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Perspective

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Amphoteric α-Boryl Aldehyde Linchpins in the Synthesis of Heterocycles

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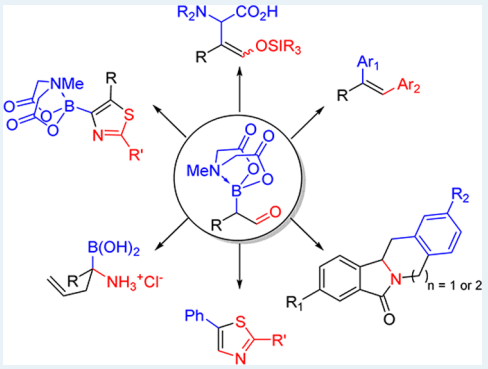
ABSTRACT: Pairing of mutually reactive functional groups in the same molecule affords enabling opportunities in chemical synthesis. Kinetically amphoteric molecules exemplify this scenario and help avoid the pitfalls of protecting-group chemistry by exploiting the innate reactivity of the functional groups. In this perspective, we highlight the recent development of MIDA (*N*-methyliminodiacetyl) α-boryl aldehydes as amphoteric building blocks that act as linchpins in the synthesis of heterocycles. This short review includes topics ranging from metal-catalyzed cyclization involving B−C−Pd intermediates to the intramolecular Suzuki−Miyaura cross-coupling that affords six- and seven-membered rings. The use of boryl aldehydes in other transformations, including halogenation and oxidation protocols, is also discussed.



KEYWORDS: *transition metal catalysis, boron, amphoteric molecules, organocatalysis, heterocycle synthesis, Suzuki−Miyaura cross-coupling*

INTRODUCTION

The term "amphoteric" originates from the Greek word "amphoteros", which means "both of two". In acid/base chemistry, an amphoteric molecule has the capability to react both as a Brønsted acid and a Brønsted base. Thus, amino acids are amphoteric in nature. Reversible proton transfer in these molecules exemplifies *thermodynamic* amphoterism.

The ability to promote chemoselective transformations in the presence of incompatible functional groups is an enduring challenge in modern organic synthesis.[1] Chemoselective transformations that minimize the requirement for protecting group manipulations are particularly sought-after. Small molecules that possess both nucleophilic and electrophilic functional groups that are stable belong to the class of *kinetically* amphoteric reagents (Figure 1). Isocyanides (1,1-amphoteric) are the most common kinetically amphoteric molecules, and our lab has reported the development and application of another class of amphoteric molecules, α-aziridine aldehydes (1,3-amphoteric) (Figure 2).[2] The Beauchemin lab has also reported *N*-isocyanates, which are another class of 1,3-amphoteric reagents.[3] Although the prevalence of 1,3-amphoteric reagents is starting to increase, there is a noticeable deficit of other amphoteric reagents ([1,*n*]-amphoteric) available to the synthetic organic chemistry community (Figure 1). In this paper, we summarize our efforts to develop 1,2-amphoteric reagents based on boron and the application toward organic synthesis and catalysis.

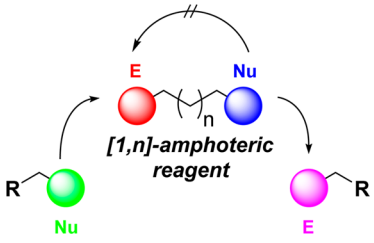


Figure 1. Reactivity of kinetically amphoteric reagents.

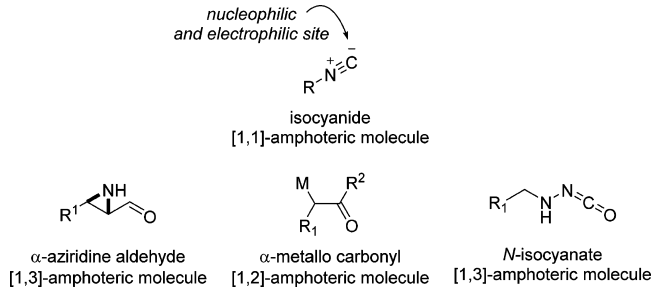


Figure 2. Examples of kinetically amphoteric molecules.

α-BORYL ALDEHYDES

Stable α-metallocarbonyls, in which a nucleophilic substituent and electrophilic carbonyl functionality are adjacent to each other, are an underexplored class of compounds (Figure 2). Of these, α-silyl carbonyl derivatives are the most common.[4] These

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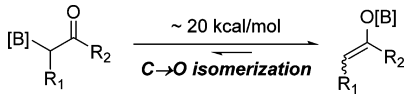
reagents are generally stable to purification and distillation. In contrast to silicon, the corresponding boron congeners have been underexplored, offering a compelling rationale to search for this elusive class of compounds.

Compared with the corresponding *O*-boron species, α-boryl carbonyl compounds are unstable, and the barrier to boryl isomerization ([1,3]-boryl shift) is ∼11.0 kcal/mol.[5] In addition, the energy difference between the O- and C-boron enolate is close to 20 kcal/mol (Scheme 1). Until recently,

Scheme 1. Facile C → O Boryl Migration



there have been few reported examples of α-boryl carbonyl compounds (Figure 3).[6] Although these molecules can be isolated, they have limited synthetic value because of the facile displacement of the ligands off the boron center. Prevention of this facile decomposition pathway would increase the synthetic utility of this class of reagents.

In 2011, our group and that of Martin Burke independently reported a new class of α-boryl aldehydes that are stabilized by a conformationally rigid trivalent ligand (Figure 4).[7,8] The ligand, *N*-methyliminodiacetic acid (MIDA), not only inhibits C → O boryl migration but also prevents interaction of external nucleophiles with the boron center.[9] This enables the exploration of the synthetic potential of typically unstable organoboronic acids, including new classes of amphoteric molecules.

PREPARATION OF α-MIDA BORYL ALDEHYDES

The preparation of α-MIDA boryl aldehydes is straightforward and utilizes readily accessible starting materials (Scheme 2). To start, the vinyl boronic acids are subjected to dehydration conditions in the presence of MIDA to form the corresponding vinyl MIDA boronates. Epoxidation of the vinyl boronates with *m*-CPBA affords epoxy-MIDA boronates in generally good yields. The subsequent [1,2]-boryl migration is mediated by $BF_3{\cdot}OEt_2$ to yield the desired α-boryl aldehydes.[7,8] These compounds are isolated as white solids and are stable to aqueous workup, silica gel chromatography, and ambient conditions.

The unprecedented [1,2]-boryl shift was investigated by deuterium labeling experiments (Scheme 3). Rearrangement of d_1-epoxy MIDA boronates confirmed that [1,2]-boryl migration was proceeding to afford the boryl aldehyde and not a competing [1,2]-alkyl shift. Concurrent with the work performed in the Yudin lab, Burke and co-workers found that the pinene-derived iminodiacetyl (PIDA-) epoxy boronates rearranged in a similar fashion in the presence of $Mg(ClO_4)_2$ with complete stereoretention.[7,8,11]

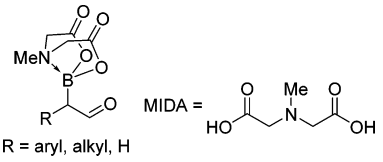
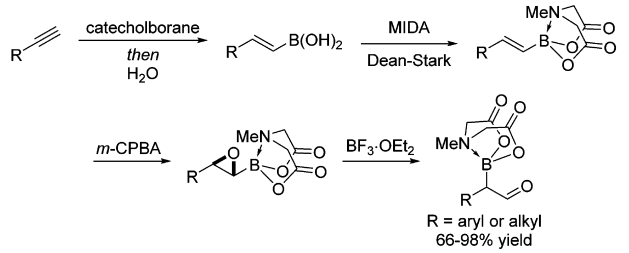
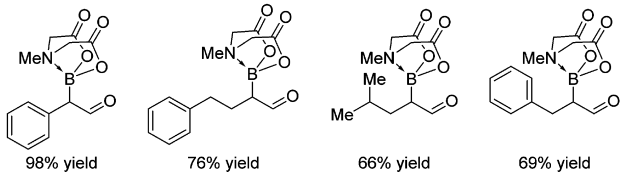


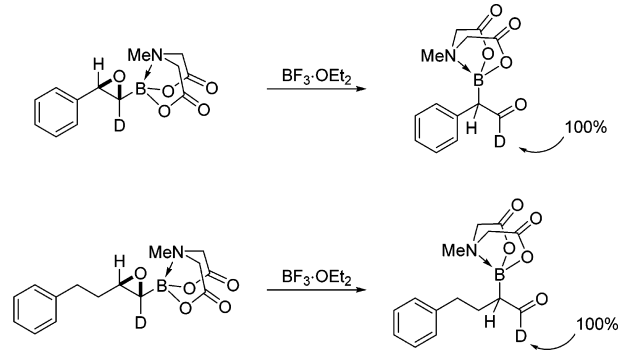
Figure 4. General structure of α-MIDA boryl aldehydes.

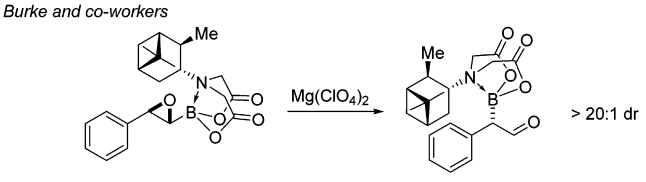
Scheme 2. General Preparation of α-MIDA Boryl Aldehydes





Scheme 3. Results of the BF_3-Promoted Rearrangement of Deuterium-Labeled Epoxy MIDA Boronates





TRANSFORMATIONS OF α-MIDA BORYL ALDEHYDES

In our initial report, the synthetic potential of α-MIDA boryl aldehydes was investigated.[7] Exploitation of the electrophilic aldehyde toward addition reactions includes the formation of

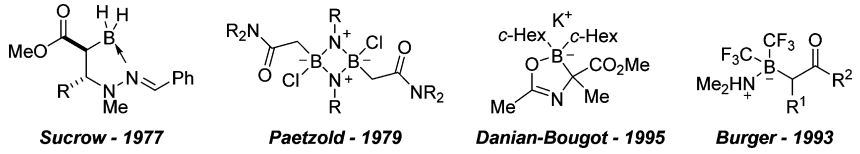


Figure 3. Examples of isolable α-boryl carbonyls.[6]

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the geometrically pure (*E*)-α-boryl-α,β-unsaturated esters via stabilized phosphorus ylide addition, *gem*-dibromoallyl MIDA boronates, and allyl indium addition, affording the homoallylic 1,2-boryl alcohols (Figure 5).[7,10] In all examples, the C−B bond was preserved, thereby affording a synthetic handle for further functionalization.

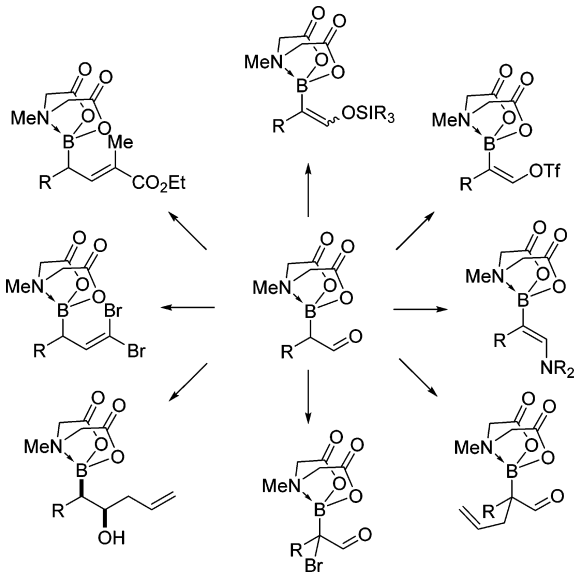


Figure 5. Synthetic transformations of α-boryl aldehydes.

Enolization of α-boryl aldehydes was also investigated. By careful control of the reaction conditions, we deduced that a combination of Et_3B and Et_3N resulted in the formation of the bis-boryl enolate. The potential of the bis-boryl enolate toward α-functionalization was then explored via Tsuji−Trost type chemistry.[12] The Pd-catalyzed α-alkylation of the bis-boryl enolates with allylic alcohols affords the expected quaternary products.[13,14] The palladium-catalyzed α-alkylation of unsymmetrical allylic alcohol derivatives was found to be under kinetic control with only the linear, trans isomer being isolated (Scheme 4).

The products of this catalytic alkylation reaction were suitable for downstream transformations, such as protection and alkaline oxidation of the C−B bond to afford the tertiary homoallylic alcohol (Scheme 5). In addition, the boryl aldehyde could also be oxidized to the carboxylic acid via conditions reported by Pinnick.[15] The resulting configurationally stable α-boryl carboxylic acid could then be methylated, affording the α-boryl methyl ester or, through a Curtius rearrangement, yielding α-boryl isocyanates.[16] These bench-stable molecules can then be subjected to various nucleophiles, including amines, alcohols, and acids to afford a range of boron-containing materials (Scheme 6). These manipulations not only leave the C−B bond intact but also provide convenient access to complex sp^3-boron-containing amines, ureas, and carbamates.[17]

The synthetic utility of the bis-boryl enolate led to further investigation in other enolization protocols. In this regard, silyl-enol ether and enol triflates could be obtained in high yields via trapping of the enolate intermediate. The successful isolation of the silyl-enol ether MIDA boronates results in a highly functionalized substrate (Scheme 7). Utilization of the vinylic C−B bond was investigated in the Petasis borono−Mannich reaction. The sp^3-MIDA boronate proved unreactive under standard reaction conditions, which is why it was necessary to effect trans-esterification of MIDA to the pinacol ester. These boronic esters were then subjected to the Petasis borono−Mannich reaction with a range of primary amines and glycolic acid resulting in the preparation of a wide variety of unnatural amino acid derivatives. The chemoselective engagement of both the nucleophilic C−B bond and electrophilic aldehyde components represents an important advance of α-boryl carbonyl chemistry and amphoteric molecules in general.[7]

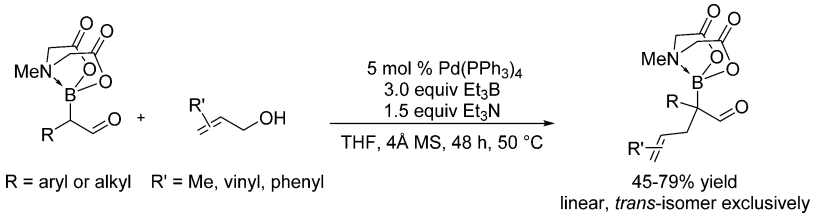
Given the stability of the MIDA ligand to displacement by external nucleophiles, the presence of an enolizable aldehyde encouraged the evaluation of its transformation into the boryl-enamine functional group. Initial attempts at the formation of the boryl-enamine with primary amines and α-boryl aldehydes resulted in the quantitative *C* → *N* boryl migration with preservation of the MIDA ligand (Scheme 8).[7] Although an interesting result, there is limited synthetic potential for these *N*-boryl enamines because the B−N bond is readily hydrolyzed upon workup.

Mitigation of this rearrangement would result in the preservation of the boryl-enamine functionality. After crucial NMR experiments, it was found that within 10 min, there is complete consumption of boryl aldehyde substrate and primary amine, resulting in a mixture of imine and enamine tautomers. Trapping of the imine/enamine mixture in situ with acyl chlorides resulted in the formation of the corresponding boryl enamides without any products from *C* → *N* boryl migration (Scheme 9).[18] This trapping methodology enables a wide range of borylated enamides that are otherwise impossible or difficult to produce via other methods.[19]

The design of the three-component boryl enamide synthesis resulted in a highly divergent method to access a number of boron-containing scaffolds. It was found that, in addition to the parent boryl aldehyde, 4-methylphenyl boryl aldehyde resulted in the trisubstituted boryl enamide product. Examination of the trisubstituted enamide by single-crystal X-ray analysis revealed the absence of conjugation between the vinyl boronate and amide functional groups (Figure 6).[18]

The synthesis of boryl enamides led us to evaluate their reactivity and applications toward nitrogen-containing heterocycles. Exposure of the halogenated boryl enamides to palladium catalysis resulted in the regioselective intramolecular

Scheme 4. Palladium-Catalyzed Tsuji−Trost Alkylation of Boryl Aldehydes



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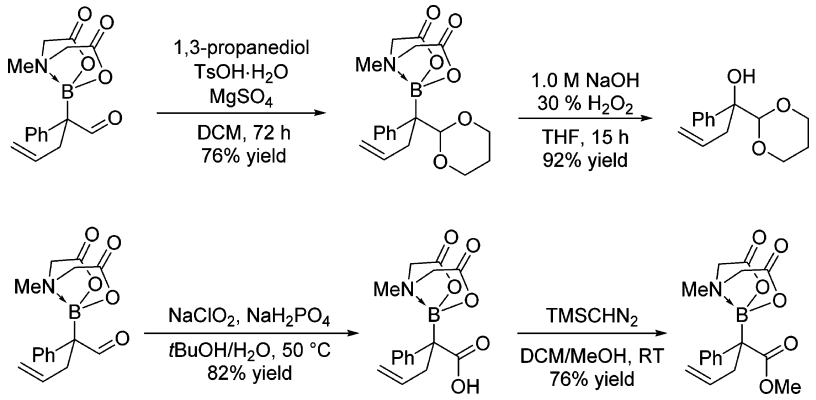
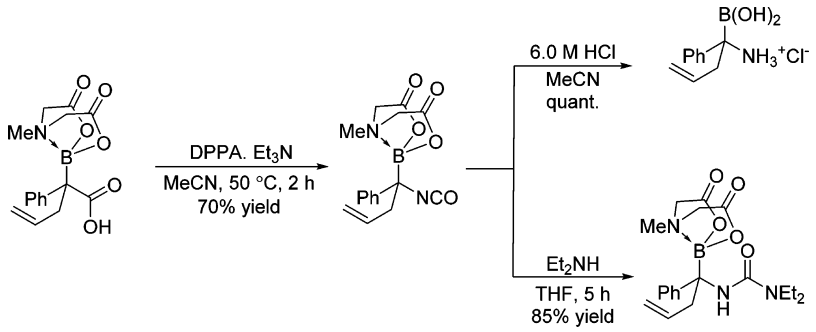
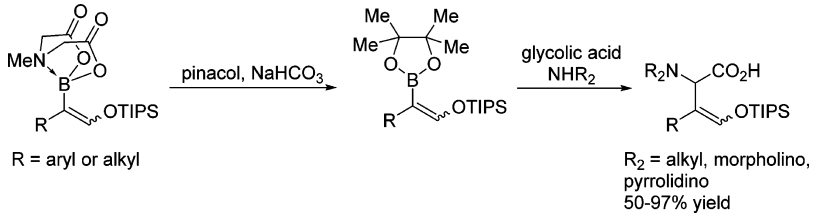
Scheme 5. Transformations of the Quaternary Boryl Aldehyde



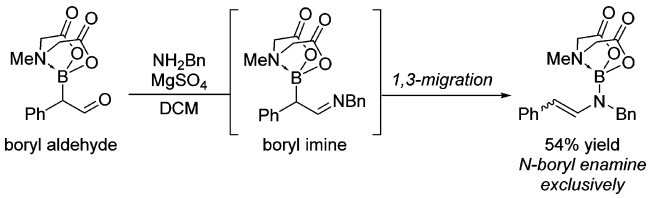
Scheme 6. Synthetic Application of Quaternary Boryl Carboxylic Acids



Scheme 7. Petasis Reaction of Vinyl Boronic Acids Derived from α-Boryl Aldehydes

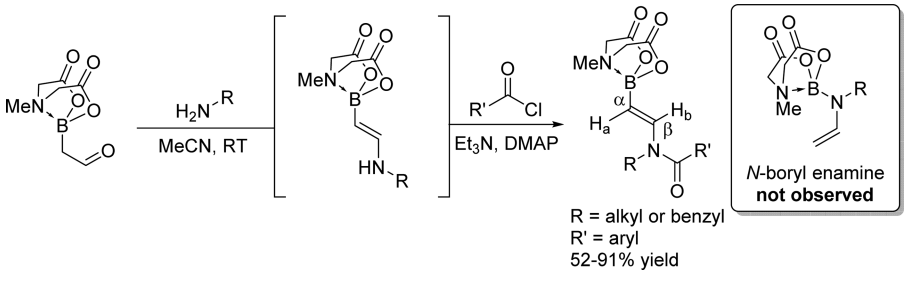


Scheme 8. Primary Amine Condensation Yields *N*-Boryl Enamine via *C* → *N* Boryl Migration



cyclization to afford the corresponding isoindolone products. Not only is the C−B bond preserved under these palladium-catalyzed conditions, but also this Heck process proceeds through a rare B−C−Pd^{II} intermediate (Scheme 10).[20] In contrast to the observed stabilization of σ-alkyl-Pd^{II} intermediates by adjacent sp^2-hybridized boron centers, this intermediate is proposed to undergo rapid β-hydride elimination as a result of the destabilizing nature of the electron-rich sp^3-boron center.[20b] To facilitate the isolation

Scheme 9. Boryl Enamides via Three-Component Condensation/Acylation Reaction



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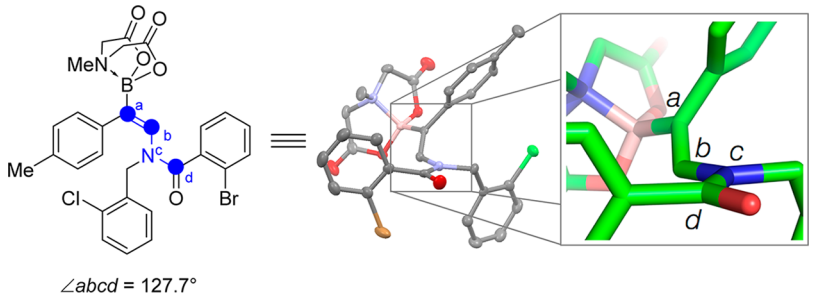
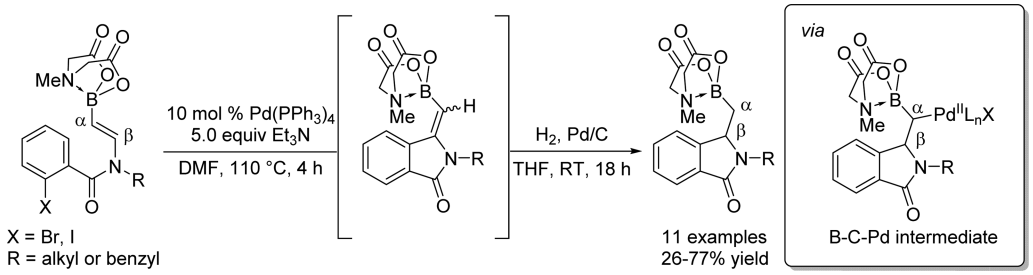
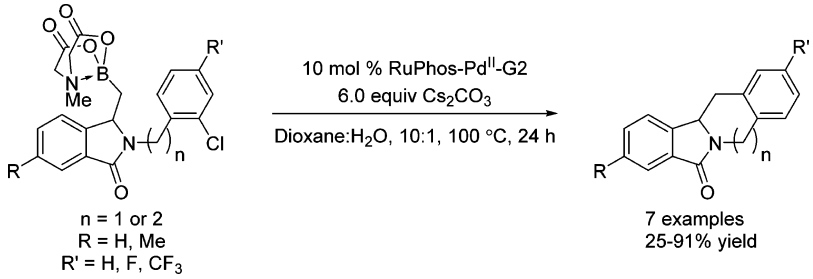


Figure 6. X-ray structure of trisubstituted enamide. Hydrogen atoms are omitted for clarity. Inset: Zoom-in of enamide geometry.

Scheme 10. Boromethyl Isoindolones via 5-exo-trig Cyclization of α-Boryl Enamides



Scheme 11. Tetracycle Synthesis via Intramolecular Suzuki–Miyaura Cross-Coupling of MIDA Boronate



process, the crude material was reduced to yield the sp^3-alkyl MIDA boronate product.

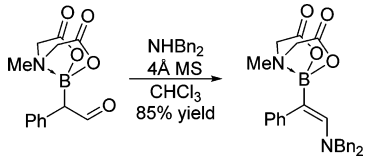
Functionalization of the sp^3-MIDA boronate was next investigated for the complete realization of linchpin reactivity of the boryl aldehyde starting material. To realize this potential, an intramolecular Suzuki–Miyaura cross-coupling (SMCC) reaction was attempted with the appropriately substituted isoindolones, resulting in the formation of a variety of tetracycles, including the [6.5.7.6] scaffold (Scheme 11). There have been only three other examples of intramolecular SMCC affording small or medium ring systems.[21] The lack of precedence is attributed to the challenges associated with transmetalation to form the medium-sized ring palladacycles.

BORYL ENAMINES AS REACTIVE INTERMEDIATES

The condensation of primary amines with boryl aldehydes required an in situ trap to avoid *C* → *N* boryl migration. In contrast, we have found that secondary amines do not result in similar boryl migration and form stable boryl enamines, which can be isolated via chromatography (Scheme 12). Alternatively, substoichiometric loading of secondary amine coupled with the reversible nature of enamine formation can be utilized for catalytic transformations.[22]

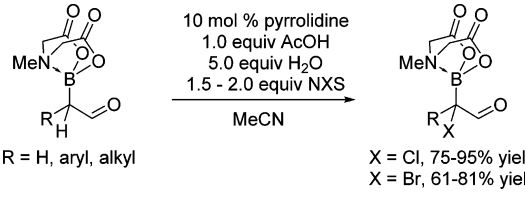
The catalytic potential of transient boryl enamines was initiated with electrophilic halogenation reagents. In the presence of only 10 mol % pyrrolidine and NBS, the

Scheme 12. Synthesis and Isolation of Dibenzyl Borylenamine



halogenation reaction of a range of boryl aldehydes resulted in the desired α-bromo product in good yields (Scheme 13).[18] The methodology was also applicable to enamine chlorination. Notably, there were no products from oxidative halodeborylation.[23] This result suggests that the reactivity of the boryl enamine intermediate toward electrophilic halogenation versus halodeborylation is a favored process.

Scheme 13. Catalytic Boryl Enamine Halogenation



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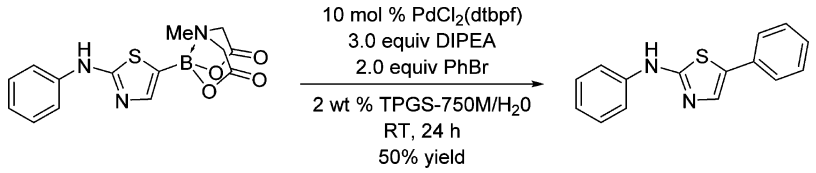
Scheme 14. Regioselective 2-Substituted 5-Boryl Thiazole Synthesis

Scheme 15. Suzuki–Miyaura Cross-Coupling of 2-Substituted 5-Boryl Thiazoles

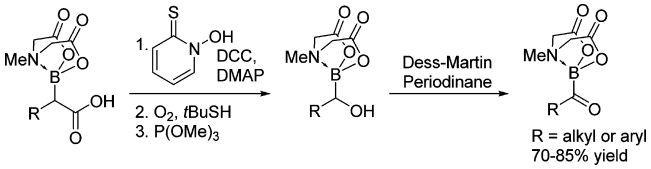


The densely functionalized parent bromo boryl aldehyde, whereby electrophile and nucleophile components exist on the same carbon, enables further functionalization based upon the innate reactivity of the substrate. Annulation of parent boryl aldehyde with a variety of thioamides and thioureas affords the corresponding thiazoles as single regioisomers (Scheme 14). This type of reactivity is unique because this annulation requires the S_N2 reaction at a nucleophilic carbon. This method generates important heterocycle but also avoids the challenges associated with a deprotonation/borylation sequence which commonly results in a mixture of regioisomers.[24]

Realization of the synthetic potential of these valuable heterocycles was a challenge because the 2-borylheterocycles are notoriously unstable.[9b,25] Through tremendous efforts in screening, it was found that the surfactant TPGS-750-M, pioneered by Lipshutz and co-workers, offered the enabling features to promote an efficient SMCC reaction of 2-substituted 5-boryl thiazoles (Scheme 15).[18,26] This development, in addition to the work by Burke and co-workers on the SMCC reaction of 2-pyridyl MIDA boronates,[25a] should find further application of 2-boryl heterocycles in medicinal chemistry and materials science.

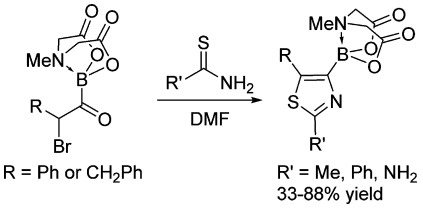
Barton esters of carboxylic acids are known to undergo radical decomposition to introduce hydroxyl groups in the presence of oxygen gas;[27] therefore, it was envisioned that the Barton ester of boryl carboxylic acids would afford an efficient entry into α-hydroxy MIDA boronates. Irradiation of the α-boryl Barton ester with a 250 W tungsten–halogen lamp in the presence of O_2 and *tert*-butyl thiol afforded the corresponding α-hydroxy MIDA boronates (Scheme 16).[28] In general, aryl-substituted α-boryl Barton esters resulted in the formation of a number of unidentifiable side-products as compared with the alkyl-substituted α-boryl Barton esters. This is attributed to the delocalization of the benzylic α-boryl radical. Oxidation of the α-hydroxy boronates was accomplished with Dess–Martin periodinane, which afforded the acyl boronate functional group.[29,30]

Scheme 16. Synthesis of the α-Hydroxy MIDA Boronate and Acyl MIDA Boronate



Alkyl-substituted acyl boronates participate in a number of transformations that enolize the α-position. Notably, exposure of the alkyl acyl boronates to Br_2 in 1,4-dioxane/DCM affords the corresponding α-bromo acyl boronate. As was the case with α-bromo boryl aldehyde, condensation with thioamides and thioureas in DMF at elevated temperatures affords the trisubstituted 4-boryl thiazoles (Scheme 17).[28] The use of α-bromo-acyl boronates and α-bromo boryl aldehydes as linchpin reagents permits access to both 4- and 5-boryl thiazoles with full control of regiochemistry.

Scheme 17. Regioselective Synthesis of 4-Boryl Thiazoles



CONCLUSION

Since the initial report on [1,2]-boryl migration of epoxy-MIDA boronates yielding α-MIDA boryl aldehydes, there has been an intense investigation into the utility of these amphoteric molecules as linchpin reagents. This study has seen the development of regio- and chemoselective transformations, enabling access to a number of boron-containing heterocycles. It is projected that our novel linchpins will enable access to other carbocyclic scaffolds that are difficult or impossible to synthesize via traditional means as well as exploration into chemoselective transformations.

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Notes

The authors declare no competing financial interest.

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