetically allowed, but also thermodynamically favorable due to the formation of a much stronger boron-oxygen bond. An effective strategy to obtain stable α-borylcarbonyl compounds is to install electron-rich boron centers that have a much weaker propensity to coordinate to the carbonyl oxygen both thermodynamically and kinetically. A few examples of these stable α-borylcarbonyl compounds, which can be isolated and fully characterized, can be found in the literature.

As regioselective hydroborations of α,β-unsaturated carbonyl compounds have proven to be effective in the construction of α-borylcarbonyl motifs, appropriate use of intramolecular ligands that are capable of providing strong dative bonding to the newly formed Lewis acidic boron center could possibly result in a stabilized α-borylcarbonyl compound. This strategy was utilized by Sucrow and co-workers. They described preparation of a class of stable α-borylcarboxylic esters **64** bearing α-hydrozonyl groups by the hydroboration of enehydrazones and their derivatives **63** (Scheme 15).[22] These compounds are crystalline solids with melting points of around 90°C. This is probably the first reported example of isolable α-borylcarbonyl compounds. The strong electron donation from the hydrazone nitrogen lone-pair to the boron center, consistent with an upfield ^{11}B NMR δ = 8 ppm, apparently leads to the stability of these molecules.

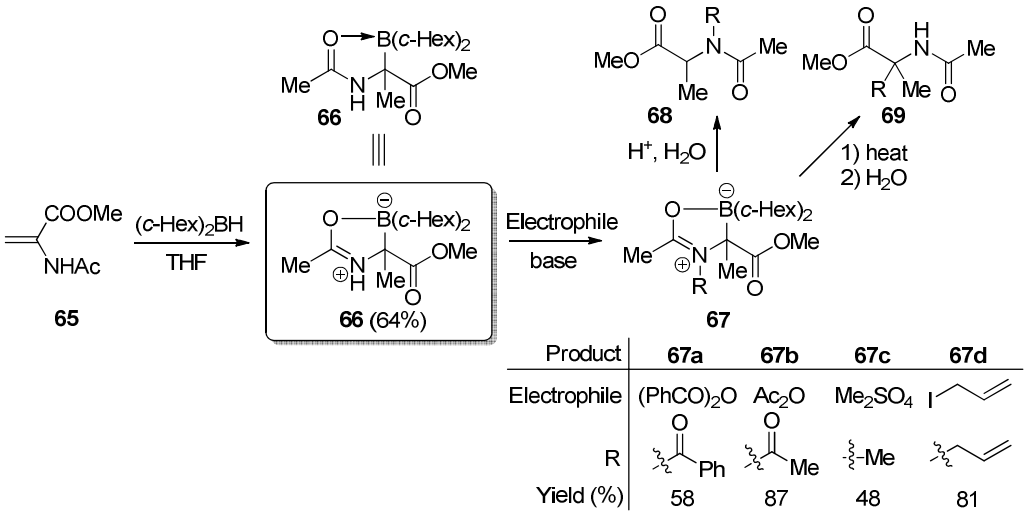
Scheme 15. Hydroboration of enehydrazones



A similar example of this hydoboration-coordination strategy has since been described by Danion-Bougot.[23] Treatment of methyl 2-acetamidoacrylate **65** with dicyclohexylborane at room temperature in dry THF for 2 hours afforded a stable heterocyclic borate complex **66** containing the α-borylcarbonyl substructure (Scheme 16), which was fully characterized by NMR spectroscopy and X-ray studies. Particularly, X-ray crystallographic analysis clearly showed that boron is in a tetrahedral environment with strong bonding to the amide oxygen. The intramolecular complexation thus prevented migration of boron to the neighboring carboxylic oxygen and therefore no *O*-enolate formation was observed.

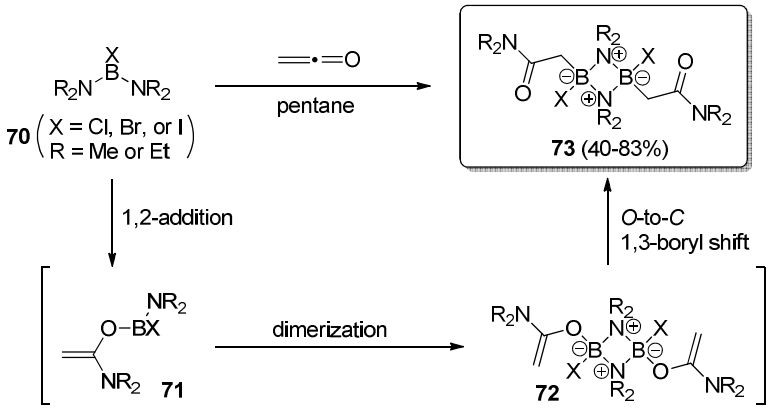
The reactivity of the zwitterionic borate complex **66** under several conditions has also been evaluated (Scheme 16). When treated with strong base, such as NaH or *t*-BuOK, followed by addition of various electrophiles at room temperature, *N*-alkylation or acylation occurs to form a series of *N*-substituted compounds **67** because the nitrogen atom is the only nucleophilic center under these conditions. Hydrolysis of **67** with strong acid in turn furnishes methyl alaninate derivatives **68** in almost quantitative yields. Thermolysis of **67a** and **67b** assisted with one equivalent of pyridine in toluene under reflux for 60 hours yields the corresponding *C*-acylsubstituted alaninates **69**. The reaction probably proceeds with initial cleavage of either the boron-oxygen or boron-carbon bond, followed by migration of the acyl group from nitrogen to the neighboring α-carbon of the methyl ester.

Scheme 16. Preparation of heterocyclic borates via hydroboration of 2-acetamidoacrylate



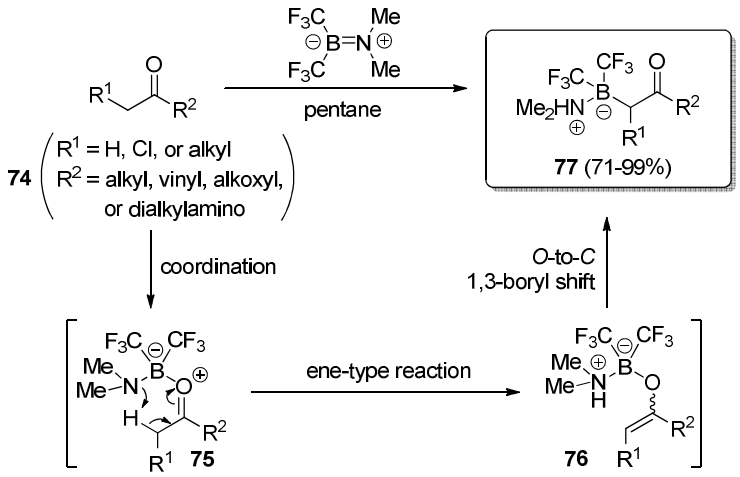
Around the same time that Sucrow reported the preparation of stable α-borylcarbonyl compounds via hydroboration, another class of stable α-boryl amides **73** with the common structure of dimeric four-membered rings were isolated by Paetzold and co-workers from the reaction between bis(dialkylamino)haloboranes and ketenes (Scheme 17).[24] The mechanism of the transformation remains unclear but is presumably initiated by 1,2-addition of the boron-nitrogen bond to the carbonyl group of the ketene. A borane adduct **71** in the form of an *O*-bound boron enolate is initially formed, which immediately dimerizes to generate a four-membered "ate" complex **72** with tetracoordinated boron centers. The electron saturation of boron is presumed to trigger a rapid rearrangement of the *O*-bound boron enolate to the more stable α-borylcarbonyl final product via a thermodynamically favored oxygen-to-carbon 1,3-boryl shift. If this truly is the case, this reaction would be the first demonstration of an energetically-favored conversion of *O*-boron enolates to their *C*-bound tautomers.

Scheme 17. α-Boryl amides dimers from the reaction between bis(dialkylamino)haloboranes and ketenes



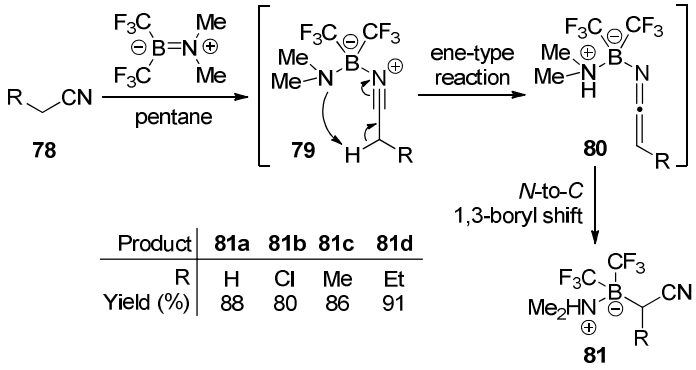
Another interesting transformation resulting in stable α-borylcarbonyl compounds, likely also involving an unusual oxygen-to-carbon boron migration, was reported by Bürger and co-workers. [25] By treating (dimethylamino)bis(trifluoromethyl)borane ($(F_3C)_2B{=}NMe_2$) with ketones, esters, or amides, a family of α-bis(trifluoromethyl)boryl ketones, esters, and amides **77** were obtained as colorless solids in almost quantitative yields (Scheme 18). These compounds are stable to both air and moisture, and are soluble in polar solvents. A considerably upfield ^{11}B NMR shift (δ = -8 to -10 ppm) of these compounds reveals the presence of exceptionally strong dative bonding between the dimethylamine nitrogen to the boron center. Mechanistically, the reaction between (dimethylamino)bis(trifluoromethyl) borane and the starting carbonyl compounds **74** is postulated to involve an ene-type transformation. The carbonyl group likely coordinates to the boron atom of (dimethylamino)bis(trifluoromethyl)borane, which leads to an increase in the acidity of the α-hydrogen atoms of the carbonyl substrate. One of the α-protons is subsequently transferred to the basic nitrogen center, thus generating an *O*-bound boron enolate species **76**. In the final step, the *O*-bound boron enolate intermediate with an electron-rich tetracoordinated boron rapidly rearranges to yield the more stable α-borylcarbonyl products.

Scheme 18. Preparation of α-boryl ketones, esters, and amides via ene-type reactions



Bürger also observed an analogous ene-type transformation with alkylnitriles **78** and (dimethylamino)bis(trifluoromethyl)borane (Scheme 19). The reaction affords good yields of α-boryl nitriles **81** via a similar mechanism involving boron-nitrile complexation, α-hydrogen abstraction, and a final step of aza-allene rearrangement (nitrogen-to-carbon 1,3-boryl shift).

Scheme 19. Preparation of α-boryl nitriles

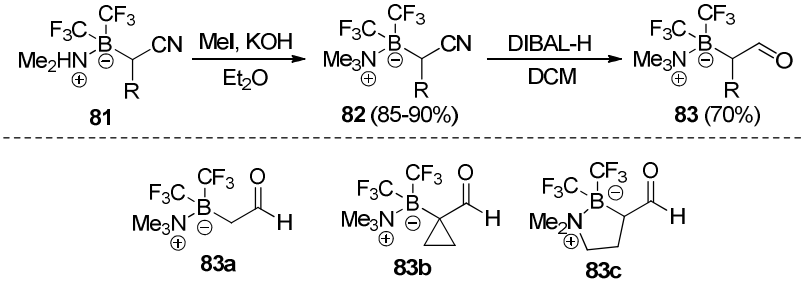


Product	81a	81b	81c	81d
R	H	Cl	Me	Et
Yield (%)	88	80	86	91

Intriguingly, further reduction of α-boryl nitriles to the corresponding aldehydes with retention of α-boryl groups can be achieved, although a protection of the acidic NH, e.g. by alkylation, is necessary. After alkylation of the aminoborates **81** with CH_3I in the presence of KOH, DIBAL-H reduction of trimethylamine-borane derivatives **82** in DCM at -50 ^{o}C successfully furnishes a series of stable α-boryl aldehydes **83** (Scheme 20).[26] These new compounds are also colorless solids and resistant to air, although upon

prolonged contact the aldehydes slowly oxidize to carboxylic acids. NMR spectroscopy (^{1}H, ^{13}C, ^{19}F, ^{11}B) and X-ray crystallography confirm the proposed structures.

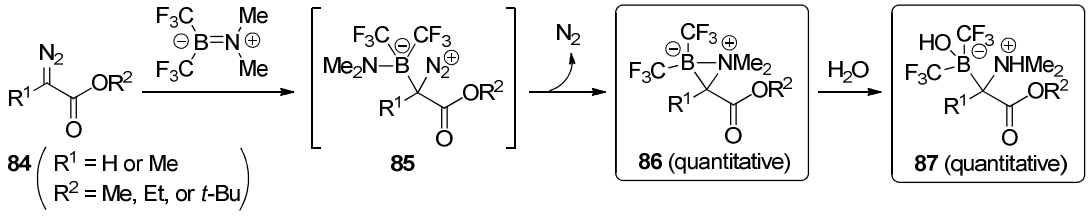
Scheme 20. Access to α-boryl aldehydes from α-boryl nitriles



As part of a project aimed at evaluation of the reactivity of (dimethylamino)bis(trifluoromethyl)borane, Bürger and co-workers discovered another reaction involving an interesting formal "cyclopropanation" by mixing diazo compounds with the aminoborane reagent in pentane at room temperature.[27] Using diazo esters as starting materials, a type of unprecedented azoniaboratacyclopropane product **86** containing the BNC three-membered heterocycle with an α-borylcarbonyl motif was quantitatively generated (Scheme 21). The formation of these heterocyclopropane products is proposed to occur via initial nucleophilic attack of the diazo carbon at the boron atom of (dimethylamino)bis(trifluoromethyl)borane. The zwitterionic intermediates **85** subsequently undergo an intramolecular substitution with the amino group to extrude nitrogen gas, thus furnishing a formal insertion of the diazo-functionalized carbon to the boron-nitrogen bond to install the three-membered heterocyclic ring structure. These new α-borylcarbonyl products are stable even at elevated temperature. X-ray crystallographic analysis revealed that the boron-nitrogen bond in the heterocyclopropane ring is the shortest found so far between tetracoordinated boron and nitrogen atoms. It is believed that the two strongly electron-withdrawing CF_3 groups contribute to the strong coordination between boron and nitrogen. In contrast to their thermal stability, hydrolysis of these azoniaboratacyclopropanes occurs within minutes and results in cleavage of the boron-nitrogen bond in the strained three-

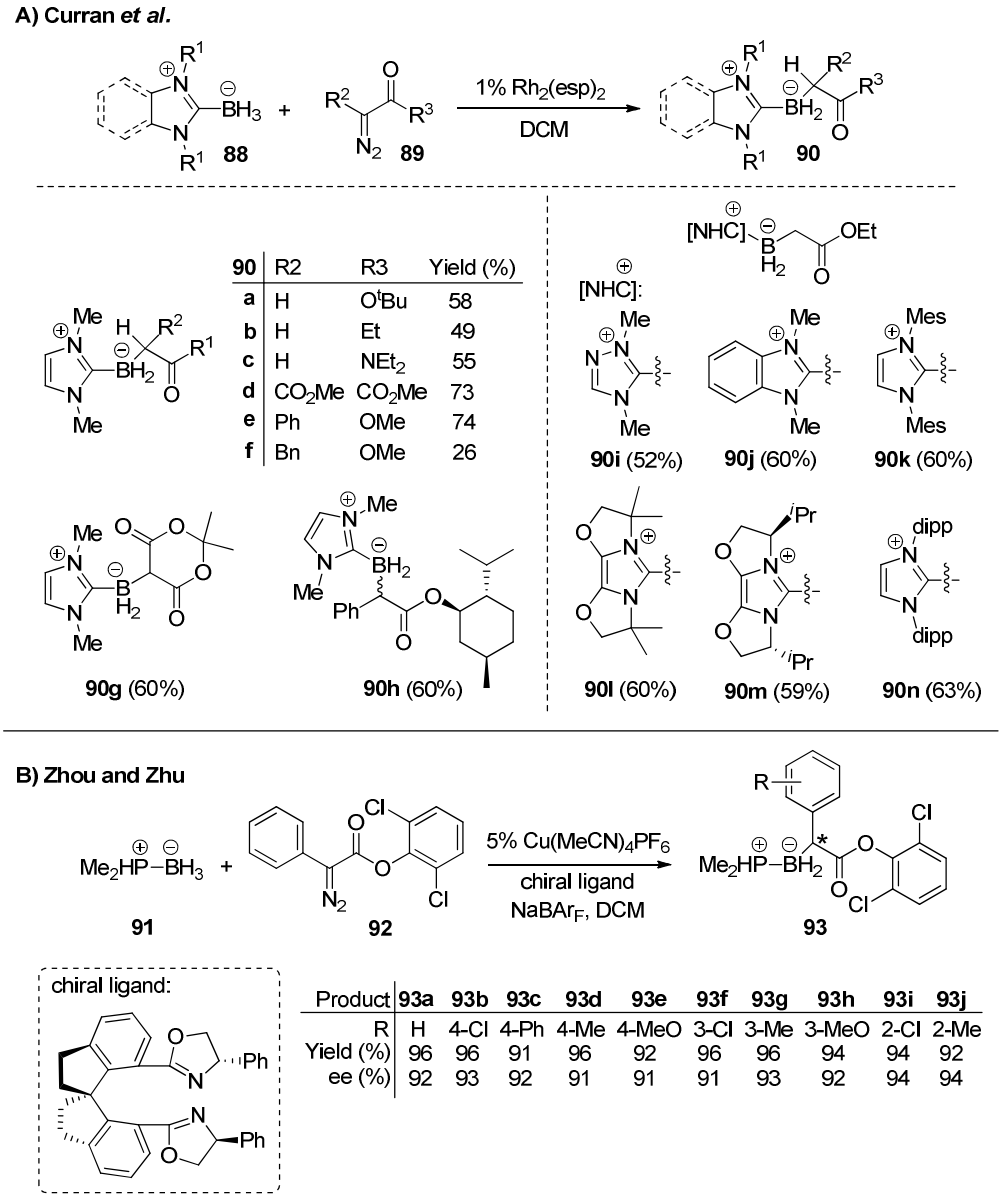
membered ring to generate an acyclic zwitterionic species **87**, which preserves the α-borylcarbonyl structure albeit with a hydroxylated electron-rich boron center.

Scheme 21. Formation of azoniaboratacyclopropanes and hydrolytic cleavage of their B-N bond



In a closely related approach, Curran *et al.* very recently demonstrated that readily available rhodium(II) salts catalyze the reaction between NHC-boranes **88** (NHC-BH_3) and diazocarbonyl compounds. This resulted in insertion of the transient rhodium carbene into the electron-rich boron-hydrogen bond of the NHC-borane compound (Scheme 22A).[28] Stable α-(NHC)boryl carbonyl compounds **90**, including ketones, esters, and amides, were isolated as colorless oils or white solids in good yields using flash chromatography. Zhou and Zhu also reported an analogous boron-hydrogen bond insertion reaction using amine- or phosphine-borane adducts in the presence of a copper catalyst (Scheme 22B).[29] Utilization of chiral spirobisoxazoline ligands enabled asymmetric synthesis of stable α-borylcarboxylic esters **93** with excellent enantioselectivity. Downstream transformation of these α-boryl esters to β-hydroxy boronates via DIBAL-H reduction with retention of carbon-boron bonds can be achieved. This has proven to be an attractive approach to chiral organoboron building blocks, which are likely to find widespread application in organic synthesis.

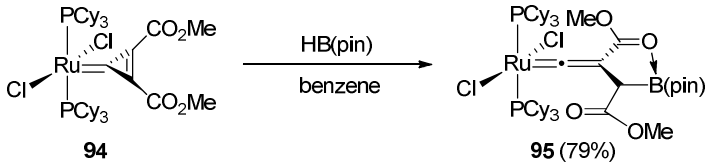
Scheme 22. Transition metal-catalyzed insertion of carbenes into boron-hydrogen bonds



The insertion reaction is not limited to electron-rich boron-hydrogen bonds and reactive metal carbenoids. Johnson and co-workers reported that treatment of a ruthenium cyclopropenylidene complex **94** with pinacolborane in benzene at room temperature generated a stable vinylidene complex **95** containing an α-borylcarboxylic ester moiety (Scheme 23).[30] The reaction is believed to occur via a 1,1-addition (insertion) of the boron-hydrogen bond into one of the distal ring carbon atoms of the cyclopropenylidene complex. The product was isolated as an orange powder and was fully characterized with NMR spectroscopy and elemental analysis. ^{11}B NMR of the compound (δ = 20 ppm)

indicated the existence of an electron-rich boron center, presumably due to an intramolecular coordination of the carbonyl oxygen from the methyl ester β to the boryl group. This structural feature is likely the key factor for the stability of the *C*-boron enolate.

Scheme 23. Preparation of a ruthenium vinylidene complex containing an α-borylcarboxylic ester

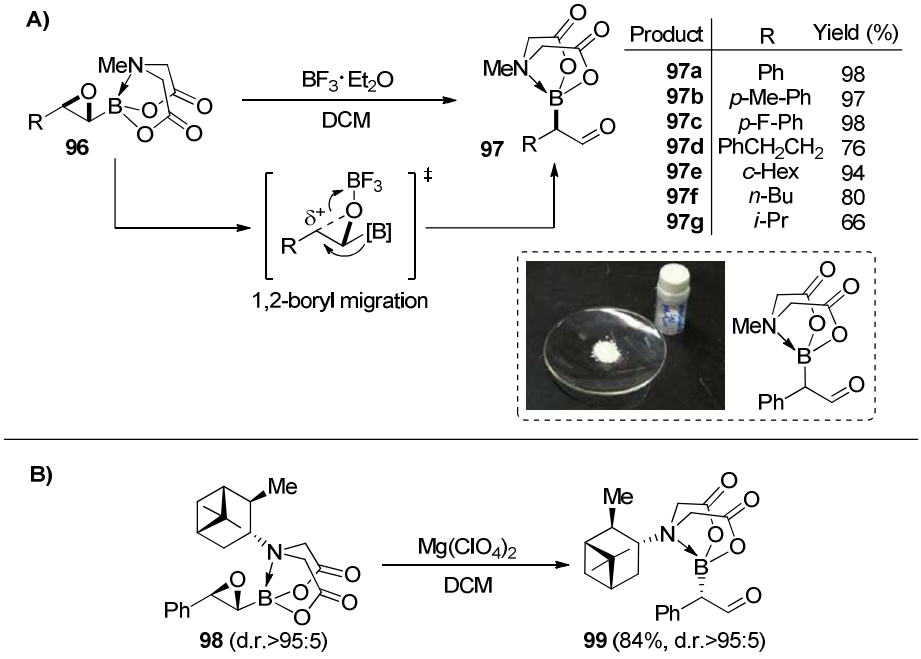


94 **95** (79%)

Although stable during isolation and characterization, most α-borylcarbonyl compounds equipped with tetracoordinated boron centers discussed above have no downstream synthetic applications, likely because of the inconvenience in handling and preparation. Functional group tolerance is likely another problem. Boryl groups in these molecules, although somewhat stabilized through dative bonding, are still expected to be vulnerable in most chemical transformations. As such, new generations of these molecules, which are amenable to further chemical manipulations to access other highly functionalized organoboron compounds, are desirable.

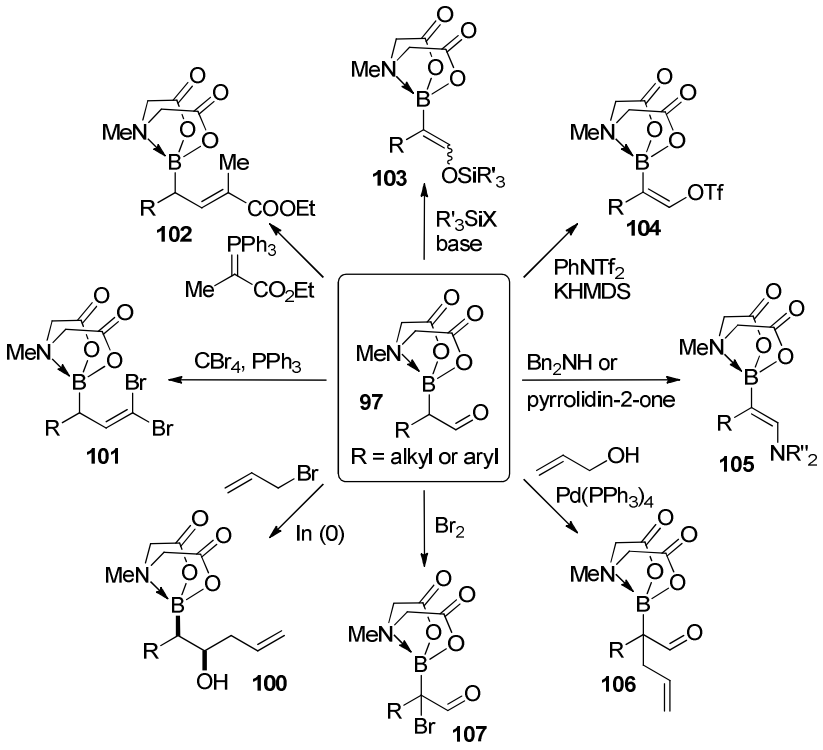
Our group recently discovered a class of stable α-boryl aldehydes **97** equipped with a tetracoordinated *N*-methyliminodiacetyl (MIDA) boryl group.[31] These compounds were prepared via a BF_3-promoted rearrangement of oxiranyl MIDA boronates **96** in dichloromethane at -30°C (Scheme 24A). Deuterium labeling experiments revealed that the epoxide rearrangement installs the α-boryl carbonyl system via an unprecedented 1,2-boryl migration. The resulting α-boryl aldehyde products **97** are usually white solids and are stable to aqueous workup, silica gel chromatography, and storage at room temperature. A similar result by Burke and co-workers, utilizing diastereomerically pure oxiranyl pinene-derived iminodiacetyl (PIDA) boronates **98** in a magnesium perchlorate-mediated epoxide rearrangement (Scheme 24B), revealed the stereospecificity of this class of transformation.[32]

Scheme 24. BF_3-promoted rearrangement of oxiranyl MIDA boronates



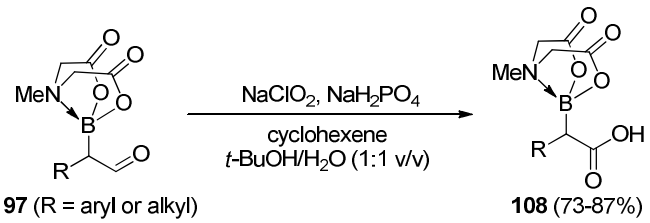
The synthetic potential of α-boryl aldehydes has been extensively evaluated (Scheme 25). Transformations of α-boryl aldehydes to the corresponding β-boryl alcohols **100**, *gem*-dibromoallyl boronates **101**, and (*E*)-α-boryl-α,β-unsaturated esters **102** using corresponding nucleophilic reagents demonstrate the reactivity of the aldehyde moiety. Enolization of the aldehyde is possible leaving the MIDA boryl group intact. A range of silyl or triflate enol ethers, enamines and enamides (**103–105**) are obtained by treating the α-boryl aldehydes with appropriate reagents under basic conditions. The synthetic potential of the enolizable α-boryl aldehydes is further demonstrated in their α-functionalization. Palladium-catalyzed α-allylation under Tamaru's conditions[33] supplies α-allylated boryl aldehydes **106** with the MIDA boryl group intact.[34] Treatment of α-boryl aldehydes with bromine also affords α-bromo-α-boryl aldehydes **107** as crystalline products.

Scheme 25. Synthetic transformations of α-boryl aldehydes



The stability of the MIDA boryl group towards various reaction conditions encouraged us to evaluate the possibility of generating α-borylcarboxylic acids from the corresponding aldehyde precursors. Under Pinnick oxidation conditions[35] a series of substituted α-borylcarboxylic acids **108** were obtained as white solids (Scheme 26).[36] Like their aldehyde precursors, the carboxylic acid products are air-stable and can be purified by silica gel chromatography or trituration.

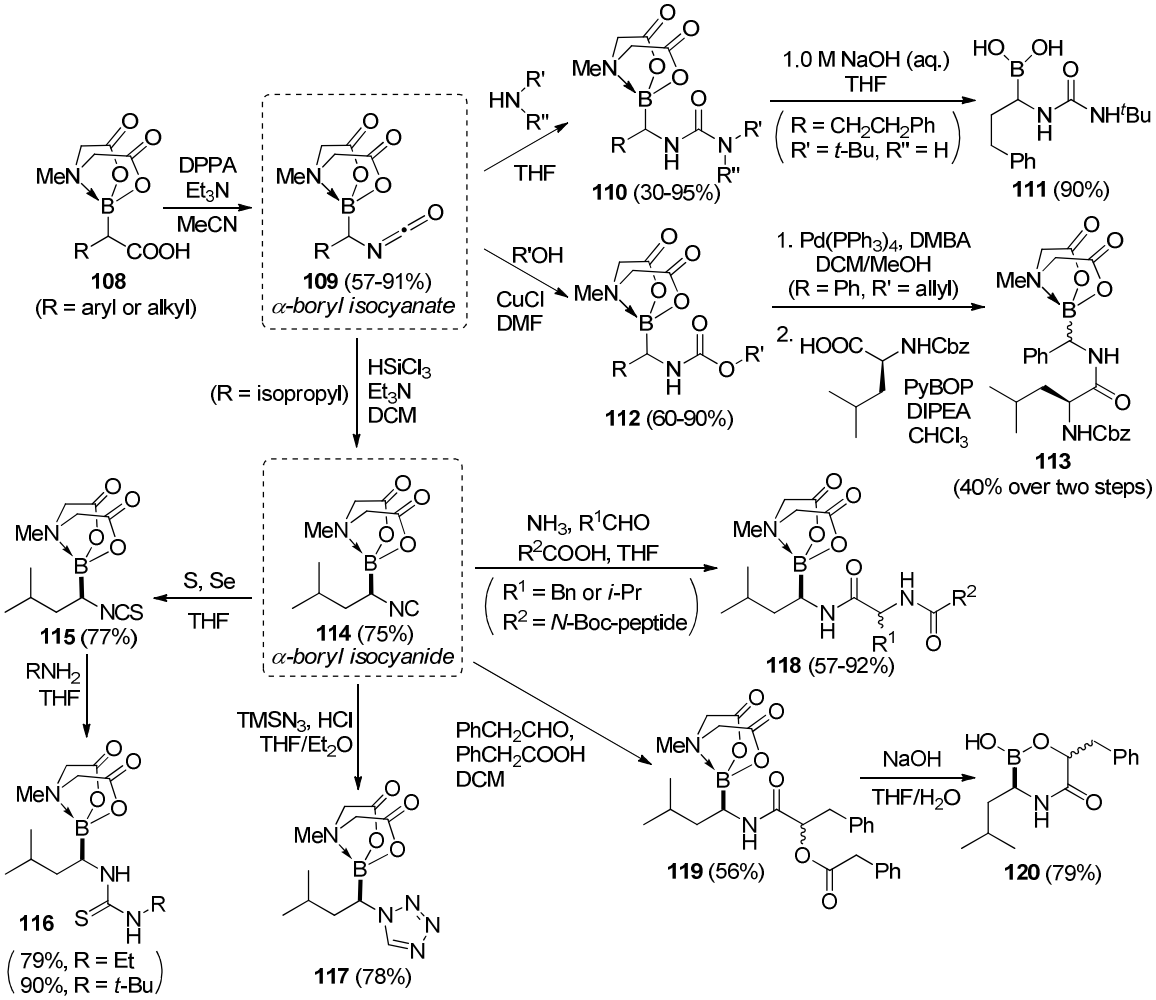
Scheme 26. Preparation of α-boryl carboxylic acids



α-Borylcarboxylic acids supply opportunities to access other multi-functionalized boron-containing molecules. A one-pot Curtius rearrangement procedure using diphenylphosphoryl azide (DPPA) in the presence of triethylamine and anhydrous

acetonitrile provided a class of air-stable α-boryl isocyanates **109** (Scheme 27).[36,37] Downstream chemoselective manipulation of either the isocyanate and/or MIDA boryl groups allowed access to a wide range of novel organoboron compounds (**110–120**), including α-boryl isocyanides, α-boryl isothiocyanates, α-boryl ureas or thioureas, α-boryl tetrazoles, and a series of boropeptides and boro-heterocycles (Scheme 27).[36, 38]

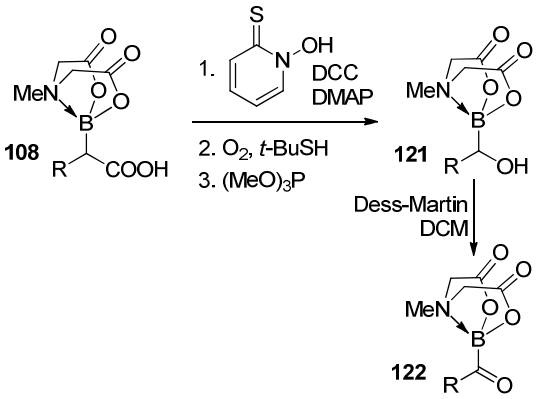
Scheme 27. Preparation and transformation of α-boryl isocyanates.



As the Curtius rearrangement of α-borylcarboxylic acids furnishes a geminal installation of the nitrogen functionality α to the boron center, analogous installation of a hydroxyl group is also feasible. We recently achieved this via Barton radical decarboxylative hydroxylation[39] of α-borylcarboxylic acids. Initial conversion to the corresponding Barton esters occured via DCC coupling. After treatment of the Barton

esters with O_2 gas in the presence of *tert*-butylthiol under tungsten-halogen light irradiation, the desired α-hydroxyboronates **121** were isolated as air-stable solids (Scheme 28).[40] Following the decarboxylation, the α-hydroxyboronate intermediates can be reacted with Dess–Martin periodinate under ambient temperature. The reaction provides access to a unique class of MIDA acylboronate products **122** as air-stable solids. No oxidative cleavage of the carbon–boron bond has been observed during this process.

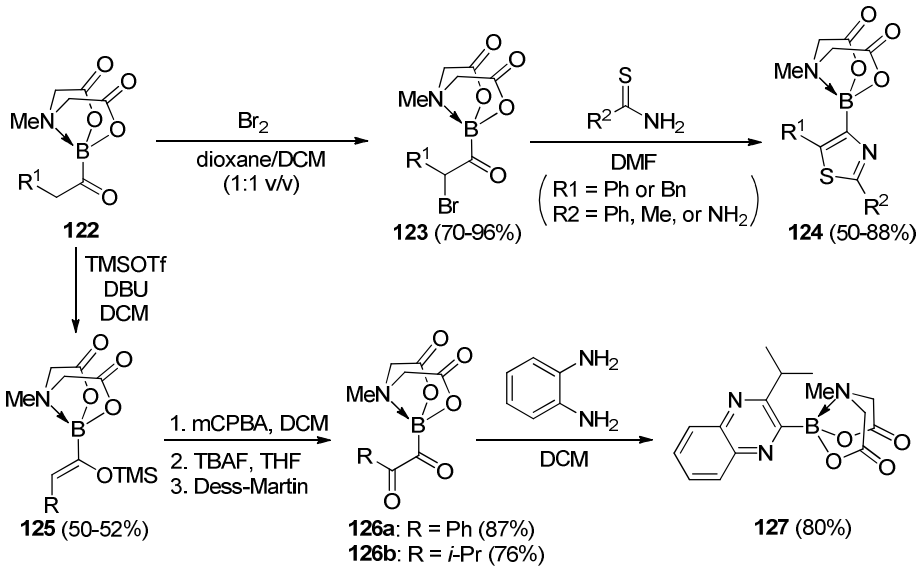
Scheme 28. Synthesis of α-hydroxyboronates and acylboroanates.



R	Yield (%) of hydroxylation	Yield (%) of oxidation
Ph	32 (**121a**)	72 (**122a**)
p-Me-Ph	32 (**121b**)	76 (**122b**)
p-F-Ph	35 (**121c**)	70 (**122c**)
p-Ph-Ph	29 (**121d**)	85 (**122d**)
$PhCH_2CH_2$	73 (**121e**)	70 (**122e**)
Bn	70 (**121f**)	66 (**122f**)
i-Pr	50 (**121g**)	70 (**122g**)
n-Bu	70 (**121h**)	60 (**122h**)
c-Hex	71 (**121i**)	85 (**122i**)

Synthesis of MIDA acylboronates prompted us to evaluate their reactivity and application in the construction of borylated heterocycles. Exposure of enolizable acylboronates to bromine resulted in the corresponding α-bromination products **123** with the carbon-boron bond intact (Scheme 29). Subsequent reaction of these α-bromoacylboronates with thioamides or thioureas in DMF at elevated temperature afforded 4-borylated thiazole derivatives **124**. On the other hand, conversion of acylboronates to 1-(silyloxy)vinylboronates, followed by Rubottom oxidation[41] and subsequent Dess–Martin oxidation, afforded a class of novel air-stable 2-oxo-acylboronate products **126** (Scheme 29). By treating the 2-oxo-acylboronate with o-phenylenediamine in dichloromethane, a 2-borylated quinoxaline **127** was obtained. This reaction further exemplifies the potential of acylboronates in the preparation of borylated heterocycles.

Scheme 29. Preparation of MIDA thiazol-4-ylboronates

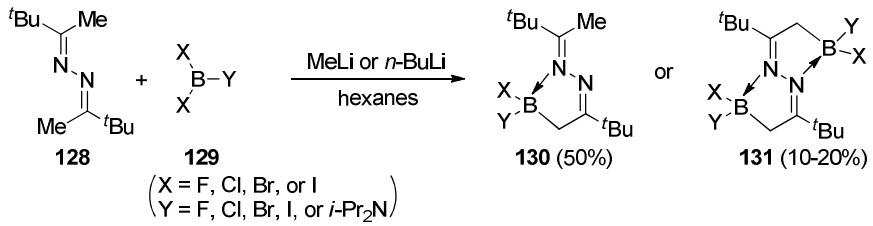


4. Other α-borylcarbonyl related compounds

4.1. α-Boryl imines

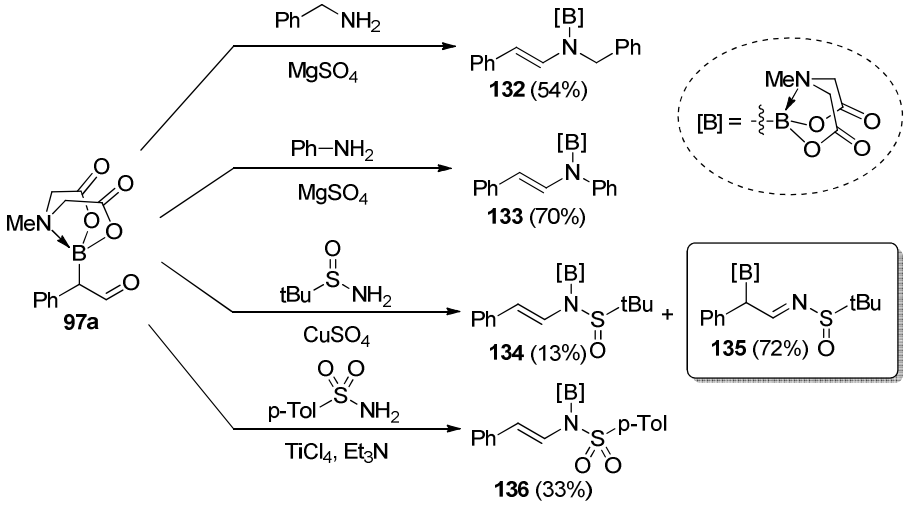
Since boron-nitrogen bonds are generally weaker than boron-oxygen bonds,[42] α-boryl imines are expected to be more stable than their oxygen analogues and thus more feasible as isolable targets. However, stable α-boryl imines are even rarer than α-borylcarbonyl compounds. A thorough literature search only results in the report of a set of α-boryl ketazines **130** and **131**, which have been prepared from lithiated ketazines with trihalo or dihaloborane reagents (Scheme 30).[43] Depending on lithiation equivalency, mono- or di-borylated products can be isolated. These α-boryl imines have been fully characterized by NMR (^{1}H, ^{13}C, ^{11}B, ^{19}F, and ^{29}Si), mass spectrometry, elemental analysis, and X-ray crystallography, revealing the five-membered heterocyclic structure constructed by the strong coordination between the boron center and the ketazine nitrogen.

Scheme 30. Synthesis of α-boryl ketazines



Therefore, we tested the possibility of preparing α-boryl imines directly from α-(MIDA)boryl aldehydes. Different classes of amines/amides, including benzylamine, aniline, *p*-toluenesulfonamide and *tert*-butanesulfinamide, were mixed with α-boryl aldehyde **97a** in the presence of dehydrating agents and/or Lewis acids (Scheme 31). However, the majority of amines tested only afforded *N*-boryl enamines, which are stable and isolable using silica gel chromatography. It is interesting that only in the case of *tert*-butanesulfinamide was the desired α-boryl imine **135** isolated as the major product along with a small amount of *N*-boryl enamine isomer **134**. Although stable in the solid state, α-boryl imine **135** was found to slowly convert to enamine isomer **134** over prolonged storage in solution (DMSO-d_6).

Scheme 31. Attempts to prepare α-amino imines



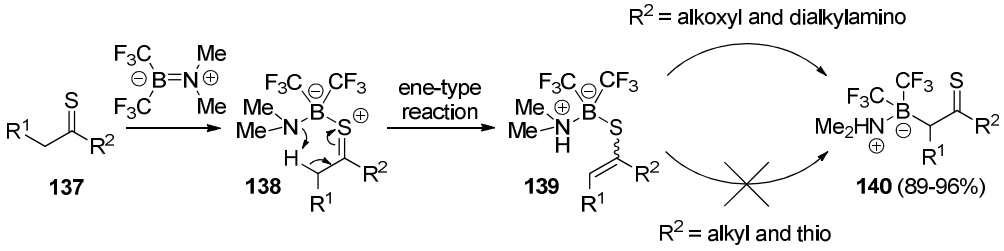
The difficulty in obtaining stable α-(MIDA)boryl imines still lacks a suitable explanation. The general B-O/B-N bonding energy trend seems to be irrelevant to the relative stability of α-boryl aldehydes and imines and thus cannot be used as a simple

guide in real cases. An intuitive explanation for the instability of α-boryl imines is the more accessible imine nitrogen lone-pair electrons, which might promote the 1,3-boron shift of the tetrahedral MIDA boryl group from the α-carbon to nitrogen.

4.2. α-Boryl thiocarbonyl compounds

α-Boryl thiocarbonyls, as another class of analogues to α-borylcarbonyl compounds, have also been investigated. In a manner similar to the preparation of carbonyl derivatives, Burger and co-workers subjected thioketones, thioates, dithoates, and thioamides to the ene-type reaction conditions in the presence of dimethylaminobis(trifluoromethyl)borane (Scheme 32). [44] The tendency toward tautomeric rearrangement furnishing the final thiocarbonyl products was found weaker than in the case of the corresponding carbonyl derivatives. The desired α-boryl thiocarbonyl products **140** have only been successfully obtained in the cases of thioates and thioamides. Moreover, while almost quantitative yields have been achieved, a much longer reaction time is required in these cases than in that of the carbonyl version of the transformation. In contrast, thioketone and dithioate substrates usually stop at the stage of the enol intermediate **139** and no desired α-boryl keto-type products have been obtained.

Scheme 32. Preparation of α-boryl thiocarbonyl compounds via ene-type reactions



5. Summary and outlook

α-Borylcarbonyl species are important molecular entities in organic chemistry. While transient *C*-boron enolates with electron-deficient boron centers have been postulated as key intermediates in many chemical transformations and have been partially supported with spectroscopic evidence in several cases, stable α-borylcarbonyl compounds with electron-rich boryl groups are also accessible. Isolation of these species

is achieved by enforcing kinetic barriers to tautomerization and other degradation processes.

Examples of stable α-borylcarbonyl compounds discussed in this review demonstrate the pivotal role of the tetracoordinate boron center in stabilizing *C*-boron enolates. By adding an extra ligand to the sp^2-boron center, the newly formed electron-saturated sp^3-boron is thermodynamically less prone to undergo migration to the carbonyl oxygen. In addition, the tetracoordinate nature of the sp^3-boron center serves as a barrier to interaction between boron and the lone-pair electrons of the adjacent carbonyl oxygen, which in the case of sp^2-boryl carbonyls initiates a 1,3-boryl migration leading to tautomerization.

Various types of thermally stable α-borylcarbonyl compounds have been synthesized by enforcing sp^3-hybridization of the boron center. Among these, several α-(MIDA)boryl derivatives (aldehydes and carboxylic acids) have proven amenable to downstream synthetic transformations. By employing the versatility of aldehyde or carboxylic acid functionalities, a wide range of functionalized organoboron compounds with an intact MIDA boryl group have been efficiently obtained. Successful aldehyde functionalizations include olefination, allylation, reduction and enolization. Curtius rearrangement of α-boryl carboxylic acids furnishes the corresponding isocyanates and isocyanides by extension. Radical decarboxylation of the carboxylic acids followed by oxidation results in acyl boronates, which have been used to prepare MIDA-boryl heteroaromatic species.

From a synthetic standpoint, α-borylcarbonyl compounds and related derivatives bearing a chemically robust boryl group tolerant of a wide range of chemical conditions are highly desirable. While the MIDA ligand has proven effective in this regard, it has yet to be determined whether other boron ligands are amenable to these protocols. For example, it is unclear whether other electron-rich boryl groups, such as tetrahedral potassium trifluoroborate (–BF_3K) [45] or the planar 1,8-diaminonaphthalenylboryl (–B(dan)) group,[46] can be installed adjacent to the carbonyl group. The sp^3 nature of BF_3K salts and the electron-rich chelation in B(dan) groups have the potential to mask the Lewis acidity of the boron center and therefore improve stability of the α-boryl carbonyl structure over its *O*-bound tautomer. The stability of these groups toward various reagents has the potential to enable new classes of α-boryl carbonyl derivatives.

In addition to exploration of new boron ligands, it remains to be shown whether the amphoterism of α-borylcarbonyl compounds can be fully taken advantage of by engaging both the nucleophilic reactivity of the carbon–boron bond and the electrophilicity of the carbonyl group in a single transformation. While this type of methodology has been well established for other kinetically amphoteric species (for example isocyanides in multi-component reactions), examples of analogous reactivity of α-borylcarbonyl species has yet to be established. Development of this methodology has significant potential to expand the horizon for the use of organoboron building blocks in modern synthesis.

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