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Air- and Moisture-Stable Amphoteric Molecules: Enabling Reagents in Synthesis

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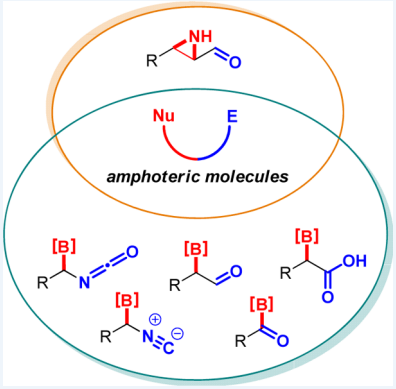
CONSPECTUS: Researchers continue to develop chemoselective synthesis strategies with the goal of rapidly assembling complex molecules. As one appealing approach, chemists are searching for new building blocks that include multiple functional groups with orthogonal chemical reactivity. Amphoteric molecules that possess nucleophilic and electrophilic sites offer a versatile platform for the development of chemoselective transformations. As part of a program focused on new methods of synthesis, we have been developing this type of reagents.



This Account highlights examples of amphoteric molecules developed by our lab since 2006. We have prepared and evaluated aziridine aldehydes, a class of stable unprotected α-amino aldehydes. Structurally, aziridine aldehydes include both a nucleophilic amine nitrogen and an electrophilic aldehyde carbon over the span of three atoms. Under ambient conditions, these compounds exist as homochiral dimers with an aziridine-fused five-membered cyclic hemiaminal structure. We have investigated chemoselective reactions of aziridine aldehydes that involve both the aziridine and aldehyde functionalities. These transformations have produced a variety of densely functionalized nitrogen-containing compounds, including amino aldehydes, 1,2-diamines, reduced hydantoins, *C*-vinyl or alkynyl aziridines, and macrocyclic peptides.

We have also developed air- and moisture-stable α-boryl aldehydes, another class of molecules that are kinetically amphoteric. The α-boryl aldehydes contain a tetracoordinated *N*-methyliminodiacetyl (MIDA) boryl substituent, which stabilizes the α-metalloid carbonyl system and prevents isomerization to its *O*-bond enolate form. Primarily taking advantage of chemoselective transformations at the aldehyde functionality, these α-boryl aldehydes have allowed us to synthesize a series of new functionalized boron-containing compounds that are difficult or impossible to prepare using established protocols, such as α-borylcarboxylic acids, boryl alcohols, enol ethers, and enamides. Using α-borylcarboxylic acids as starting materials, we have also prepared several new amphoteric borylated reagents, such as α-boryl isocyanates, isocyanides, and acylboronates. These compounds are versatile building blocks in their own right, enabling the rapid synthesis of other boron-containing molecules.

1. INTRODUCTION: AMPHOTERIC MOLECULES

The term "amphoteric" originates from the Greek word "amphoteros", which literally means "both of two".[1] In acid/base chemistry, the concept of amphoterism has been used in reference to molecules that behave both as a Brønsted acid and a base. For instance, α-amino acids are amphoteric. They exemplify thermodynamic amphoterism characterized by the reversibility of the diffusion-limited proton transfer.

Molecules that contain both nucleophilic (Nu) and electrophilic (E) sites are considered kinetically amphoteric.[2] Such molecules can be systematically classified as [1,*n*] systems depending on the distance between the Nu and E sites. The well-known isocyanides are prototypical amphoteric molecules of the kinetic class. The terminal carbon of an isocyanide functional group displays both electrophilic and nucleophilic properties, which is why isocyanides are said to belong to the [1,1] group. The amphoteric nature of isocyanides is instrumental in multicomponent transformations such as the Passerini three-component reaction (P3CR) and the Ugi four-component reaction (U4CR).[3] In these processes, the isocyanide terminal carbon establishes a connection with both the carboxylic acid (nucleophile) and the aldehyde or imine (electrophile) in a chemoselective fashion.

The search for kinetically amphoteric molecules is a promising strategy for the development of new synthetic methods. In the past several years, our research has been focused on amphoteric building blocks. This undertaking has enabled efficient and selective synthesis of a range of densely functionalized molecules with interesting biological[4] and synthetic applications. In this Account, a variety of new amphoteric reagents developed by our group, including [1,3], [1,2], and [1,1] amphoteric systems, is discussed. We also describe the mechanistic underpinnings behind the reactivity profiles of our reagents.

2. THE [1,3] AMPHOTERIC SYSTEM: UNPROTECTED AZIRIDINE ALDEHYDES

The versatility of amine and aldehyde functionalities in chemical synthesis makes α-amino aldehydes an attractive class of [1,3] amphoteric building blocks. However, an amine and an aldehyde typically do not coexist for a prolonged period of time without undergoing inter- or intramolecular condensation or

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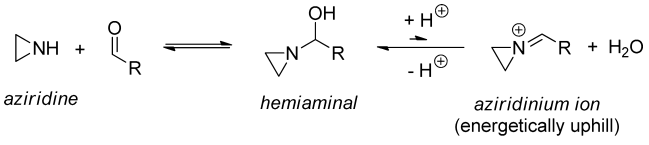
decomposition via hemiaminal, imine, or enamine formation.[5] This poses a challenge to the preparation and synthetic application of unprotected amino aldehydes.[6]

In contrast to typical primary or secondary amines, three-membered cyclic amines, aziridines, provide a means of inhibiting the formation of imines and iminium ions. The high kinetic barrier to the formation of an aziridinium ion obstructs the amine/aldehyde condensation (Scheme 1), thereby preventing decomposition of the

Scheme 1. Formation of Aziridinium Ions from Aziridines and Aldehydes

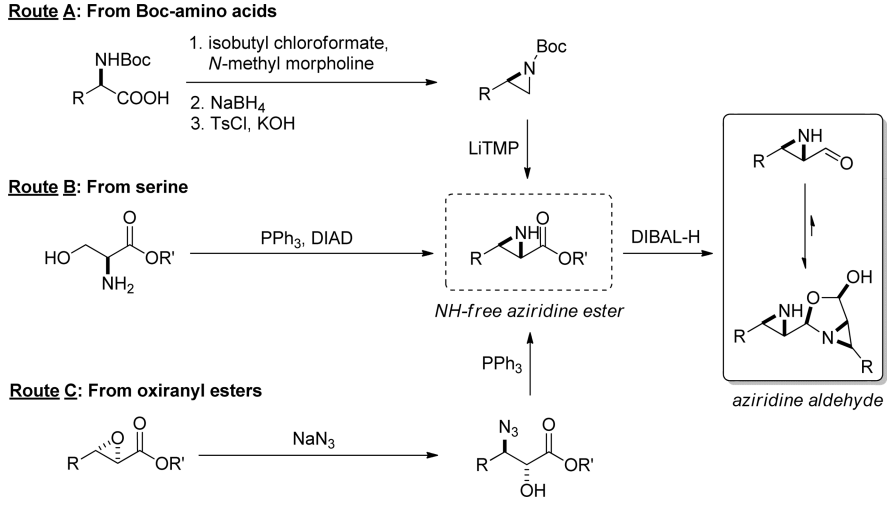


amino aldehyde system.[7] Based on this fact, our group has synthesized a new class of bench-stable unprotected α-amino aldehydes, aziridine aldehydes, via DIBAL-H reduction of the corresponding *NH*-free aziridine esters (Scheme 2).[8,9] There are three approaches to the synthesis of the aziridine ester precursors. Route A employs a lithiation-promoted *N*-to-*C* Boc-transfer of the Boc protected aziridine,[10] which can be obtained from the corresponding Boc-protected α-amino acid through a sequence of transformations involving carbamate formation, sodium borohydride reduction, tosylation, and cyclization. Route B uses serine as the starting material. After converting the α-amino acid to its corresponding ester, a Mitsunobu reaction generates the *NH*-free aziridine ring. Route C starts with oxiranyl carboxylic esters. The ring-opening of epoxides with sodium azide is followed by a Staudinger reaction to install the aziridine ring.

The molecules of aziridine aldehydes rest as dimers possessing the aziridine-fused five-membered ring structure under ambient conditions (Figure 1). The dimerization process is believed to proceed via an open-dimer intermediate generated from the attack of the nucleophilic nitrogen of one aziridine aldehyde monomer to the aldehyde moiety of another (Scheme 3). No evidence of monomers or dimeric six-membered symmetrical hemiacetal rings has been obtained in solution. A crystal structure of the phenyl-substituted aziridine aldehyde dimer has revealed that the compound exists as a single diastereomer. A hydrogen bonding interaction between the aziridine NH and the hemiacetal was observed (Figure 2). This interaction, in addition to the intrinsic kinetic barrier to aziridinium ion formation, is believed to contribute to the stability of homochiral aziridine aldehyde dimer molecules.

Since their discovery, aziridine aldehyde dimers have been studied to determine whether their amine and aldehyde functionalities can be functionalized separately or simultaneously in a single transformation. This program started with tests of aziridine aldehyde dimers under reduction and reductive amination conditions (Scheme 4A).[8] When treated with sodium borohydride in a methanol−tetrahydrofuran solvent system, the aziridine aldehyde dimer being tested produced the corresponding aziridine alcohol in quantitative yield. Reactions in the presence of aniline and sodium cyanoborohydride afford vicinal aziridine amines. These results reveal the reversibility of the formation/dissociation of hemiacetal

Scheme 2. Synthetic Routes to Unprotected Aziridine Aldehydes



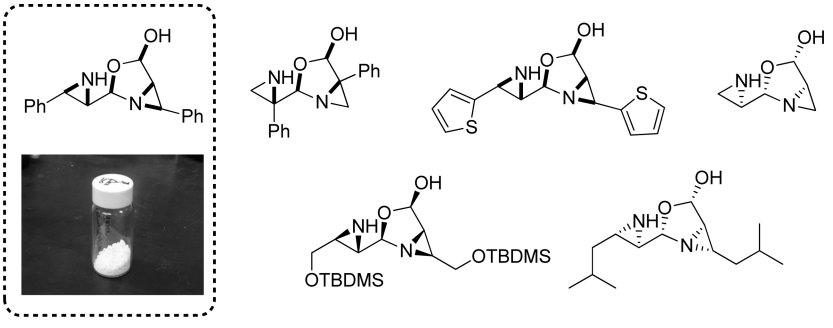


Figure 1. Examples of aziridine aldehyde dimers.

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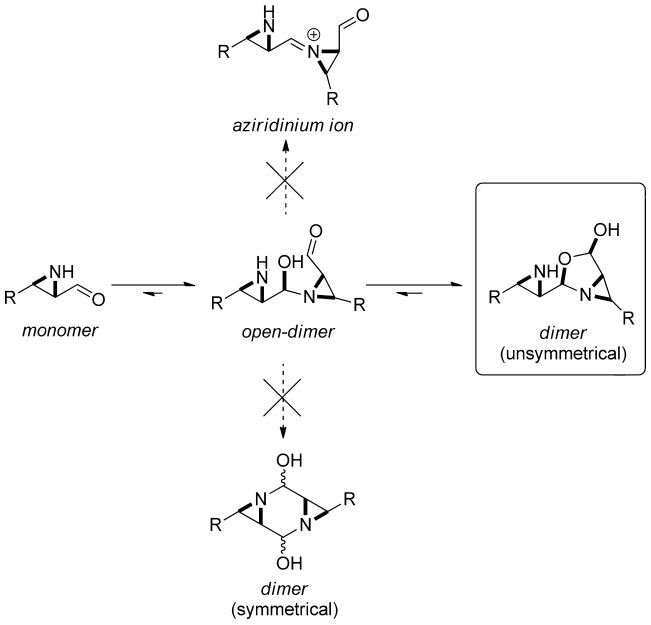
Scheme 3. Dimerization of Aziridine Aldehydes



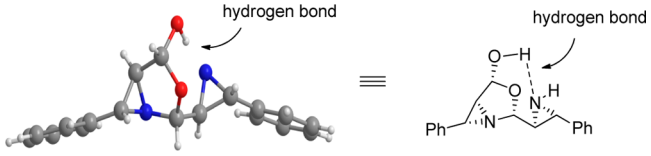
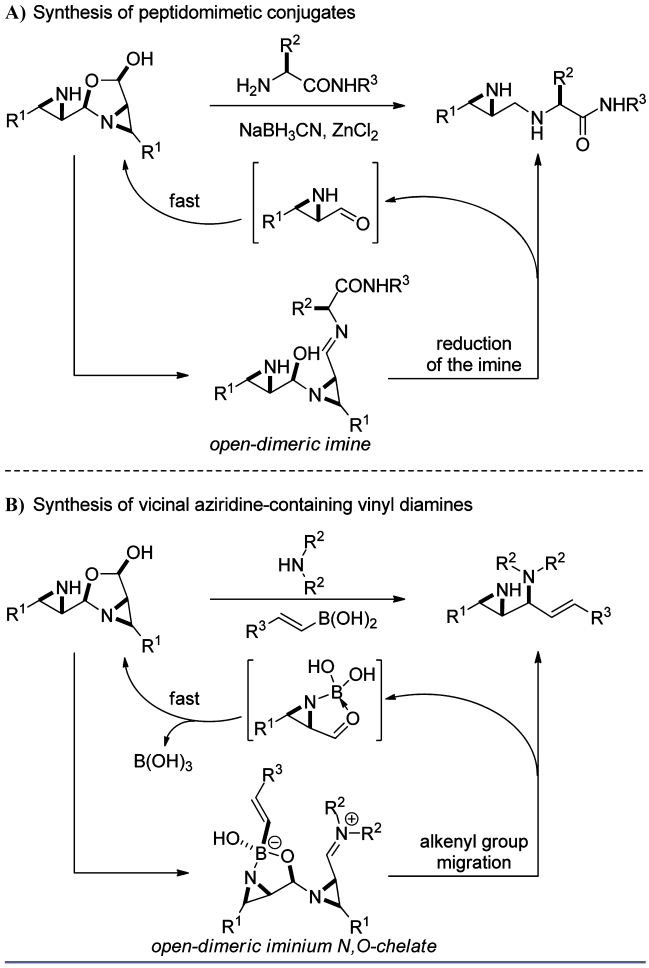


Figure 2. X-ray structure of *trans*-phenylaziridine aldehyde dimer.

structures in aziridine aldehyde dimers, which release the aldehyde functional group for attack by external nucleophiles (Scheme 4B). Kinetic studies[9] demonstrate that the partial dissociation from dimers to open-dimer intermediates is the rate-limiting step for these transformations. However, a simple first-order relationship in the dimeric aziridine aldehyde has not been observed. This could be attributed to a fast redimerization of the remaining half of the original aziridine aldehyde dimer after consumption of the exposed aldehyde group, which provides a feedback to the starting material pool. Although they rest as dimers under ambient conditions, aziridine aldehydes are synthetically equivalent to their corresponding monomeric structures.

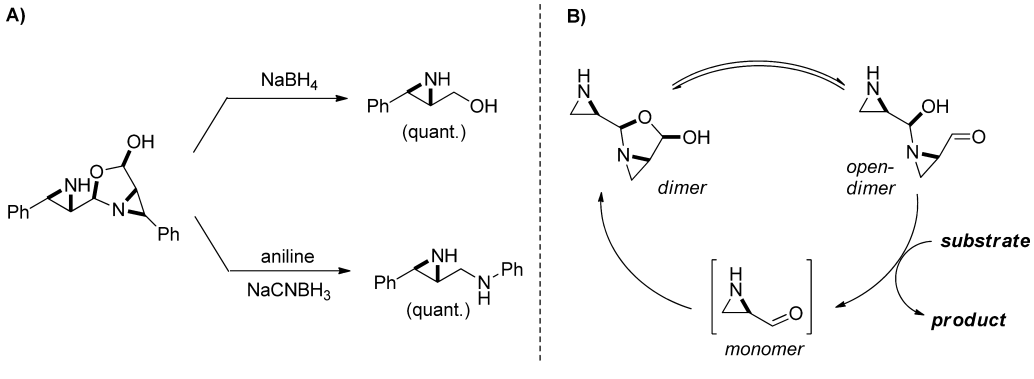
Similarly, treatment of aziridine aldehyde dimers and natural amino acid derivatives with sodium cyanoborohydride in the presence of zinc chloride has provided a facile protecting-group-free

Scheme 5. Synthesis of Diamine Derivatives from Aziridine Aldehyde Dimers



synthesis of peptidomimetic conjugates equipped with aziridine amine linkages (Scheme 5A).[11a] No epimerization or overalkylation has been observed in this transformation. The absence of epimerization is attributed to the energetically uphill enolization of the strained aziridine aldehyde and the short lifetime of the open-dimeric imine intermediate. It is hypothesized that the steric hindrance of the open-dimer intermediate and the low concentration of the free monomeric aldehyde prevent overalkylation. Vicinal aziridine-containing vinyl diamines have been obtained by subjecting aziridine aldehyde dimers to the borono-Mannich reaction.[11b] This process exemplifies the first exclusively *syn* selective borono-Mannich process that generates aziridine-containing vicinal diamine products.

Scheme 4. Reductive Transformation of Aziridine Aldehyde Dimers and General Dissociation/Feedback Mechanism



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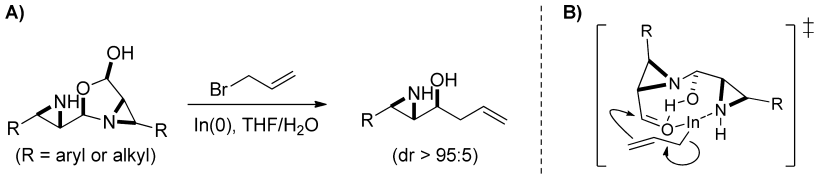
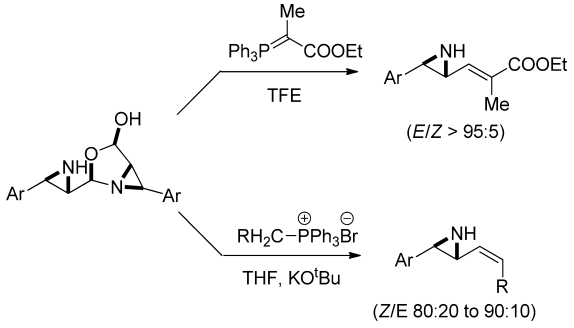
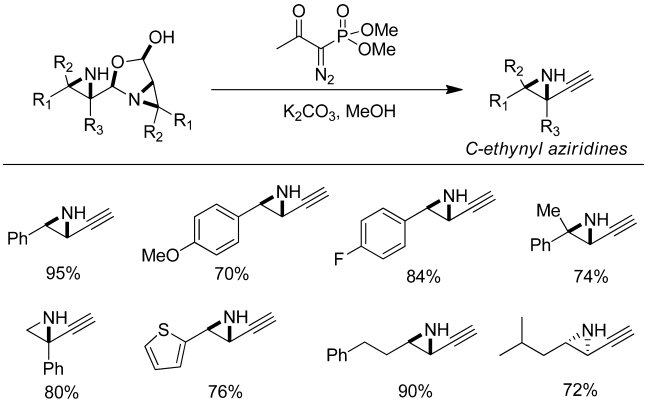
Scheme 6. Indium(0)-Mediated Diastereoselective Allylation of Aziridine Aldehydes



Scheme 7. Preparation of *C*-Vinyl Aziridines from Aziridine Aldehydes



Scheme 8. Preparation of *C*-Ethynyl Aziridines from Aziridine Aldehydes



A mechanistic rationale explaining the observed stereoselectivity involves a half-open dimeric iminium *N*,*O*-chelate, which undergoes alkenyl group migration onto the *si* face of the iminium ion (Scheme 5B). The aziridine-containing diamines were found to exhibit high solvent and nucleophile dependent regioselectivity of ring-opening to produce 1,2- or 1,3-diamines containing three contiguous stereocenters.

The electrophilic reactivity of the aldehyde functionality in aziridine aldehydes has been further evaluated in an indium(0)-mediated allylation. Treatment of aziridine aldehyde dimers with allyl bromides in the presence of indium(0) metal using tetrahydrofuran−water as the solvent system affords a range of aziridine alcohols as single diastereomers (Scheme 6A).[12] The reaction is also believed to occur via an open-dimer intermediate. DFT analysis of the transition structure of the transformation is consistent with a pocket made of one nitrogen and two oxygen atoms surrounding the indium center (Scheme 6B). This organized transition structure would account for the high level of diastereoselectivity of the transformation.

Other functionalizations of the aldehyde moiety of aziridine aldehydes include its conversion to carbon−carbon multiple bonds by using nucleophilic phosphorus reagents. Horner−Wadsworth−Emmons or Wittig reactions of aziridine aldehyde dimers in 2,2,2-trifluoroethanol (TFE) or anhydrous tetrahydrofuran afford unprotected *C*-vinyl aziridines (Scheme 7).[13] In addition, treatment of aziridine aldehydes under conditions for Seyferth−Gilbert homologation in methanol using the Bestmann−Ohira reagent successfully provides *NH*-free *C*-ethynyl aziridines in good yields (Scheme 8).[14] These aziridine/π conjugating molecules have proven versatile in the synthesis of nitrogen-containing compounds.

In order to expand the synthetic applications of amphoteric aziridine aldehydes, reactions involving the nucleophilic aziridine nitrogen have also been investigated. Assisted by initial interaction of the aldehyde functionality with nucleophiles, the aziridine nitrogen could participate in the downstream transformation of a cascade process. It has been found that reactions between aziridine aldehyde dimers and *N*-benzyl tryptamine result in complex pentacyclic alkaloid cores through a single cascade transformation in TFE or toluene (Scheme 9).[8] The structure of the products implies that an intercepted Pictet−Spengler reaction,[15] initiated by the trapping of the aldehyde functional group via iminium ion formation, has taken place. The electrophilic aromatic addition of the iminium ion to the *ipso*-position of the indole ring constructs a *spiro* five-membered ring with concomitant generation of a cyclic iminium ion. The nascent iminium ion is subsequently attacked by the aziridine nitrogen intramolecularly to afford the final pentacyclic scaffold. Stereoselectivity of this transformation can be controlled by selecting solvent media and temperature. When the reaction is carried out in toluene at 80 °C, a 1:2 diastereomeric mixture of pentacycles **I** and **II** is isolated. On the other hand, reactions in protic solvent TFE at −20 °C result in exclusively *syn*-product **I** (dr > 20:1) in nearly quantitative yield.

By utilizing both the aldehyde and aziridine nitrogen reactivity in an intercepted Ugi-type transformation, our group has developed a macrocyclization of linear peptides using amphoteric aziridine aldehydes.[16] When treated with terminally unprotected linear peptides and *tert*-butyl isocyanide in TFE or 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), aziridine aldehydes produce macrocyclic peptide derivatives (Scheme 10). Unlike typical Ugi cyclizations using monofunctionalized aldehydes,[17] which usually afford low yields of cyclic peptides accompanied by poor diastereoselectivity and dominant cyclodimerization byproducts, the aziridine aldehyde-induced multicomponent macrocyclization affords high yields of expected cyclic peptide products with high diastereoselectivity. Epimerization has not been detected throughout the course of the reaction, nor during product isolation. This method produces peptide macrocycles at high molar concentrations. No dimerization or oligomerization byproducts of the starting peptides have been observed. A variety of challenging medium-sized rings have been readily prepared.

Mechanistically, the macrocyclization initially follows the course of a typical Ugi reaction using amino acids or peptides (Scheme 11). The iminium ion formation between the aldehyde center of an aziridine aldehyde and the N-terminus

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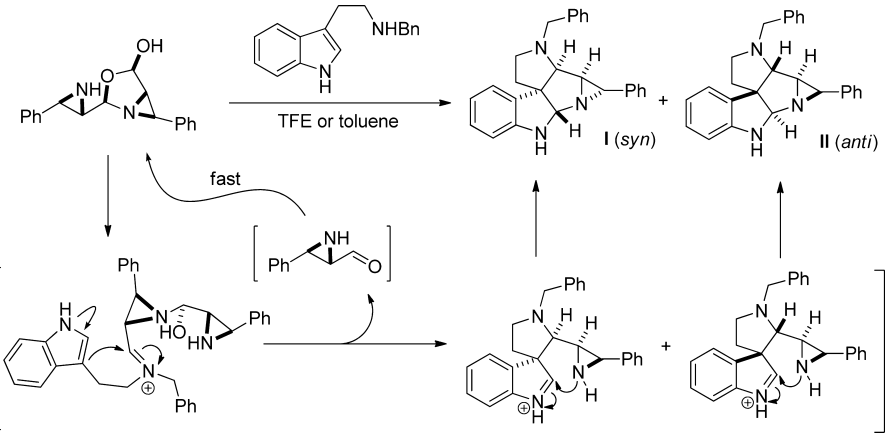
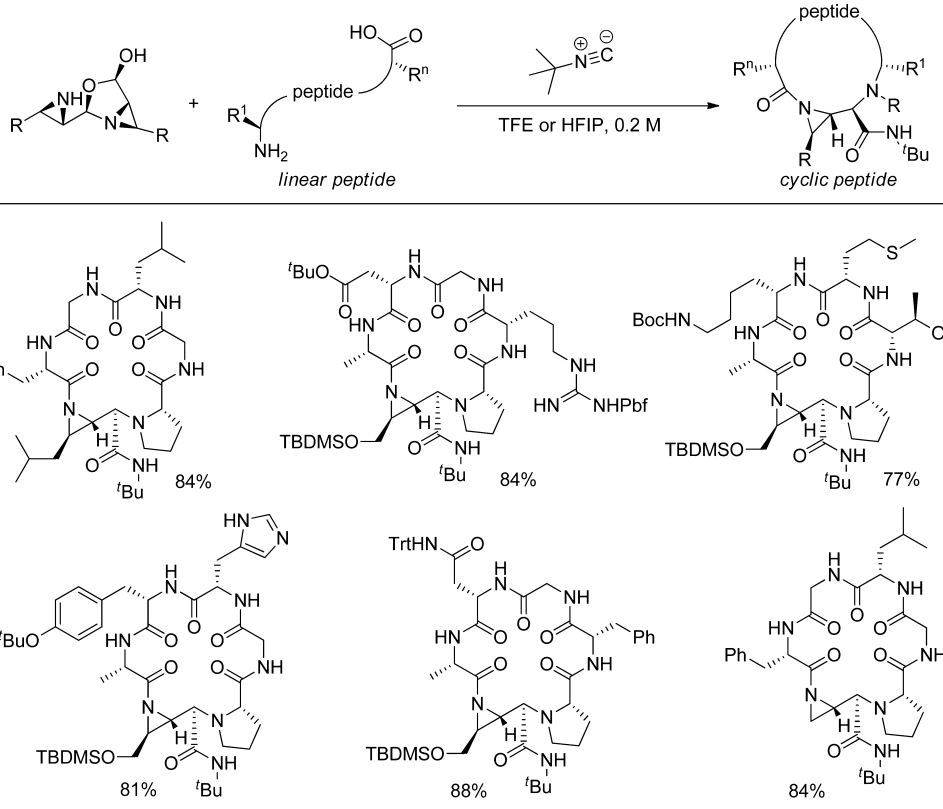
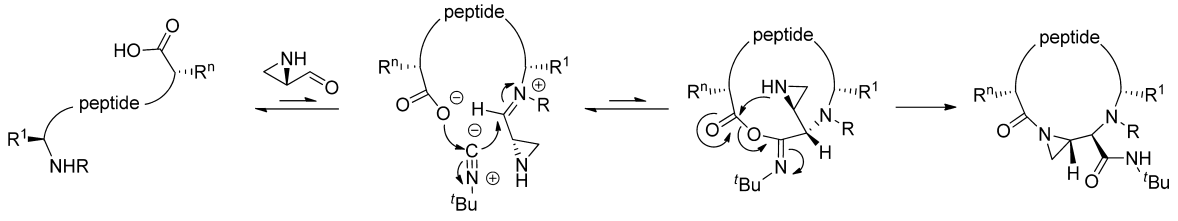
Scheme 9. Intercepted Pictet–Spengler Reaction of Aziridine Aldehydes



Scheme 10. Macrocyclizations of Linear Peptides Using Aziridine Aldehydes and Isocyanides



Scheme 11. Mechanism of Macrocyclization Mediated by Aziridine Aldehydes



of a linear peptide precursor is thought to occur via an electrostatically stabilized ion pair. After isocyanide α-addition resulting in formation of the cyclic mixed anhydride intermediate, the exocyclic nucleophilic aziridine undergoes a fast transannular attack to the activated C-terminus to provide the final macrocyclic system. It is believed that the presence of the nucleophilic aziridine nitrogen center at the α-position of the aldehyde functional group is responsible for the high yields and diastereoselectivities.

The reactivity of aziridine aldehydes is not limited to reactions initiated by the electrophilicity of the aldehyde functionality. Cascade processes starting directly with the

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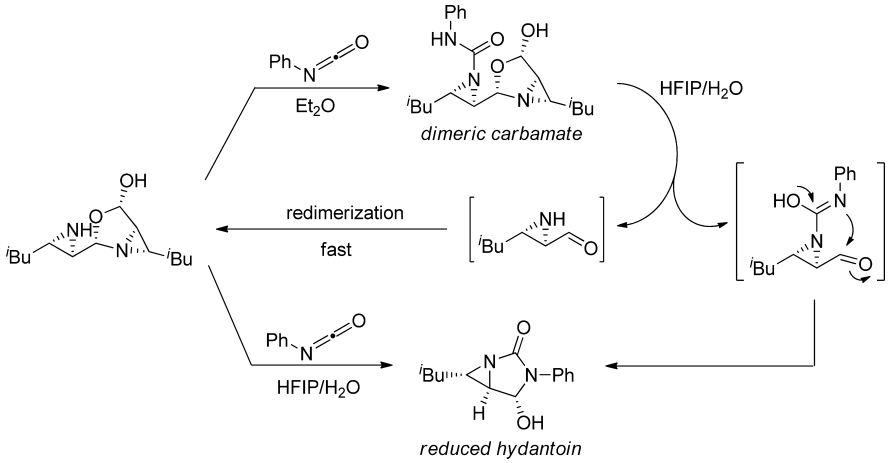
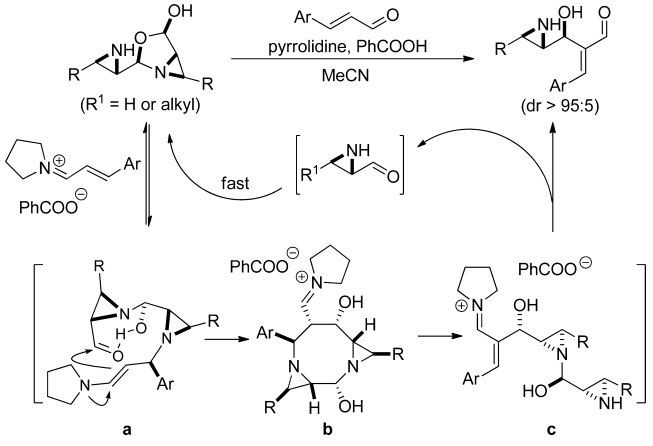
Scheme 12. Reactions between Aziridine Aldehyde Dimers and Isocyanates



nucleophilic attack of the aziridine nitrogen have also been developed. It has been shown that treatment of aziridine aldehyde dimers with phenyl isocyanate in diethyl ether affords dimeric carbamate derivatives in quantitative yield as a result of simple addition of the aziridine aldehyde dimer to the carbon−nitrogen double bond of the isocyanate (Scheme 12). In comparison, reactions in a protic HFIP/water (8:2 v/v) solvent system result in exclusive formation of an aziridine-fused bicyclic product (a reduced hydantoin, Scheme 12).[18] HFIP is believed to promote aziridine aldehyde dimer dissociation. The production of the reduced hydantoin product in HFIP/water is hypothesized to result from collapse of the dimeric carbamate intermediate followed by an intramolecular 5-(enol-*endo*)-*exo*-trig cyclization. This hypothesis is supported by the fact that the same hydantoin product is obtained when the dimeric carbamate intermediate, which is isolated from the reaction in diethyl ether, is subjected to the same HFIP/water solvent system.

Another reaction initiated by nucleophilic aziridine attack occurs when dimeric aziridine aldehydes are treated with α,β-unsaturated aldehydes in the presence of benzoic acid and pyrrolidine in acetonitrile.[19] Formal Baylis−Hillman products have been obtained with exclusive diastereoselectivity (Scheme 13). It is hypothesized that, in polar aprotic solvents, an eight-membered cyclic intermediate **b** is formed via initial attack of the available aziridine aldehyde dimer nitrogen to the α,β-unsaturated aldehyde, followed by intramolecular interaction between the enamine and the aldehyde group. Subsequent elimination of the aziridine regenerates the conjugated system **c**, which ultimately affords the final products. The released monomeric aziridine aldehyde again redimerizes to form the starting aziridine aldehyde dimer. The high diastereoselectivity of this process is likely a result of the rigid stereochemical environment supplied by the dimeric intermediate **a** (Scheme 13). The transition state is believed to exhibit an intramolecular hydrogen bond between the aldehyde oxygen and the hemiaminal hydrogen, which governs the facial selectivity for enamine attack on the aldehyde.

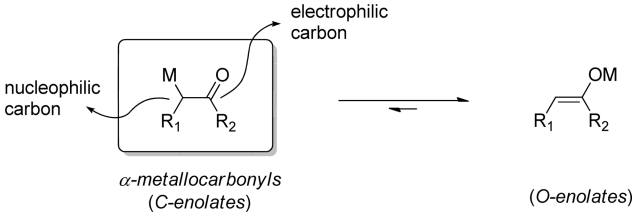
Scheme 13. Reactions between Aziridine Aldehyde Dimers and α,β-Unsaturated Aldehydes



3. THE [1,2] AMPHOTERIC SYSTEM: α-BORYL ALDEHYDES AND CARBOXYLIC ACIDS

The synthetic potential of amphoteric aziridine aldehydes equipped with the nucleophilic nitrogen and electrophilic carbon in a [1,3] relationship encouraged us to develop new types of stable amphoteric reagents for organic synthesis. In this regard, α-metallocarbonyl species (*C*-enolates) are valuable candidates for [1,2] amphoteric building blocks. Compared with their *O*-binding tautomers, α-metallocarbonyl compounds possessing main-group metals or metalloids are typically thermodynamically unstable and cannot be isolated under ambient conditions (Scheme 14). Development of stable amphoteric main-group α-metallocarbonyl reagents for common synthetic applications remains a challenge.

Scheme 14. Equilibrium between *C*- and *O*-Enolates



Some classes of relatively stable main-group α-metallocarbonyl compounds, although rare, have been described in the literature. The most extensively investigated case is that of α-silylcarbonyl compounds,[20] which can be isolated by silica gel

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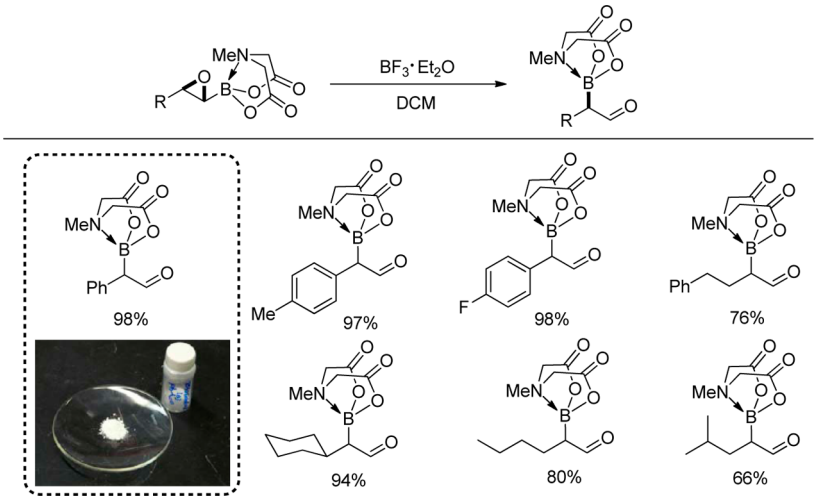
Scheme 15. BF_3-Promoted Rearrangement of Oxiranyl MIDA Boronates



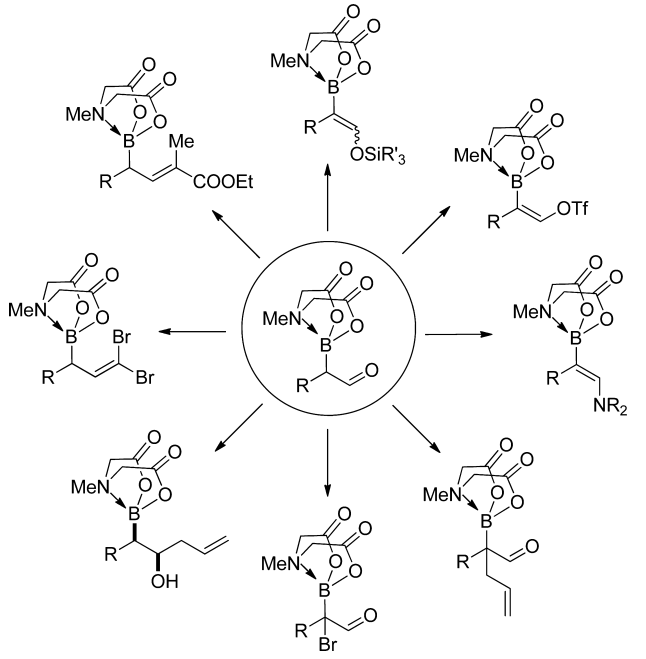
chromatography or distillation. From the stability of α-silylcarbonyl molecules, one can infer the possibility of stable α-metallocarbonyl compounds derived from another metalloid element, boron. However, *O*-bond boron enolates are much more thermodynamically stable than their *C*-bound isomers with a typical energy difference of ∼20 kcal/mol.[21] The strong affinity of electron-deficient sp^2-hybridized boron for oxygen provides the driving force for the isomerization.

A conceivable strategy for stabilization of 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.[22] Our group has recently discovered a class of stable amphoteric α-boryl aldehydes equipped with a tetracoordinated *N*-methyliminodiacetyl (MIDA) boryl group.[23] The molecules are prepared via a boron trifluoride-promoted rearrangement of oxiranyl MIDA boronates in dichloromethane at −30 °C (Scheme 15). Deuterium labeling experiments reveal that the epoxide rearrangement installs the α-boryl carbonyl system via an unprecedented 1,2-boryl migration. The resulting α-boryl aldehyde products have proven to be stable during aqueous work-up, silica gel chromatography, and storage in solid form at room temperature under air. A contemporaneous study by Burke and co-workers, utilizing diastereomerically pure oxiranyl pinene-derived iminodiacetyl (PIDA) boronates in a magnesium perchlorate-mediated epoxide rearrangement, reveals the stereospecificity of this class of transformation.[24]

The synthetic potential of α-boryl aldehydes has been extensively evaluated (Scheme 16).[23] Transformations of α-boryl aldehydes to the corresponding (*E*)-α-boryl-α,β-unsaturated esters, *gem*-dibromoallyl boronates, and boryl alcohols using corresponding nucleophilic reagents demonstrate the reactivity of the aldehyde moiety. Enolization of the aldehyde is possible leaving the MIDA boryl group at the α-position intact. A range of silyl or triflate enol ethers, enamines, and enamides are obtained by treating the α-boryl aldehyde with appropriate reagents under basic conditions. The synthetic potential of the enolizable α-boryl aldehydes is further demonstrated in their α-functionalization. Treatment of α-boryl aldehydes with bromine affords α-bromo-α-borylaldehyde as a crystalline product. Palladium-catalyzed α-allylation also supplies α-allylated boryl aldehydes with the MIDA boryl group intact.[25]

Besides the reactivity of the aldehyde moiety, chemoselective transformations of the carbon−boron bonds in the functionalized

Scheme 16. Synthetic Transformations of α-Boryl Aldehydes



vinyl boronates formally realize the nucleophilic reactivity of the original α-carbon of α-boryl aldehydes. These functionalized vinyl MIDA boronates are first transformed into the corresponding pinacolyl boronates, which are subsequently subjected to the Petasis reaction conditions with glyoxylic acid in the presence of different secondary or primary amines with HFIP as the solvent.[23] A series of unnatural amino acid derivatives has been prepared using this method (Scheme 17).

The stability of the MIDA boryl group toward various reaction conditions has encouraged us to evaluate the possibility of generating α-borylcarboxylic acids, another class of [1,2] amphoteric building blocks, from the corresponding aldehyde precursors. Treatment of α-boryl aldehydes under Pinnick oxidation conditions using sodium chlorite and sodium dihydrophosphate in the presence of cyclohexene in a mixture of *tert*-butanol and water results in oxidative conversion (Scheme 18).[26] A series of substituted α-borylcarboxylic acids are obtained as white solids. Like their aldehyde precursors, the

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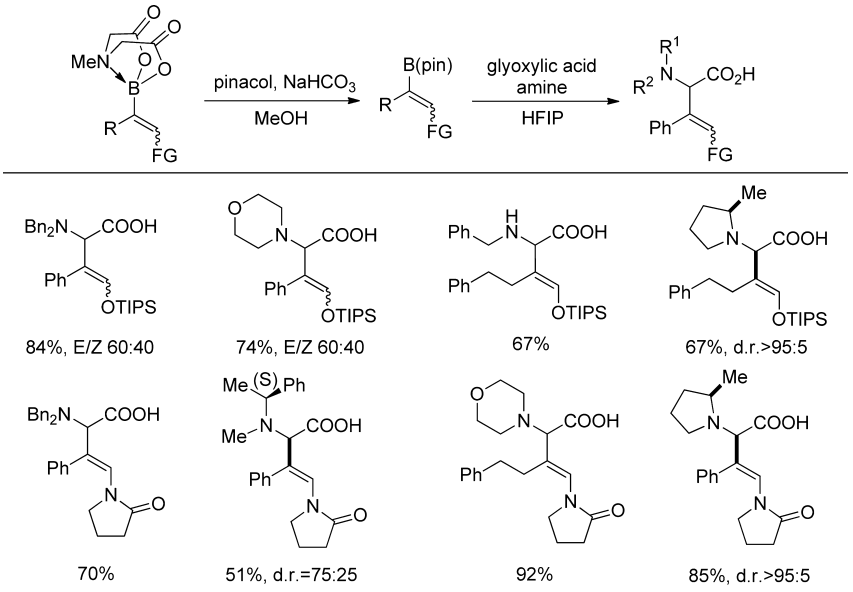
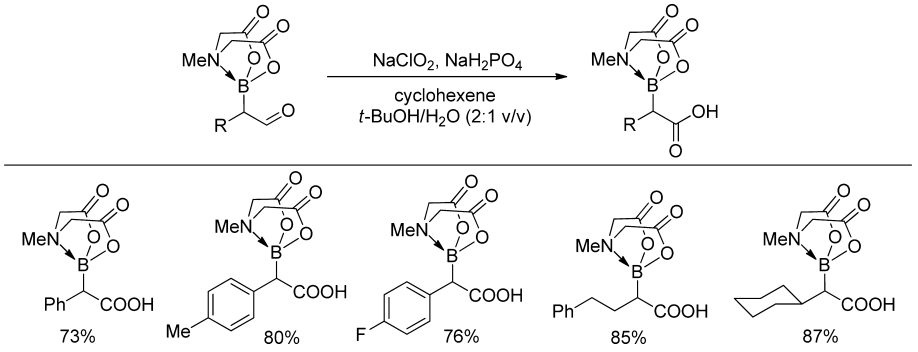
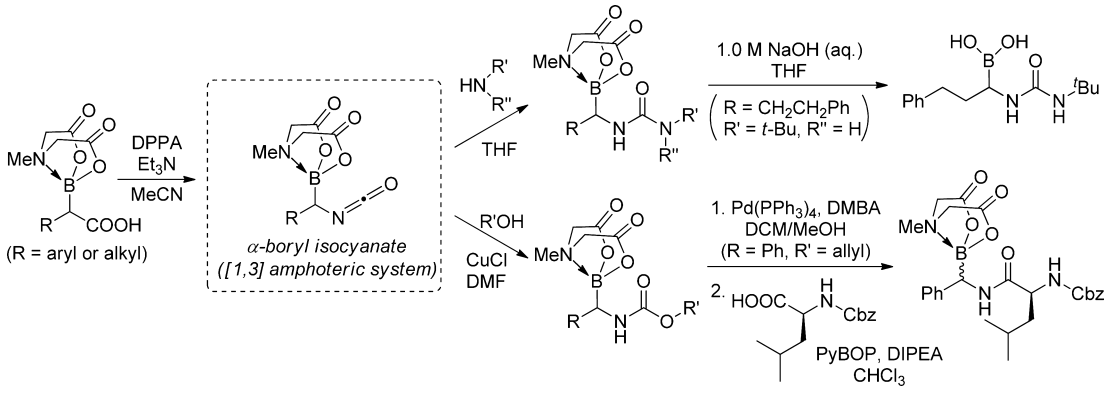
Scheme 17. Unnatural Amino Acids from Siloxy or Amido Vinyl Boronates



Scheme 18. Preparation of α-Boryl Carboxylic Acids



Scheme 19. Preparation and Transformation of α-Boryl Isocyanates



carboxylic acid products are air-stable and can be purified by silica gel chromatography or recrystallization.

4. THE [1,3] AMPHOTERIC SYSTEM: α-BORYL ISOCYANATES AND ISOCYANIDES

α-Borylcarboxylic acids supply opportunities to access other multifunctionalized boron-containing amphoteric molecules. A one-pot Curtius rearrangement procedure using diphenylphosphoryl azide (DPPA) in the presence of triethylamine and anhydrous acetonitrile provides a class of air-stable α-boryl isocyanates (Scheme 19). Given the versatility of the electrophilic isocyanate functionality and nucleophilic carbon−boron bonds, α-boryl isocyanates can be considered amphoteric molecules with two orthogonal reactive carbon centers in a [1,3] relationship. Downstream chemoselective manipulation of either the isocyanate or MIDA boryl groups allows access to α-aminoboronic acid derivatives, including boron-containing carbamates, ureas, and boropeptides (Scheme 19).

The preparation of α-boryl isocyanates enables us to obtain the corresponding isocyanide derivatives directly via a

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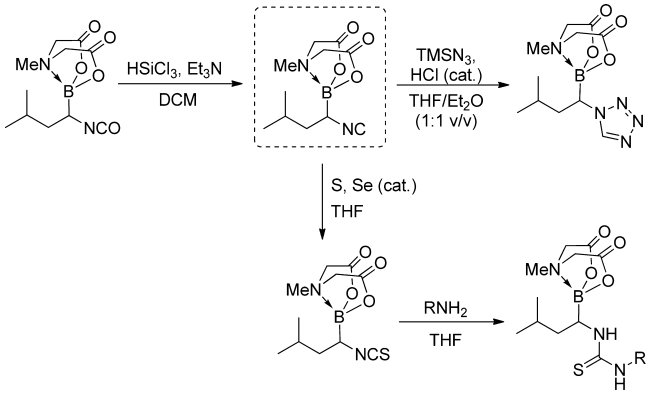
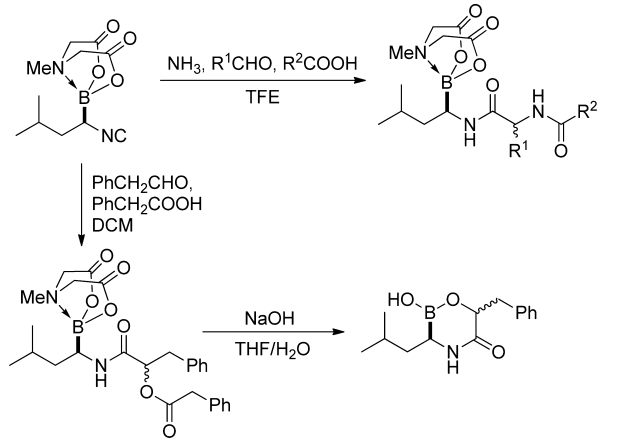
Scheme 20. Preparation and Functionalization of α-Boryl Isocyanides



Scheme 21. Multicomponent Reactions Utilizing α-Boryl Isocyanides



trichlorosilane-mediated deoxygenation (Scheme 20).[27] Given the nucleophilic property of the carbon−boron bond and the amphoteric nature of the isocyanide terminal carbon, the newly formed α-boryl isocyanide structure can be considered a combination of two amphoteric systems, namely, a [1,3] and a [1,1] system. Further selenium-catalyzed sulfurization of the isocyanide group gives rise to borylated isothiocyanates. Reaction of the isothiocyanate with several amines affords the corresponding thioureas. In addition, chemoselective reaction of α-boryl isocyanides with *in situ* generated hydrazoic acid yields the α-boryl tetrazole.

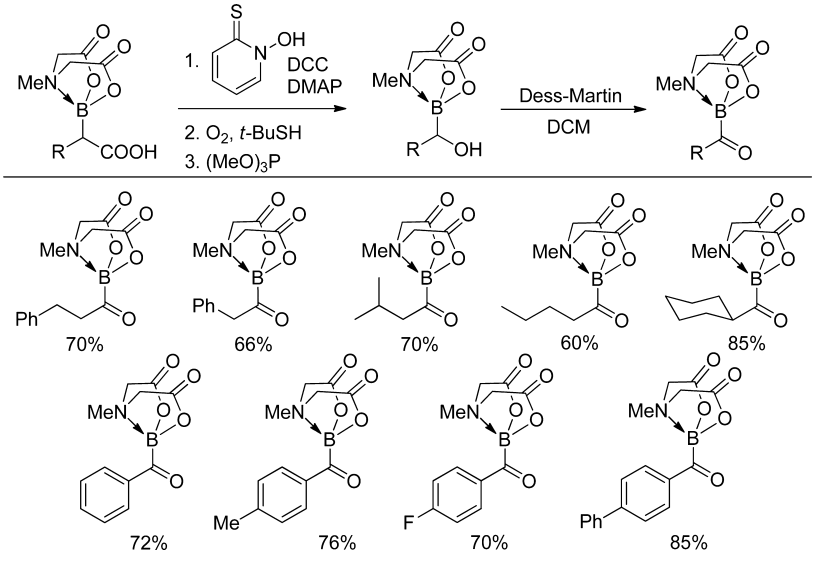
Retention of the carbon−boron bond during functionalization of α-boryl isocyanides has prompted us to investigate new approaches to access boropeptides via multicomponent reactions. We have found that the α-boryl isocyanide participated in an U4CR with ammonia, an aldehyde, and a carboxylic acid component to yield the corresponding MIDA-protected boropeptide derivatives (Scheme 21).[27] In the absence of an amine, the reaction produces boryl acyloxyamide derivatives via a P3CR. Upon deprotection/condensation, the P3CR products cyclize to produce 6-boromorpholinones. These borocyclic peptide derivatives exhibit inhibition of the chymotrypsin-like members of the 20S proteasome with low nanomolar IC_{50} values and selectivity comparable to bortezomib, the first and only boropeptide approved by the FDA for the treatment of multiple myeloma.[28]

5. THE [1,1] AMPHOTERIC SYSTEM: ACYLBORONATES

Given the widespread use of the venerable isocyanides, development of new [1,1] systems has been a particularly important goal in our work. We have recently reached this objective by a successful preparation of air-stable acylboronates and their downstream applications in heterocycle synthesis.

Because the Curtius rearrangement of α-borylcarboxylic acids furnishes a geminal installation of nitrogen functionality at the position α to the boron center, we envisioned that the Barton radical decarboxylative hydroxylation would provide an efficient way to introduce an oxygen atom geminal to the boryl group. The resulting α-hydroxyboronates could be subsequently transferred to acylboronates through oxidation of the hydroxyl group. Structurally, acylboron species[29] are [1,1] amphoteric molecules. The electrophilic carbonyl carbon is also nucleophilic due to the presence of the boron atom. α-Borylcarboxylic acid precursors are initially converted to the corresponding Barton esters via DCC coupling. After treatment of the Barton esters with O_2 gas in the presence of

Scheme 22. Synthesis of α-Hydroxyboronates and Acylboronates



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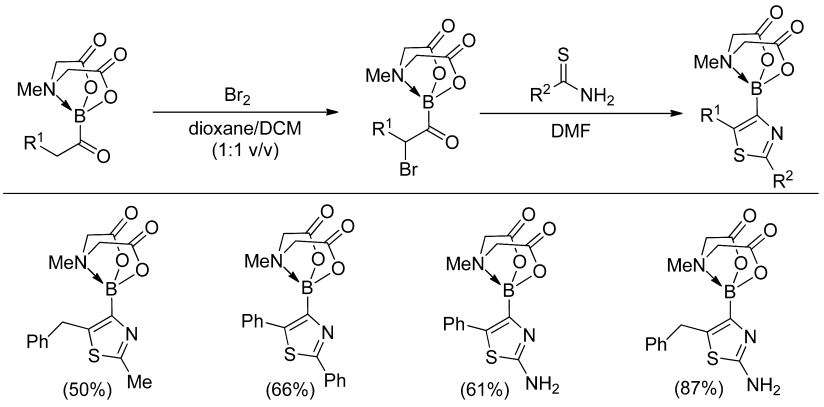
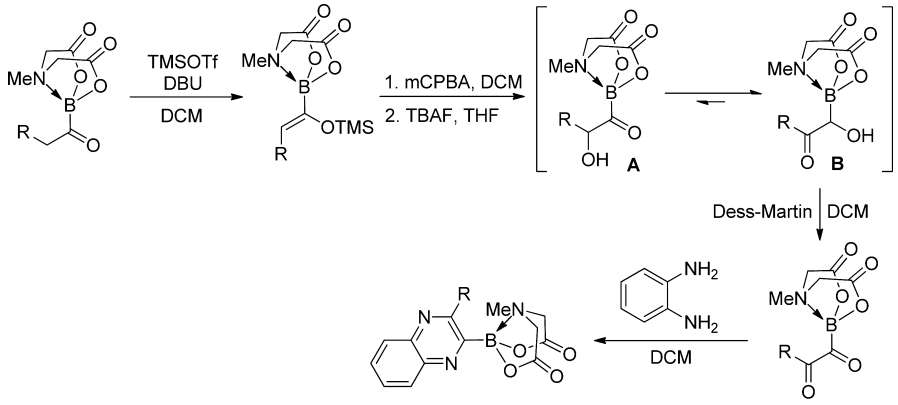
Scheme 23. Preparation of MIDA Thiazol-4-ylboronates



Scheme 24. Conversion of MIDA Acylboronates to α-Hydroxy-α-boryl ketones, 2-Oxo-acylboronate, and 2-Borylated Quinoxalines



tert-butylthiol under tungsten−halogen light irradiation, the desired α-hydroxyboronates are isolated as air-stable solids (Scheme 22).[30] We have found that alkyl-substituted substrates generally afford the desired MIDA α-hydroxyboronates in good yields, whereas the starting α-borylcarboxylic acids with aryl substituents result in the isolation of products with poor yields. The delocalization of the α-boryl radical to the aromatic ring, thereby triggering the generation of unidentified byproducts, is likely the main cause of the low yield of aryl-substituted α-hydroxyboronates. Following the decarboxylation, the α-hydroxyboronate intermediates are reacted with Dess−Martin periodinate under ambient temperature. The reaction provides the desired MIDA acylboronate products as air-stable solids.

Synthesis of MIDA acylboronates prompted us to evaluate their reactivity and application in the construction of borylated heterocycles.[30] Exposure of enolizable acylboronates to bromine results in the corresponding α-bromination product with the carbon−boron bond intact. Subsequent reaction of these α-bromoacylboronates with thioamides or thioureas in DMF under elevated temperature affords 4-borylated thiazole derivatives (Scheme 23). On the other hand, conversion of acylboronates to 1-(silyloxy)vinylboronates, followed by Rubottom oxidation affords α-hydroxy-α-boryl ketones **B**, rather than the desired α-hydroxyacylboronates **A**, as the final products (Scheme 24). The isomerization from **A** to **B** can be attributed to the stabilizing conjugative interaction between the π* orbital of the carbonyl group and the electron-rich carbon−boron bond. Subsequent Dess−Martin oxidation converts α-hydroxy-α-boryl ketones to the air-stable 2-oxo-acylboronate products. This class of 1,2-diketo compounds equipped with boryl groups are hitherto unknown. Their X-ray structure reveals a set of ordinary 1,2-diketone carbonyl groups in the molecule. Subsequently, by treating the 2-oxo-acylboronate with *o*-phenylenediamine in dichloromethane, a 2-borylated quinoxaline is obtained. This reaction further exemplifies the potential of acylboronates in the preparation of borylated heterocycles.

6. CONCLUSION

Our research program has targeted the development of kinetically amphoteric molecules and their application in chemical synthesis. Aziridine aldehydes, our initial contribution in this area, are [1,3] amphoteric systems that contain an orthogonal nucleophile (amine) and electrophile (aldehyde) in close proximity. The relative stability of amphoteric aziridine aldehydes results from the strain imposed by the three-membered aziridine ring on the iminium ion formation. The dimeric nature of these molecules comes from the thermodynamic gains made during self-association but does not play merely a stabilizing role. We have found evidence pointing to reactivity control elements present in the dimeric form of aziridine aldehydes. A range of transformations involving aziridine aldehydes have targeted the synthesis of densely functionalized compounds, underscoring the bond-forming efficiency of open dimer intermediates. In addition to ring strain, we considered coordinative stabilization as a means to prevent premature Nu/E reactivity. In efforts to find isolable molecules equipped with a metalloid nucleophile, we introduced α-boryl aldehydes as versatile [1,2] amphoteric entities. The electron-rich tetracoordinate MIDA boryl group stabilizes *C*-bound α-boryl aldehydes and prevents their isomerization to *O*-bond enolates.

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We have demonstrated the utility of these reagents in the synthesis of boron-containing molecules via late-stage functional group manipulation that proceeds with retention of the boron moiety. This approach has enabled efficient access to novel functionalized boron-containing molecules that are difficult or impossible to obtain through established methodologies, including other new amphoteric building blocks, such as [1,2] amphoteric α-borylcarboxylic acids, [1,3] amphoteric α-boryl isocyanates, α-boryl isocyanides, and [1,1] amphoteric acylboronates. We anticipate that other strategies based on kinetic stabilization against premature Nu/E reactivity will deliver additional examples of stable amphoteric reagents.

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Notes

The authors declare no competing financial interest.

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