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Organoboron Acids and Their Derivatives as Catalysts for Organic Synthesis

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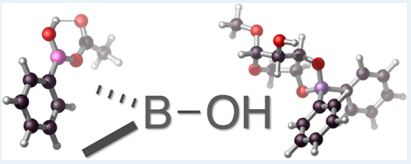
ABSTRACT: An overview of the applications of boronic and borinic acids in catalysis is presented. Taking advantage of the Lewis acidity of trivalent boron and the reversible covalent interactions of organoboron acids with OH groups, diverse modes of catalytic reactivity have been achieved. Interactions with carbonyl compounds enable acceleration of addition and cycloaddition processes, whereas binding of their enol tautomers can lead to organoboron-catalyzed aldol and related reactions. Binding of organoboron acids to hydroxyl and carboxyl OH groups has been employed as a mode of electrophilic activation for catalysis of substitution, cycloaddition, rearrangement, and elimination reactions. By altering the nature of the interaction with the organoboron acid catalyst, activation of OH groups as pronucleophiles is also possible, resulting in catalyst-controlled methods for regioselective functionalization of diols and carbohydrate derivatives. Applications of organoboron acids in bifunctional and assisted catalysis are also discussed.



KEYWORDS: *boronic acids, catalysis, condensation, cycloadditions, Lewis acids*

1. INTRODUCTION AND SCOPE

The renewal of interest in organic molecules as reaction catalysts ("organocatalysis") has represented a major direction of research over the past 10−15 years.[1] In principle, organic molecules provide several advantages as a catalyst class, including their relatively low cost and toxicity as well as their high functional group tolerance. Perhaps the most significant advantages of organocatalysts derive from their ease of structural modification, which enables empirical tuning of the attractive and repulsive noncovalent interactions that determine enantio-, diastereo-, or regioselectivity in catalyzed processes. The fact that organocatalytic pathways are well suited to computational modeling provides opportunities for fundamental insight, especially when combined with catalyst structure−activity relationship data.

Organoboron compounds possess many of the advantageous features of organocatalysts listed in the preceding paragraph. Boron-derived substituents are readily incorporated into organic molecules, including functionalized and stereochemically complex frameworks, and compounds containing carbon−boron bonds are often stable to a wide range of reaction conditions. However, boron-based compounds display reactivity patterns that are distinct from those of the common organic functional groups: these include the ability of trivalent boron to act as a Lewis acid and, in the case of organoboron acids (i.e., boronic acids $RB(OH)_2$ and borinic acids R^1R^2BOH), reversible covalent interactions with acidic functional groups, such as hydroxyl and carboxyl groups. This latter property, which has been exploited for decades as the basis for applications of organoboron acids in molecular recognition, can also be harnessed to achieve unique modes of catalyst−substrate complexation or to fine-tune catalyst structures.

This Review article will discuss applications of boronic and borinic acids in catalysis, with the aim of highlighting the diverse activation modes that are possible. Transformations that are catalyzed by derivatives of organoboron acids (e.g., boronic or borinic esters) will also be included. Although catalysis by borates ($(RO)_3B$) and boranes (R_3B) will generally be considered to fall outside the scope of this review, a few examples will be discussed to place the work in context. Emphasis will be placed on results that have been reported since the publication of previous reviews covering related topics.[2,3]

2. BORONIC AND BORINIC ESTERS AS LEWIS ACIDS

2.1. Activation of Carbonyl Electrophiles. Applications of organoboron acid derivatives as Lewis acids for activation of carbonyl compounds are among the first examples of catalysis by this class of compounds, and constitute an important chapter in the early history of asymmetric catalysis. Because these advances have been documented previously,[3] only a brief discussion is provided herein. Diastereoselective cycloadditions of chiral diol-derived borate complexes were an important first step in this direction: the groups of Kelly[4] and Yamamoto[5] achieved high levels of asymmetric induction in Diels−Alder reactions of 5-hydroxy-1,4-naphthoquinone-derivatived borates **1a** and **1b** (Figure 1). The development of chiral boron-based Lewis acids that could be employed in substoichiometric quantities for enantioselective Diels−Alder reactions followed soon after. Complexes employed in these pioneering studies included acyloxyboranes,[6,7] dihaloboranes,[8] and oxazaborolidines (**2**−**4**, Figure 1).[9,10] Boron-based complexes have also been employed as chiral catalysts for enantioselective additions to carbonyl compounds, including hetero-Diels−Alder,[11] Mukaiyama aldol,[12,13] and Sakurai−Hosomi allylation reactions.[14] It is noteworthy that these were among the first efficient

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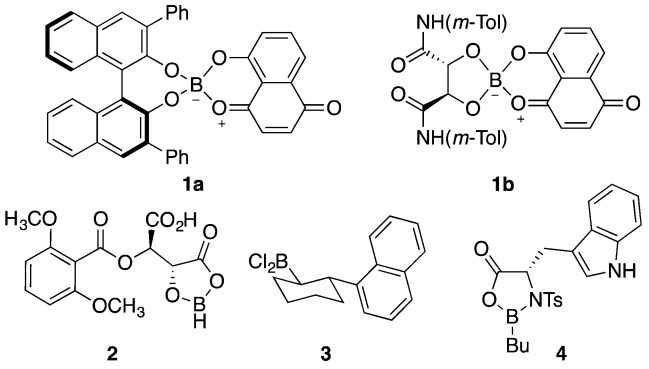

Figure 1. Boron-based chiral auxiliaries and catalysts for stereoselective Diels–Alder cycloadditions.

enantioselective catalysts to be identified for each of the reactions shown.

Boronic esters generally display relatively moderate levels of Lewis acidity, and thus several approaches have been taken to enhance this key property. Yamamoto has developed Brønsted acid-assisted Lewis acids (BLA) in which an intramolecular hydrogen bond to a ligating group serves to increase the Lewis acidity of the complex, leading to improved activity in catalysis of Diels–Alder cycloadditions.[15] Although this concept was first implemented in the design of chiral borates, such as **5a**,[16] it was later extended to esters of boronic and borinic acids (i.e., **5b** and **5c**, Figure 2).[17] Dienophiles that displayed sluggish reactivity or poor stereoselectivity using BLA **5a** were efficiently activated by **5b** or **5c**, presumably reflecting the improved Lewis acidities of the latter relative to that of the borate.

Brønsted acid enhancement of Lewis acidity also underlies the design of oxazaborolidinium triflate **6a**,[18] bis(triflimide) **6b**,[19] and bis(triflylmethanide) **6c**,[20] which are generated by protonation of the corresponding oxazaborolidine with the strong acids TfOH, Tf_2NH, and $C_6F_5CH(Tf)_2$, respectively.[21] Corey and co-workers have demonstrated that **6a** and **6b** display exceptional levels of activity and generality for enantioselective, catalytic Diels–Alder reactions of α,β-unsaturated aldehydes, ketones, and esters, as well as quinones (Scheme 1, eqs 1 and 2). Catalyst **6c**, developed by the group of Yamamoto, enables enantioselective cycloadditions of acetylenic ketones, as well as those of substituted cyclopentadienes (eq 3).

Cycloadditions catalyzed by **6b** have been employed as key steps in the syntheses of numerous complex natural products and bioactive targets.[22] An impressive demonstration of the utility of catalyst **6b** is its application to the enantioselective type I Diels–Alder macrobicyclization of **7**, which was employed as a key step in the synthesis of dolabellane-type marine natural products (Scheme 2).[23] The unique effectiveness of oxazaborolidinium cations in promoting challenging classes of [4 + 2] cycloadditions is further evident from Balskus and Jacobsen's studies of stereoselective, transannular Diels–Alder reactions: catalyst **6d** was shown to provide high levels of enantioselectivity and was able to override inherent substrate bias when a chiral macrolactone was employed.[24] Applications of oxazaborolidinium salts are not restricted to [4 + 2] cycloadditions (Scheme 3). An enantioselective, formal [3 + 2] cycloaddition between 1,4-benzoquinones and 2,3-dihydrofuran was achieved using **6b** as catalyst and was employed in the synthesis of aflatoxin B2, a mutagenic mycotoxin.[25] Formal [2 + 2] cycloadditions between ketenes and aldehydes are catalyzed by zwitterionic borate **6e**, providing access to enantioenriched β-lactones.[26]

Activation of a Lewis acid complex by a second Lewis acid (Lewis acid-assisted Lewis acid catalysis, or LLA[15]) is also possible; examples of organoboron catalysts that benefit from this phenomenon are discussed below. Reilly and Oh studied bis(boron) Lewis acids derived from the 1,8-naphthalenediyl scaffold[27] and found that chiral complex **7** promotes moderately enantioselective Diels–Alder reactions between cyclopentadiene and acrolein derivatives (Scheme 4). Whereas these species were intended to interact with carbonyl compounds through simultaneous coordination of both lone pairs, studies of catalyst–substrate complexation equilibria suggested that **7** most likely acts as a Lewis acid-assisted Lewis acid through an intramolecular B–Cl interaction.[28] In contrast, Shea and co-workers have synthesized chiral bisoxazaborolidine **8** and have provided evidence suggesting that this compound indeed interacts with carbonyl compounds through simultaneous complexation of both lone pairs of electrons.[29] For the cycloaddition of cinnamaldehyde and cyclopentadiene, catalyst **8** displayed superior catalytic activity, endo:exo selectivity, and enantioselectivity in comparison with a monodentate oxazaborolidine derived from *N*-Ts valine (21% yield, 91:9 d.r., 31% ee under the conditions shown in Scheme 4).

More recently, the group of Yamamoto and Shibatomi employed $SnCl_4$ as a Lewis acid activator of chiral oxazaborolidines derived from valine, revealing an improvement in enantioselectivity relative to the corresponding Tf_2NH-activated catalyst.[30] Lewis acid-assisted Lewis acid **6f** was applied in cycloadditions of α-halogen-[30b] and β-(fluoromethyl)-substituted dienophiles,[30c] providing novel methods of access to chiral, halogenated carbocycles (Scheme 5). Lewis acid activation of oxazaborolidines has also been explored by Corey and co-workers, who discovered that the oxaborolidine–aluminum(III) bromide complex **6g** shows improved catalytic activity over cations **6a** and **6b** in several classes of Diels–Alder cycloadditions.[31,32] The choice of $AlBr_3$ as the Lewis acid activator of the proline-derived oxazaborolidine was critical because the majority of candidates did not result in useful levels of catalysis,

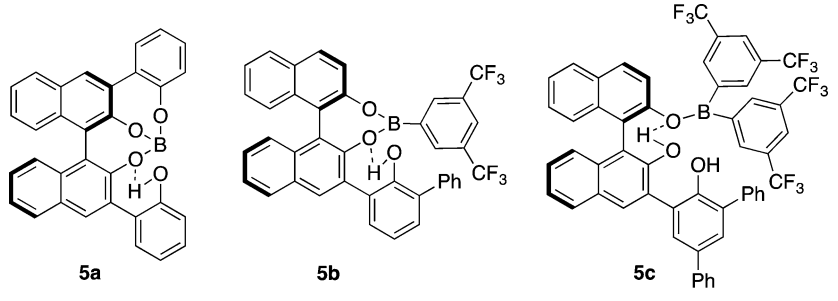

Figure 2. Brønsted acid-assisted boron Lewis acids.

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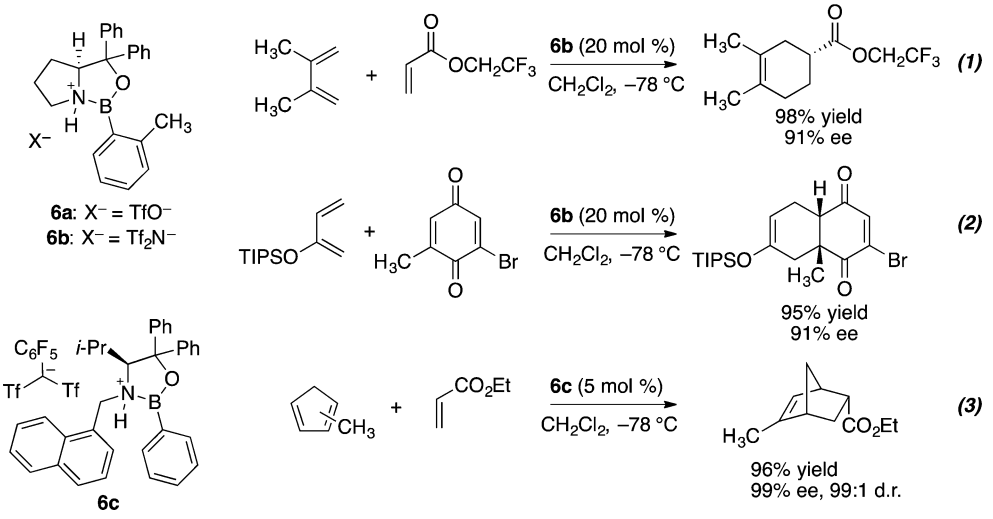
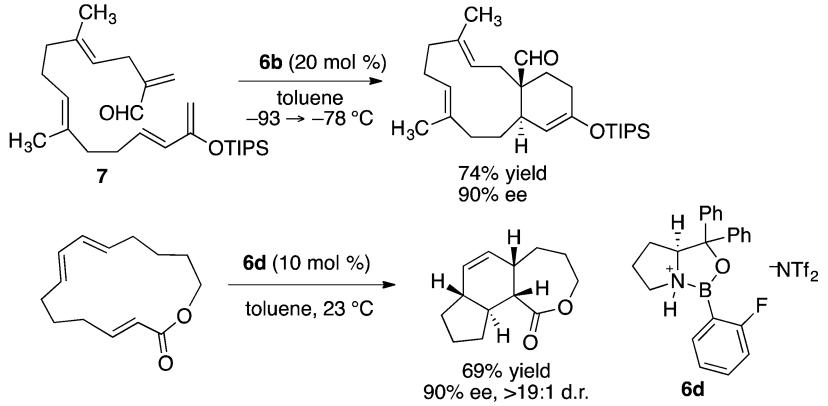
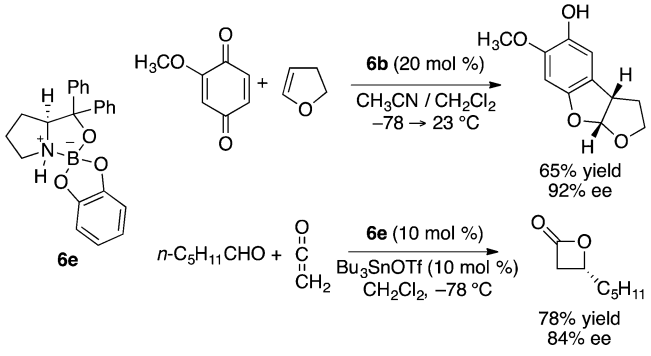
Scheme 1. Oxazaborolidinium Cations 6a–6c As Catalysts for Enantioselective Diels–Alder cycloadditions



Scheme 2. Catalysis of Macrobicyclization and Transannular Cycloaddition by Oxazaborolidinium Bis(triflimide)s 6b and 6d



Scheme 3. Formal [3 + 2] and [2 + 2] cycloadditions catalyzed by oxazaborolidinium Lewis acids



and even the closely related $AlCl_3$ and $GaCl_3$ showed markedly inferior results. Catalyst **6g** has also been shown to be useful for enantioselective [2 + 2] reactions of trifluoroethyl acrylate with enol ethers.[33] In addition to interaction with a Brønsted or Lewis acid, *N*-alkylation has been shown to result in electrostatic activation of oxazaborolidines as Lewis acids. In particular, *N*-methyloxazaborolidinium triflimide **6h** (generated in situ by protonation of the corresponding borohydride) displays catalytic activity similar to, and in certain instances higher than, that of aluminum(III) bromide complex **6g**.[34]

The group of Ishihara has developed Lewis acid-assisted Lewis acids that are assembled from an arylboronic acid, a phosphine oxide-substituted chiral biaryl ligand, and tris(pentafluorophenyl)borane.[35] Catalysts of this type displayed high enantioselectivity and anomalous endo/exo selectivity for Diels–Alder reactions of acrolein derivatives. For example, catalyst **9** mediated an endo-selective cycloaddition of α-fluoroacrolein with cyclopentadiene; control experiments with Lewis acids such as Et_2AlCl or $BF_3{\cdot}OEt$ displayed significant levels of exo selectivity (Scheme 6). The modular nature of this catalyst was a key advantage because different biaryl and boronic acid components were found to be optimal for particular aldehyde substrates.

The search for chiral Lewis acids continues to inspire the creative design of novel organoboron compounds. Fu and co-workers reported the synthesis of planar chiral Lewis acid **10** based on the (η^5-1,2-azaborolyl)iron framework.[36] High levels of stereochemical control were observed using **10** as a promoter of Mukaiyama aldol reactions of electron-rich aldehydes (Scheme 7). The rate law was consistent with a mechanism involving rate-determining displacement of tosylate by aldehyde substrate at the Lewis acidic boron center. Because of the strength of the alkoxide–boron complexation in this system, the development of a variant that employs **10** as a catalyst rather than a promoter has been elusive; however, this work represents a unique application of the B–N-analogs of aromatic compounds, a class of substances that have recently attracted attention in diverse research areas.[37]

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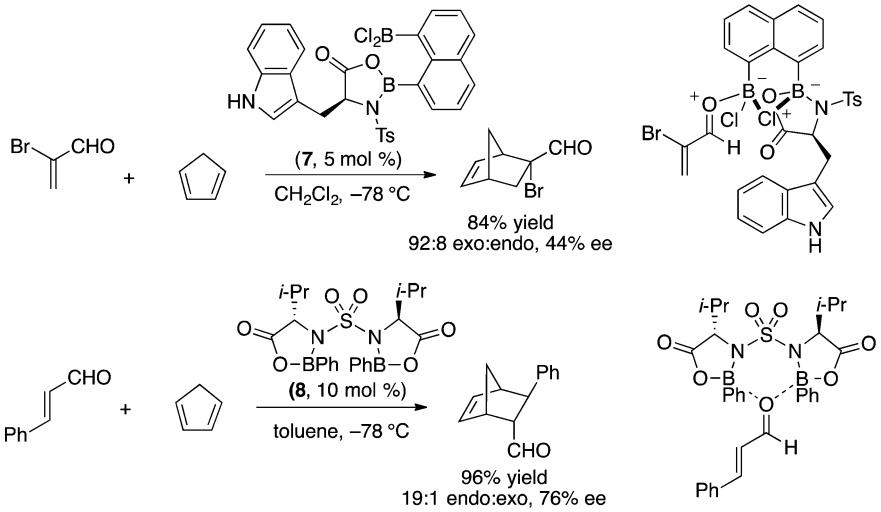
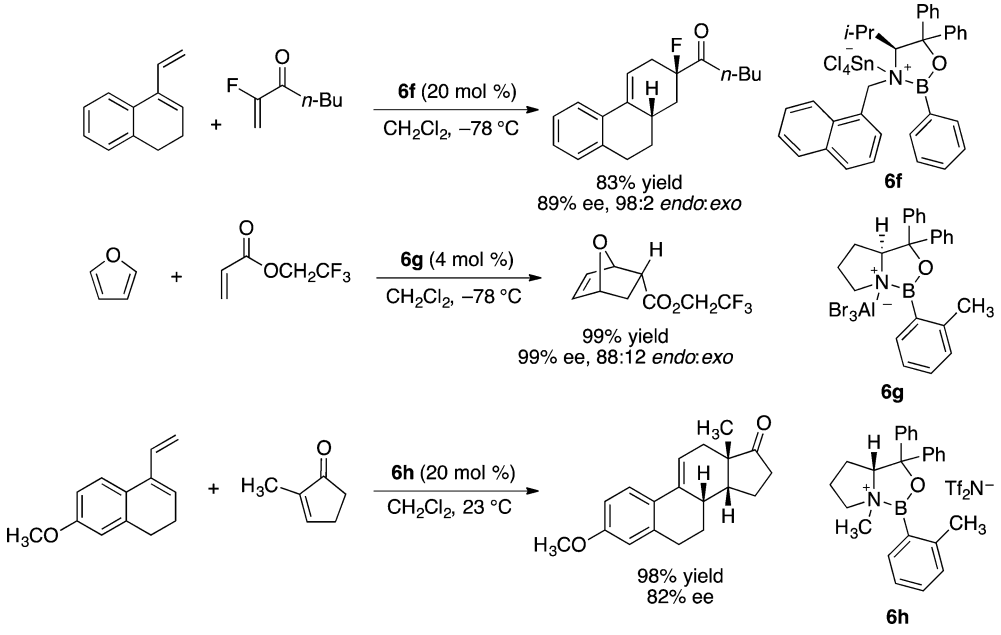
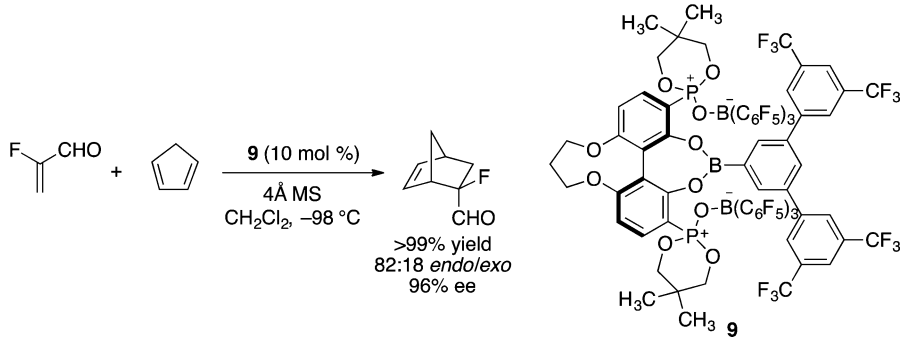
Scheme 4. Enantioselective Diels–Alder Reactions Catalyzed by Bis(boron) Lewis Acids 7 and 8: The Proposed Mode of Substrate Complexation Is Depicted for Each



Scheme 5. Lewis Acid- and Electrostatically-Assisted Oxazaborolidine-Derived Chiral Lewis Acids



Scheme 6. Unusual Endo Selectivity in the Catalytic Diels–Alder Reaction of α-Fluoroacrolein



2.2. Organoboron Lewis Acids As Components of Bifunctional Catalysis. Bifunctional catalysts that incorporate both acidic and basic sites (of either the Brønsted or Lewis classification) often show unique reactivity or selectivity. Boron-based Lewis acids play prominent roles as components of bifunctional catalysts, perhaps a reflection of the relative ease of incorporation of boron into complex organic frameworks and the functional group tolerance of many organoboron derivatives. The

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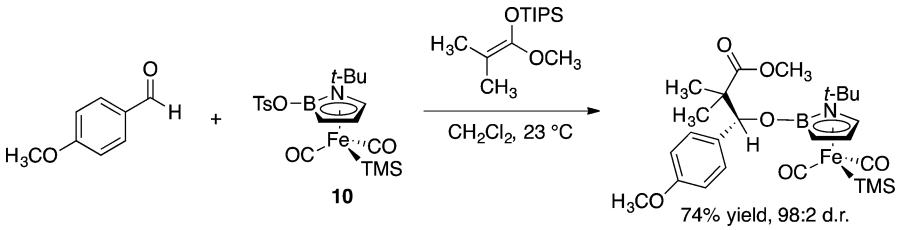
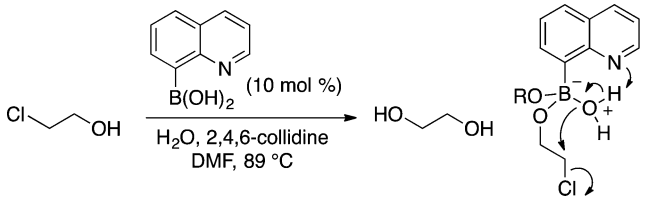
Scheme 7. An (η^5-1,2-Azaborolyl)iron-Derived Planar Chiral Lewis Acid



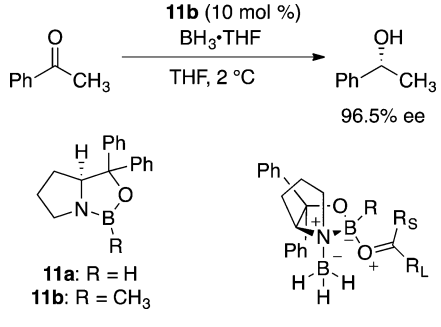
8-quinolineboronic acid-promoted hydrolysis of 2-chloroethanol, reported by Letsinger and co-workers in 1963, was among the first examples of bifunctional catalysis by a synthetic system.[38] The observed substrate specificity, as well as the results of stereochemical and kinetics experiments, suggests a mechanism wherein the boronic acid group serves to anchor the substrate through the formation of a B–O linkage while the quinoline moiety acts as a Brønsted base (Scheme 8). The Letsinger group further demonstrated that etherification reactions of 2-chloroethanol could be promoted by a benzimidazole-functionalized boronic acid catalyst.[39]

Scheme 8. 8-Quinolineboronic Acid As a Bifunctional Catalyst for the Hydrolysis of 2-Chloroethanol



Among the most familiar examples of bifunctional catalysis involving boron is the oxazaborolidine-catalyzed reduction of ketones, which serves as a broadly useful method for the synthesis of enantioenriched secondary alcohols. The development, scope, and mechanism of these reactions have been discussed in detail elsewhere,[40] so only a brief description will be provided here. Both the parent oxazaborolidine, **11a**, and its *B*-methyl derivative **11b** are efficient reduction catalysts. The generally accepted mechanism for the catalytic transformation involves simultaneous activation of the borane reductant (by Lewis base catalysis) and the ketone (by Lewis acid catalysis), as depicted in Scheme 9. The absolute stereochemical outcome can be accounted for by a model involving minimization of steric strain upon coordination of the ketone substrate (Scheme 9: R_S is less sterically demanding than R_L). Spectroscopic studies of

Scheme 9. Enantioselective, Oxazaborolidine-Catalyzed Reduction of Ketones



catalyst composition;[41] computation;[42] and, most recently, a detailed analysis of kinetic isotope effects for the enantioselective reduction[43] are consistent with the model described above.

Homoboroproline derivatives **12a–12d**, which have been employed by the group of Whiting as catalysts for the direct aldol reaction of acetone and 4-nitrobenzaldehyde, represent another class of boron-based Lewis acid/Lewis base bifunctional molecules.[44] Their design was based on the premise that the Lewis acidic boronic acid or ester moiety could serve as a surrogate for the carboxyl group, which acts as a Brønsted acid in the generally accepted mechanism of proline-catalyzed direct aldol reactions.[45] The fact that the enantioselectivity of the direct aldol reaction depended on the structure of the boron-bound substituents was consistent with this hypothesis, suggesting a transition state of the type depicted in Scheme 10. The absence of a matching/mismatching effect for the two catalyst diastereomers **12c** and **12d** indicated that the homoboroproline stereochemistry, and not that of the chiral diolate ligand, exerted the dominant influence on the enantioselectivity of this process.

The group of Schmidt has explored organoboron Lewis acids as bifunctional catalysts for S_N2-type glycosylation reactions.[46] On the basis of the hypothesis that a catalyst capable of simultaneously delivering an alkoxide nucleophile and a proton could engage trichloroacetimidate glycosyl donors in a concerted substitution pathway, the authors investigated promoters containing B–F bonds. Both $PhBF_2$ and Ph_2BF provided enhanced stereoselectivity relative to conventional catalysts (TMSOTf, BF_3·OEt_2) for β-configured product using α-trichloroacetimidate donor **13** (Scheme 11). Promising levels of stereocontrol for the formation of α-configured product from a β-trichloroacetimidate substrate were also obtained.

2.3. Boron-Derived Lewis Acid-Assisted Brønsted Acid Catalysts. The acidification of protic functional groups that accompanies coordination to a Lewis acid underlies the concept of Lewis acid-assisted Brønsted acid catalysis.[15] Boron-based complexes serve as useful Lewis acidic components of such systems. The group of Wulff developed an enantioselective aziridination method in which benzhydryl imines were coupled with ethyl diazoacetate in the presence of catalysts generated from the "vaulted" biaryl ligands VANOL or VAPOL and BH_3·THF[47a] or $B(OPh_3)$.[47b,c] Although this reactivity was initially attributed to Lewis acid catalysis by a tricoordinate (mesoborate or pyroborate) species, subsequent spectroscopic and crystallographic studies suggested that VAPOL/BX_3 mixtures function as Brønsted acid catalysts, generating an iminium boroxinate ion pair (that generated from VAPOL, $B(OPh)_3$ and an imine is depicted in Scheme 12).[48] The VANOL/VAPOL-derived boroxinates also serve as efficient chiral catalysts for hetero-Diels–Alder reactions of imines[49] and aminoallylations of aldehydes.[50] Achiral, borate-derived Lewis acid-assisted Brønsted acids have also been employed as catalysts for Ritter reactions of benzylic alcohols with nitriles.[51,52]

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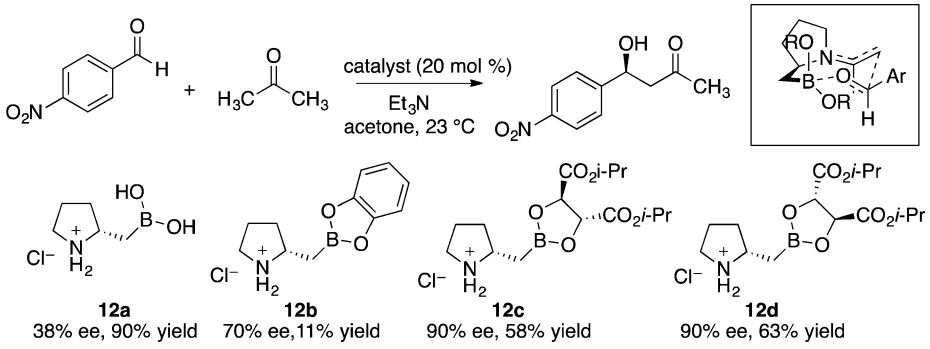
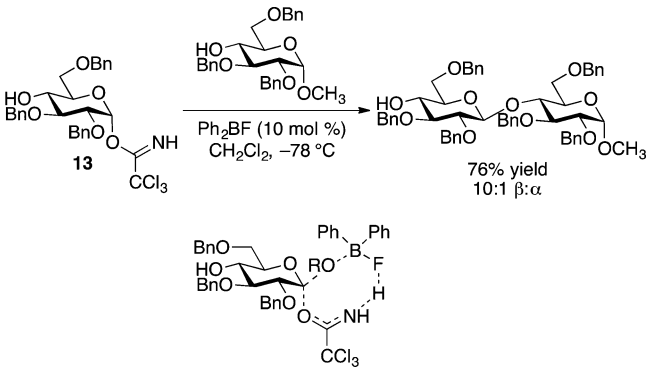
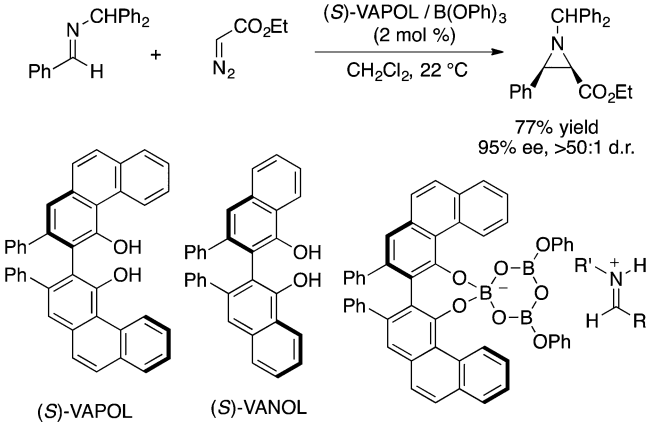
Scheme 10. Enantioselective Direct Aldol Reactions Catalyzed by Homoboroproline Derivatives



Scheme 11. Ph_2BF As a Bifunctional Glycosylation Catalyst



Scheme 12. Boroxinates as Lewis Acid-Assisted Brønsted Acids



Mattson and co-workers have investigated the use of internal Lewis acid coordination as a means to enhance the activity of urea-based organocatalysts. The group of Smith had previously determined that urea **14a** displays higher affinity for anions than the corresponding aniline-derived control compound and ascribed this behavior to polarization enhancement of hydrogen bond donor ability through an intramolecular B−O interaction.[53] Consistent with this observation, ureas **14b** and **14c** were more active than control urea **15** in catalyzing the conjugate addition of indole to trans-β-nitrostyrene, as judged by isolated yields and pseudo-first-order rate constants (Scheme 13).[54] The pK_a values of **14b** and **15** (7.5 and 8.5, respectively, in DMSO solvent) highlight the acidifying role of the difluoroboron substituent.[55] The identity of the boron substituents influenced the enantioselectivity of reactions catalyzed by aminoindanol-derived ureas **16a**−**b** (with pinacolate-substituted **16b** providing higher selectivity), thus providing an interesting way to tune this class of chiral catalyst. Difluoroboronate urea **14b** displayed high catalytic activity for nucleophilic ring-opening reactions of nitrocyclopropane carboxylates[56] and N−H insertions of α-nitro-α-diazoesters.[57]

3. ACTIVATION OF CARBONYL PRONUCLEOPHILES

3.1. Catalysis of Aldol Reactions via Organoboron Enolates. The stereospecific nature of aldol reactions of boron enolates—interpreted as a consequence of a "closed", chairlike transition state wherein the carbonyl group coordinates to the Lewis acidic boron moiety—has been exploited extensively in the development of modern variants of this important carbon−carbon bond-forming process. The group of Kobayashi has devised an organoboron-*catalyzed* process that displays the stereospecificity characteristic of aldol reactions of boron enolates: diphenylborinic acid was found to catalyze additions of silyl enol ethers to aldehydes in water, using sodium dodecyl sulfate surfactant and benzoic acid as a cocatalyst (Scheme 14).[58] The high syn selectivities evident in reactions of benzaldehyde with *Z*-configured silyl enol ethers (e.g., **17**) were consistent with the involvement of a boron enolate generated by Si−B exchange. The zero-order kinetic dependence on aldehyde concentration and first-order kinetics in silyl enol ether suggested that this exchange step was turnover-limiting. Catalyst substituent effect studies revealed that the electron-deficient bis(4-trifluoromethylphenyl)borinic acid displayed enhanced activity while maintaining high levels of syn selectivity. It should be noted that bis(3,4,5-trifluorophenyl)borinic acid had earlier been identified by the group of Yamamoto as an active catalyst for Mukaiyama aldol reactions in dichloromethane at −78 °C; Lewis acid catalysis, rather than Si−B exchange, was proposed as the mechanism for this process.[59] In addition, $Ph_2B(OCH_3)$ and related borinic esters have been shown to act as catalysts for Mannich reactions of silyl ketene acetals with iminium ions generated in situ from secondary amines and aldehydes.[60] The authors proposed that the borinic ester accelerated the formation of the iminium ion rather than the carbon−carbon bond-forming step.

An organoboron-catalyzed aldol reaction proceeding through direct enolization, rather than Si−B enolate exchange, was achieved by Whiting and co-workers.[61] Bifunctional aminoboronic acid-derived ate complex **18a** catalyzed direct aldol reactions of acetone, 2-butanone, and hydroxyacetone in water: aldol condensation products predominated for reactions of acetone and 2-butanone, whereas hydroxyacetone led to syn-configured α,β-dihydroxyketones as the major products (Scheme 15). Phenylboronic acid and its NaOH-derived ate complex were not active catalysts for the direct aldol reaction, nor was boronic acid **18b**. The proposed

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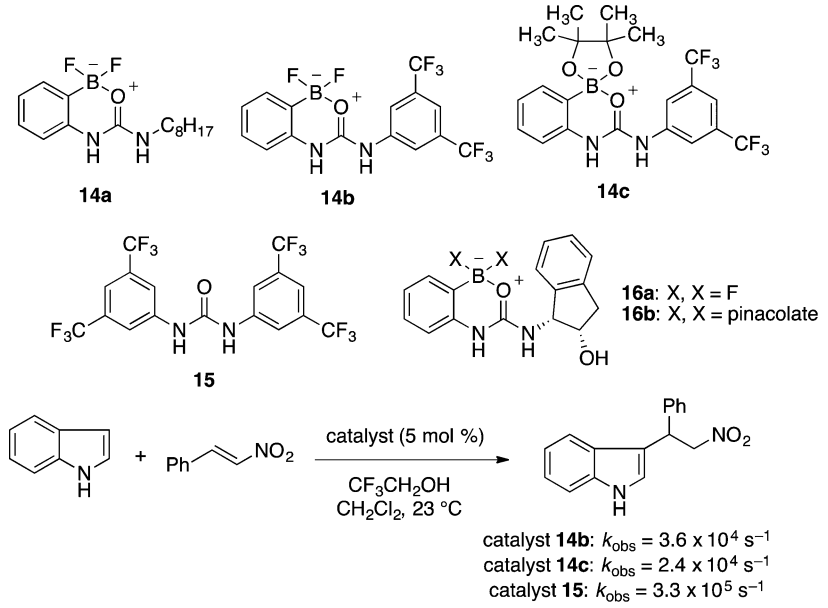
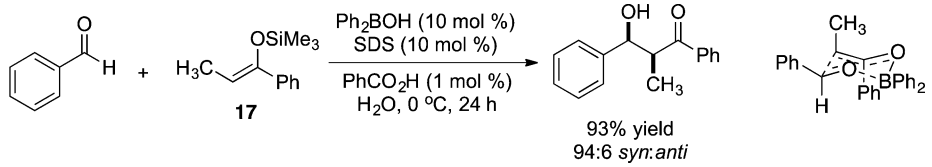
Scheme 13. Boronate-Assisted Urea Organocatalysts



Scheme 14. Borinic Acid-Catalyzed Mukaiyama Aldol Reaction and Proposed Closed Transition State



catalytic cycle involves boronate activation by the benzimidazole, accelerating the deprotonation step that generates boron enolate **18c**. The tetracoordinate nature of this enolate would preclude a closed transition state for the aldol addition. Accordingly, the syn-selective hydroxyacetone additions were rationalized in terms of an open transition state involving stabilizing hydrogen bonding interactions.

The two-point binding of organoboron compounds to the enol tautomers of pyruvic acids has been exploited in our laboratory as the basis for catalytic, direct aldol reactions.[62] Diphenylborinic acid displayed superior catalytic activity to boronic acids for the synthesis of isotetronic acids through an aldol addition/lactonization sequence in aqueous solvent (Scheme 16). The favorable formation of the dioxoborolanone adduct permitted the use of enolizable aldehyde electrophiles, including acetaldehyde. Similarly to the chemistry of Whiting described in the preceding paragraph, an open transition state for the aldol addition is most likely, given the tetracoordinate nature of the putative boron enolate.

3.2. Activation of 1,3-Dicarbonyl Pronucleophiles. Phenylboronic acid is a catalyst for the Biginelli and Hantzsch reactions, which are multicomponent condensations of β-dicarbonyl substrates that generate 3,4-dihydropyrimidinones and 1,4-dihydropyridines, respectively (Scheme 17).[63,64] The boronic acid was proposed to accelerate carbon−carbon bond formation in both processes, with the organoboron enolate of ethyl acetoacetate representing a possible common intermediate.

Cyclizations of acetylenic dicarbonyl compounds via boronic acid-catalyzed intramolecular Conia-ene reactions have also been developed.[65] Under optimized conditions, carbocyclizations of 1,3-dicarbonyl derivatives bearing pendant alkynyl groups were achieved with 5 mol % of 3-nitrophenylbenzeneboronic acid (**19**) in refluxing toluene (Scheme 18). On the basis of deuterium labeling studies that indicated a syn-addition to the alkyne, the authors proposed a catalyst-promoted enolization of the β-ketoester, which then underwent concerted ene cyclization (Scheme 18, path A). A mechanism involving the intermediacy of a boron enolate can also be envisioned (path B).

4. ACTIVATION OF CARBOXYLIC ACIDS BY ACYLOXYBORANE FORMATION

Acyloxyboranes exhibit enhanced electrophilicity relative to carboxylic acids and esters, an effect that is thought to underlie the high reactivity of BH_3 as a reducing agent for carboxylic acids. The reactivity of acyloxyboranes with heteroatom-centered nucleophiles enables activation of carboxylic acids toward condensation reactions: as demonstrated by the group of Ganem, aminolysis of catechol-derived acyloxyboranes is an efficient method for amide synthesis.[66] Catalytic processes based on this mode of reactivity have been developed, taking advantage of the reversible formation of acyloxyboranes from organoboron acids. These methods enable the direct formation of amides, esters, anhydrides, and related condensation products from carboxylic acids without the need for dehydrative activating reagents, such as carbodiimides, phosphonium or uronium salts. (Although boric acid[67−69] and borate esters[70,71] also serve as useful catalysts or promoters of condensation reactions involving carboxylic acids, this section will focus on applications of boronic acids.) A related mode of catalytic reactivity involves activation of unsaturated (acrylic and propiolic) acids by acyloxyborane formation, accelerating the rates of cycloaddition reactions.

4.1. Direct Amide Synthesis. In 1996, the group of Yamamoto demonstrated that 3,4,5-trifluorophenylboronic acid catalyzes condensations between amines and carboxylic acids at

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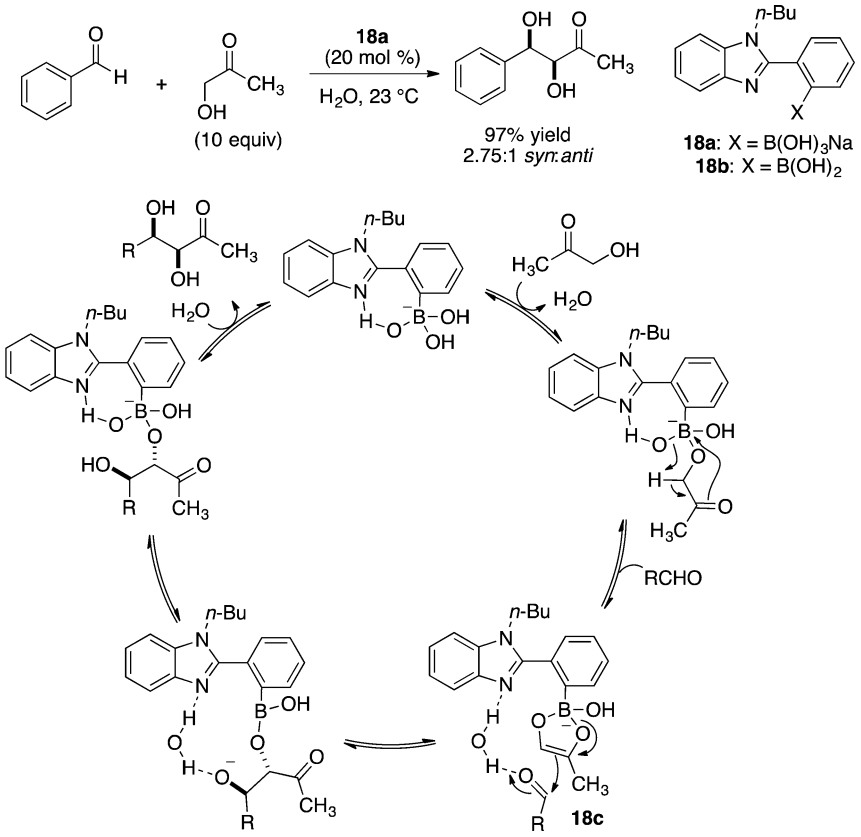
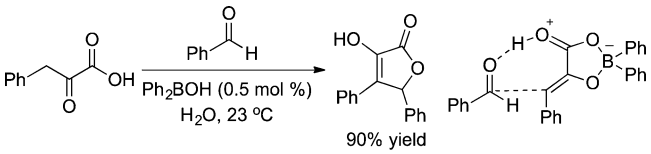
Scheme 15. Direct Aldol Reaction Catalyzed by a Bifunctional Organoboron -ate Complex[a]



[a]Adapted with permission from ref 61. Copyright 2008 John Wiley & Sons, Ltd.

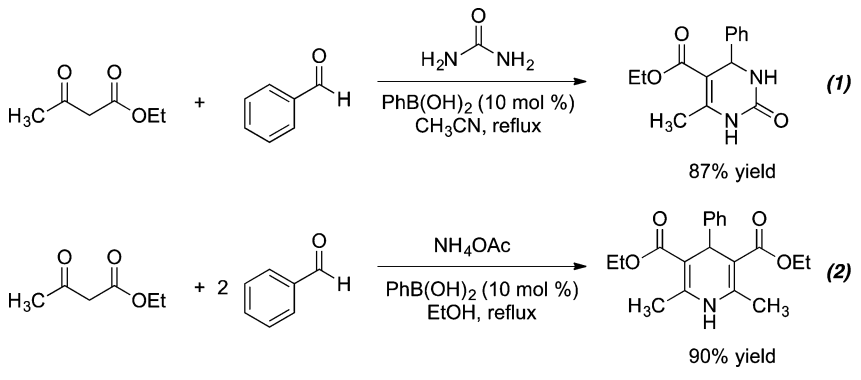
Scheme 16. Direct Borinic Acid-Catalyzed Aldol Reactions of Pyruvic Acids



elevated temperatures (refluxing toluene, xylene, mesitylene, or anisole) with removal of water using 4 Å molecular sieves in a Soxhlet apparatus (Scheme 19).[72] Studies of the catalyst–substrate complexation equilibrium pointed to the involvement of monoacyloxyborane intermediate **20**: the authors speculated that the formation, rather than the aminolysis, of such a species constituted the turnover-limiting step of the catalytic cycle. Extensions of this work have led to the use of electron deficient arylboronic acids as catalysts for the synthesis of nylon-6,6 and other polycondensation products.[73] Related nucleophiles, such as ureas[74] and sodium azide,[75] have been converted to their N-acylated derivatives. Similarly, amino alcohols and amino thiols resulted in the formation of oxazolines and thiazolines, respectively, through a tandem condensation/cyclodehydration process (Scheme 20).[76] Carboxylic acid activation via acyloxyboranes has also allowed for reduction to alcohols under relatively mild conditions using sodium borohydride.[77]

Structural modifications of the electron-deficient boronic acid have been investigated to facilitate catalyst separation and reuse (Figure 3). Installment of a perfluoroalkane group allowed for catalyst partitioning into fluorous solvent or precipitation from the reaction medium; up to 10 reaction cycles were carried out

Scheme 17. Boronic Acid-Catalyzed Biginelli and Hantzsch Multicomponent Condensations



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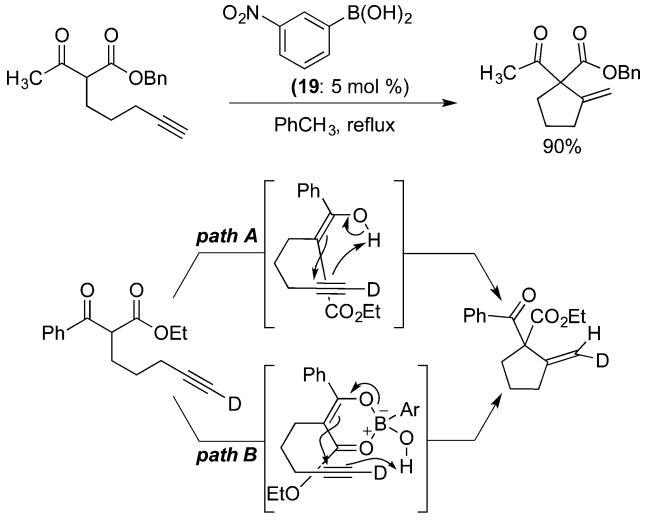
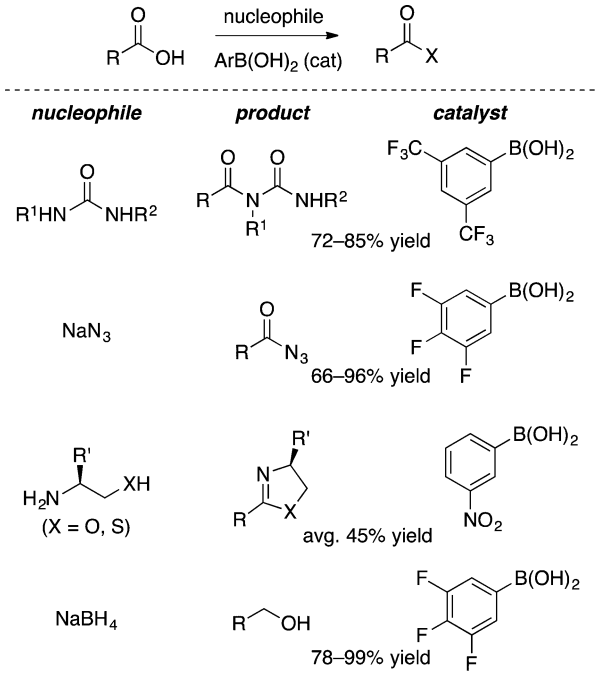
Scheme 18. Intramolecular Conia-ene Reaction Catalyzed by 3-Nitrophenylboronic Acid



with a single batch of catalyst by simply decanting the reaction mixture from the solid catalyst.[78] A pyridinium-3-boronic acid covalently bound to Merrifield's resin was shown by Wang and co-workers to be an active and recyclable amidation catalyst.[79] Yamamoto and Ishihara also explored polymer-bound pyridiniumboronic acid catalysts and found that polystyrene-bound 4-boronopyridinium chloride maintained its catalytic activity over multiple reaction cycles to a greater extent than did its 3-boronopyridinium isomer.[80] Thermostability studies indicating the higher resistance toward protiodeboronation of *N*-alkyl-4-borono- versus *N*-alkyl-3-boronopyridinium salts provided a rationale for this behavior.[71b] Another strategy for recycling of pyridiniumboronic acids exploits the solubility of **21** in the ionic liquid 1-ethyl-3-methylimidazolium trifluoromethanesulfonate ([emim][OTf]). After reactions were carried out in a biphasic mixture of toluene/[emim][OTf], the amide product was recovered through repeated Et_2O extractions of the ionic liquid phase. The latter could be iteratively reused without loss in reactivity over three runs.

Building on the early work of Letsinger on Brønsted base-assisted boronic acid catalysts (see above),[38] the group of Whiting has explored amine-functionalized boronic acids as amidation catalysts (Scheme 21).[81] *N,N*-Diisopropylbenzylamine boronic acid **22** emerged as a promising catalyst, with the suppression of N−B chelation due to the sterically hindered amine substituents being a key structural feature. For the

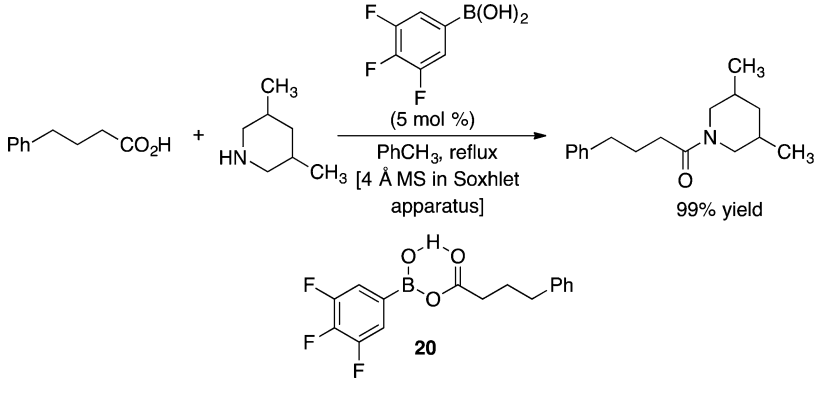
Scheme 20. Boronic Acid-Catalyzed Condensation and Reduction Reactions of Carboxylic Acids



coupling of benzylamine and benzoic acid in refluxing fluorobenzene (a set of conditions under which uncatalyzed condensation was minimized), catalyst **22** was found to provide higher yields than $B(OH)_3$ and 3,4,5-trifluorophenylboronic acid. Electronic tuning revealed that the installation of a CF_3 group para to the boronic acid substituent led to increased catalyst activity, whereas the presence of an *ortho*-methoxy group had a deleterious effect.[82] Whiting's group has also developed chiral bifunctional aminoboronic acids for kinetic resolutions proceeding through direct amidation.[83] Planar chiral, ferrocene-derived aminoboronic acid **23** provided 41% ee (21% conversion) for the condensation of benzoic acid with racemic α-methylbenzylamine (Scheme 21, eq 2). The relatively high reaction temperature required, competition with an uncatalyzed reaction pathway, and the potential decomposition of the chiral catalyst to $B(OH)_3$ (an active but achiral catalyst) are challenges to be overcome in the development of a highly enantioselective process of this type.

The relatively high reaction temperatures (≥85 °C) needed for the direct amidation reactions described in the preceding

Scheme 19. Direct Amidation Catalyzed by 3,4,5-Trifluorobenzeneboronic Acid



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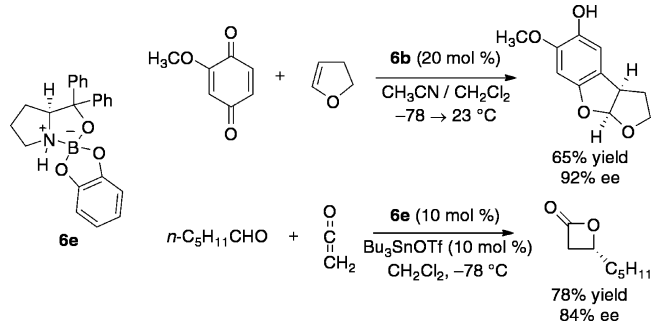
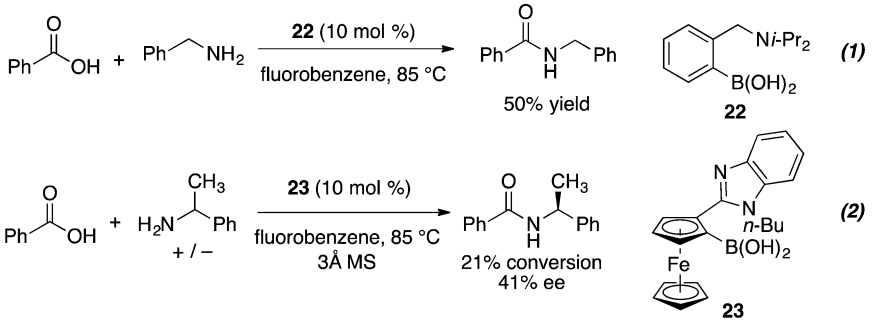


Figure 3. Recyclable boronic acid catalysts for direct amidation. Shaded circles denote cross-linked polystyrene beads.

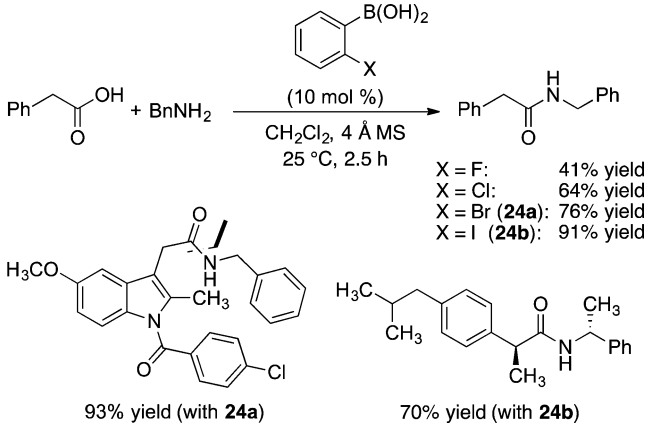
Scheme 21. Direct Amidation Reactions Catalyzed by Bifunctional Boronic Acid–Lewis Base Catalysts



paragraphs may limit certain applications. For example, boronopyridinium-catalyzed peptide coupling generated Cbz-Phe-Ala–O–*t*-Bu in 85% yield, but with complete racemization of the phenylalanine moiety.[79] Hall and co-workers' efforts to develop more active amidation catalysts have been focused on investigation of 2-functionalized arylboronic acids, based on the hypothesis that an ortho substituent can interact directly with the Lewis acidic boron center or activate a bound reagent or substrate. Evaluation of 46 boronic acids of this type led to the identification of 2-halophenylboronic acids as highly active catalysts, with 2-iodophenylboronic acid **24b** providing a 91% yield for the condensation of benzylamine and phenylacetic acid at 25 °C (CH_2Cl_2, 4 Å molecular sieves).[84] The conditions were tolerant of functionalized substrates such as the NSAID indomethacin and enabled the coupling of (*S*)-ibuprofen and (*R*)-α-methylbenzylamine with less than 5% racemization at either site (Scheme 22).

The unusual accelerating effect of the *ortho*-iodo substituent in **24b** motivated Marcelli to conduct a computational study of the direct amidation using density functional theory.[85] After evaluation of catalytic pathways involving charged and neutral intermediates and mono- and diacyloxyboronates, the author suggested that elimination of water from the catalyst-bound orthoaminal intermediate, a step that had been largely overlooked in prior mechanistic proposals, is turnover-limiting. A water-assisted transition state structure was calculated for this step, with the halogen substituents of the 2-haloarylboronic acid accepting an O–H···X hydrogen bond from a boron-bound hydroxyl group (Figure 4). The proposal that **24b** acts as a bifunctional catalyst has been supported by catalyst fine-tuning and mechanistic studies carried out in the Hall group.[86] Although the introduction of strongly electron-withdrawing groups—a modification shown to be beneficial in previous studies[72,81a]—led to less efficient catalysts, 5-methoxy-2-iodophenylboronic acid displayed enhanced activity. The introduction of a methoxy substituent para to the iodine group would be expected to increase its hydrogen bond-accepting ability while potentially

Scheme 22. Direct Amidation Catalyzed by *ortho*-Halophenylboronic Acids



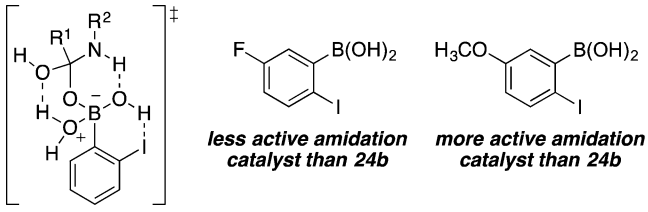


Figure 4. Calculated transition state structure for water-assisted orthoaminal breakdown using catalyst **24b**; substituent effects on the catalytic activity of 2-iodophenylboronic acid.

acting as a modest electron-withdrawing group toward the meta-positioned boronic acid. Additional experiments revealed a first-order kinetic dependence on catalyst concentration and indicated that boronic acids, rather than their dehydrated, trimeric boroxine congeners, are likely the active catalytic species. This study also highlighted the complexity of the catalytic system,

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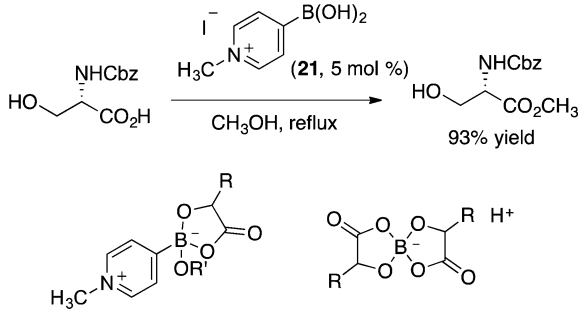
as reflected by (i) an inhibitory effect of the amine reagent, (ii) a dependence of the reaction rate on the order of addition of the substrates to the catalyst, and (iii) the potential dual role of molecular sieves as a drying agent and a source of small amounts of water.

4.2. Acylation of Alcohols. Following Houston's report that boric acid is an efficient catalyst for chemoselective esterification of α-hydroxycarboxylic acids,[69] Yamamoto and Ishihara compared the catalytic efficiencies of $B(OH)_3$ and electron-deficient boronic acids for couplings of this type.[87] Their studies indicated that boric acid is a more efficient catalyst when equimolar mixtures of the acid and alcohol are used, whereas **21** is more active when excess alcohol is employed as the reaction solvent. On the basis of these observations, the authors proposed that spiro-4-oxo-1,3,2-dioxaborolan-2-uides, generated by condensation of boric acid with 2 equiv of α-hydroxy acid, displayed particularly high reactivity as acylating agents (Scheme 23).

Scheme 23. Boronic Acid 21 As a Catalyst for Condensations of Alcohols with Hydroxycarboxylic Acids; Structures of Putative Tetracoordinate Acyloxyborane and Spiro-4-oxo-1,3,2-dioxaborolan-2-uide Intermediates



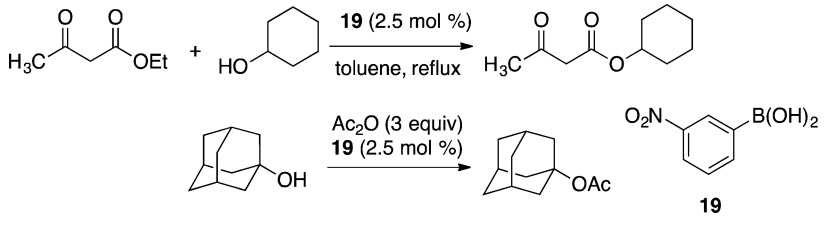
3-Nitrobenzeneboronic acid (**19**) has been applied as a catalyst for the transesterification of β-ketoesters in refluxing toluene (Scheme 24).[88a] Considering the selectivity of the method for β- over α- and γ-ketoesters as well as simple unfunctionalized esters, the authors speculated that an acylketene intermediate was involved. This same catalyst accelerates the acetylation of primary, secondary, tertiary, allylic, and propargylic alcohols with acetic anhydride.[88b] A mechanism for this second process was not proposed, and it is not clear whether acyloxyboranes of the type proposed in direct amidation reactions (see above) are involved.

Amine-functionalized borinic esters **25a** and **25b** are efficient catalysts for the alcoholysis of imides and related β-dicarbonyl electrophiles under near-neutral conditions and at loadings as low as 0.04 mol %.[89] Sterically unhindered alcohol nucleophiles were activated selectively: the relative rates of methanol versus ethanol activation by **25a** were 6.3:1, as established by competition experiments. Steric control was also evident with regard to the regioselectivity of attack on the imide functional group. For example, the methanolysis of the exocyclic carbonyl of *N*-acyloxazolidinone **26** was achieved with a greater level of selectivity using **25a** than with $NaOCH_3$, thus minimizing fragmentation of the chiral auxiliary (Scheme 25). The key step of the proposed catalytic cycle involves the addition of an ate complex-derived alkoxide to the imide carbonyl group, which is activated through hydrogen bonding to the ammonium moiety.

4.3. Synthesis of Carboxylic Anhydrides and Imides. Bifunctional boronic acid catalysis has been employed by Ishihara and co-workers for the synthesis of anhydrides from carboxylic acids without chemical dehydrating agents or high reaction temperatures. Electron-deficient boronic acid catalysts of the type employed previously in direct amidation were found to be ineffective, perhaps reflecting the poor nucleophilicity of carboxylic acids compared with amines. However, bis-(tetramethylpiperidinyl)-functionalized boronic acid **27** displayed excellent activity in refluxing propionitrile or heptane with azeotropic removal of water (Scheme 26). Spectroscopic and crystallographic studies suggested important roles for the bulky amine substituents, including suppression of intramolecular N–B interactions and stabilization of monomeric boronic acids through intramolecular hydrogen bonding. Calculations suggested that the amine acts as a Brønsted base to activate the carboxylic acid toward nucleophilic attack at the acyloxyboron center. A similar synergistic H-bonding network could then promote the collapse of the tetrahedral intermediate with extrusion of the anhydride product.[90] This strategy has also been applied for the direct synthesis of diimides from tetracarboxylic acids and primary amines, a reaction of potential utility for the direct synthesis of aromatic polyimides (Scheme 26). High yields were obtained for the condensation between aniline and **28**, without significant loss of catalytic ability upon recovery and reuse of the boronic acid by a simple filtration/solvent concentration procedure used for product and catalyst isolation.

4.4. Cycloadditions of Unsaturated Carboxylic Acids. Acyloxyboron intermediates generated from α,β-unsaturated carboxylic acids display enhanced reactivity as dienophiles, thus providing a unique mode of cycloaddition catalysis. Yamamoto and co-workers, who developed enantioselective Diels–Alder reactions between cyclopentadiene and methacrylic acid using **2** as a catalyst, proposed the involvement of an intermediate of this type (Scheme 27).[6] Further developments exploiting this type of substrate activation did not appear for almost two decades, until the group of Hall disclosed that 2-iodophenylboronic acid (**24b**) gave rise to high levels of rate acceleration for cycloadditions of acrylic acids with 2,3-dimethybutadiene, cyclopentadiene, or furan (Scheme 28).[84] A competition study between acylic acid and methyl acrylate revealed selective activation of the former, an outcome that would be difficult to achieve with conventional Lewis acid catalysis. Both the addition of exogenous water and

Scheme 24. Transesterification and Acetylation Catalyzed by 3-Nitrophenylboronic Acid



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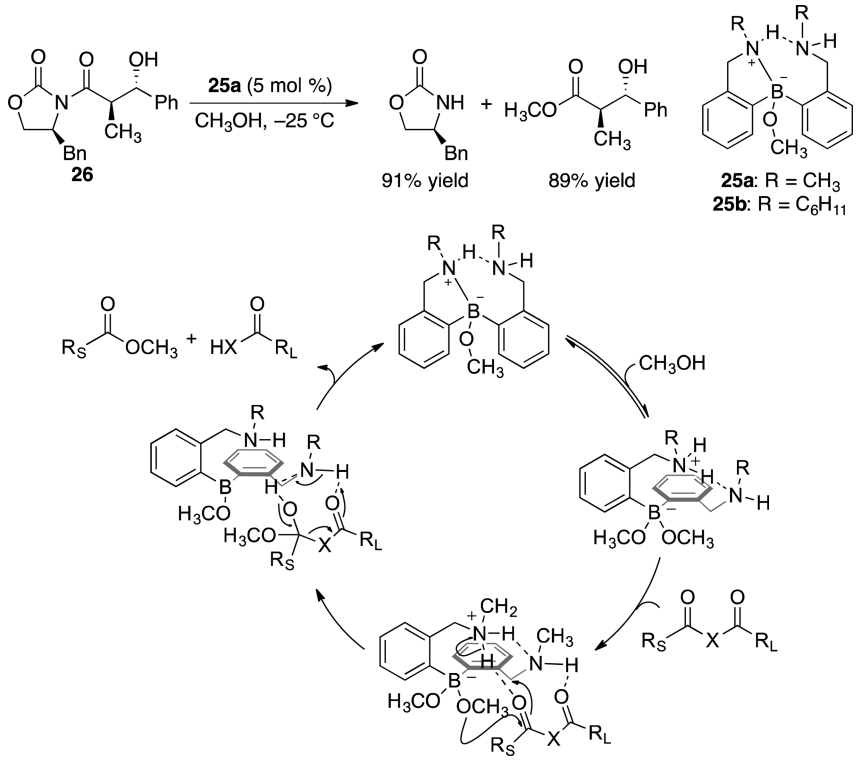
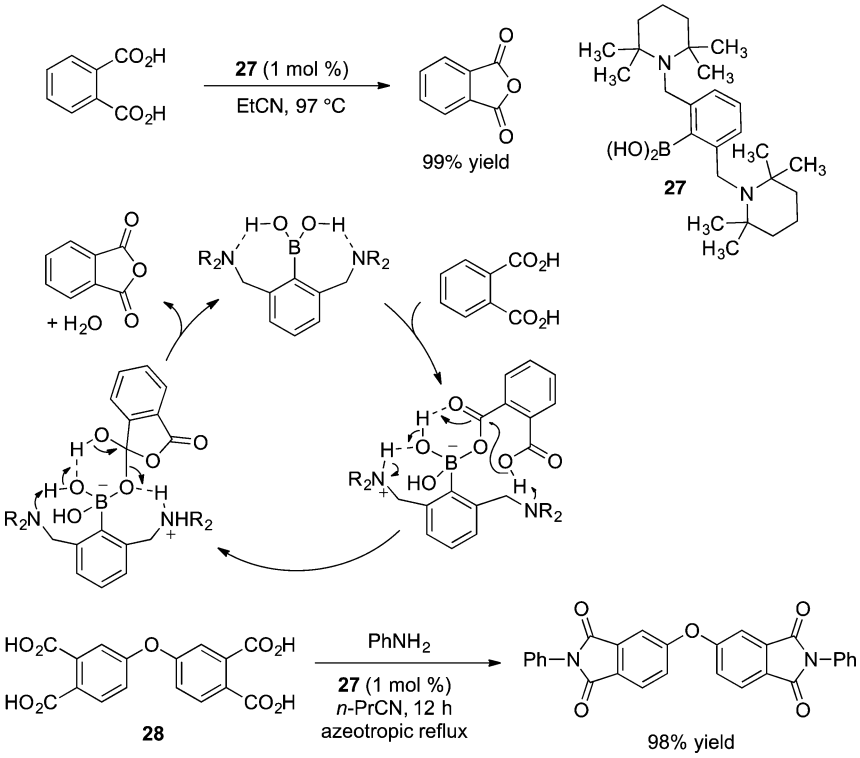
Scheme 25. Imide Alcoholysis by Bifunctional Borinic Acid Catalysts 25a and 25b, and Proposed Catalytic Cycle[a]



[a]R_S is less sterically demanding than R_L. Adapted with permission from reference 89. Copyright 2012 John Wiley & Sons, Ltd.

Scheme 26. Condensations of Dicarboxylic Acids Catalyzed by Bifunctional Boronic Acid 27[a]



[a]Adapted with permission from reference 90a. Copyright 2011 American Chemical Society, Ltd.

the use of a drying agent (molecular sieves) were found to be detrimental to reaction yield, suggesting that a low concentration of water was required for catalyst turnover and an excess caused inhibition. Taking advantage of the activity of **24b** as a catalyst for direct amidation (see Section 3.1), a one-pot cascade cycloaddition/amidation process was effected by simply charging the

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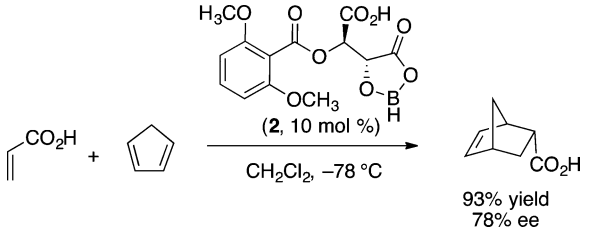
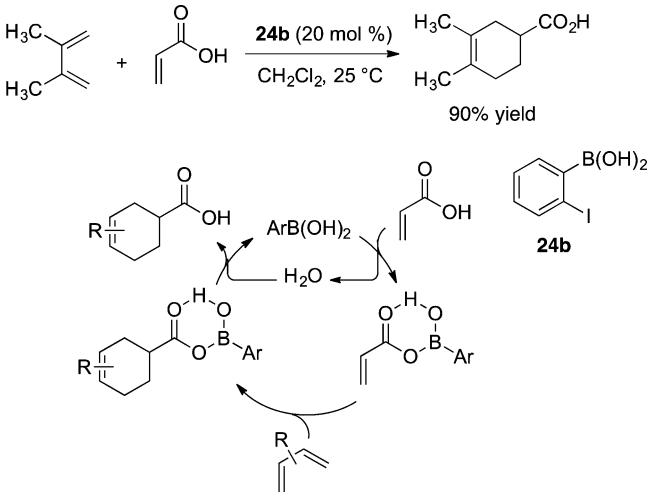
Scheme 27. Enantioselective Diels–Alder Cycloaddition of Acrylic Acid Catalyzed by a Chiral Acyloxyborane



Scheme 28. Boronic Acid-Catalyzed Diels–Alder Cycloaddition; Proposed Catalytic Cycle



reaction flask with amine and molecular sieves after completion of the cycloaddition.

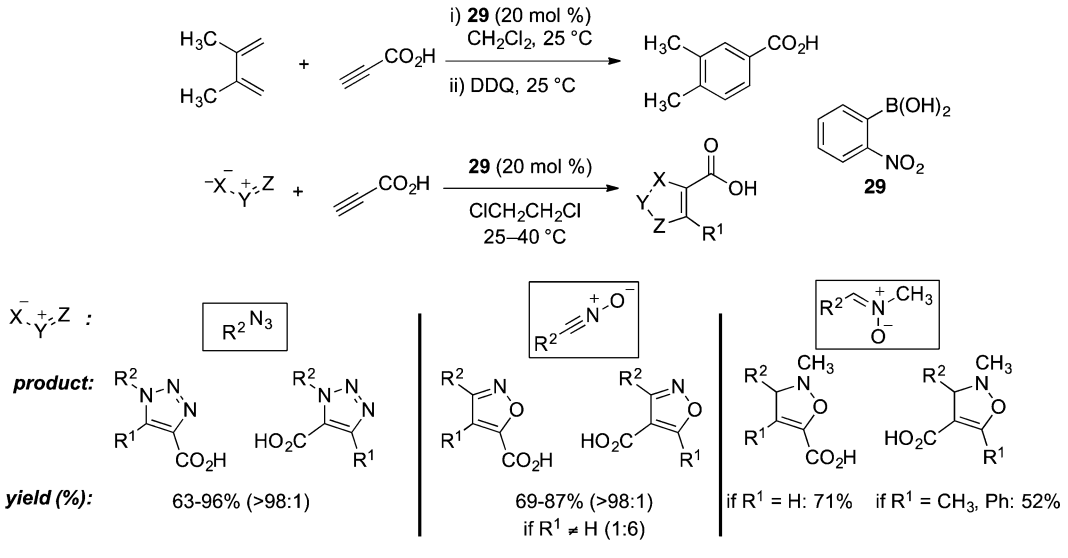
The scope of the boronic acid-catalyzed cycloaddition protocol has been extended to include 2-alkynoic acids as dienophiles, enabling the synthesis of substituted benzoic acids through a cycloaddition/aromatization one-pot sequence (Scheme 29).[91] The methodology was likewise amenable to [3 + 2] dipolar cycloadditions involving numerous partners, including azides, nitrile oxides, and nitrones.[92] In addition to significant levels of rate acceleration, the boronic acid-catalyzed reactions exhibited enhanced regioselectivity relative to the uncatalyzed process; the mild conditions employed in the catalytic protocol efficiently suppressed side reactions, such as the Beckmann rearrangement of nitrones and the decarboxylation of triazolecarboxylic acids generated by azide–alkynoic acid cycloaddition. The optimal catalyst identified for these transformations was *ortho*-nitrophenylboronic acid (**29**), with an internally hydrogen-bonded monoacyloxyborane again being proposed as the key intermediate. The change in ^{13}C NMR chemical shift of the β-carbon of crotonic acid, in analogy to the method of Childs, suggested a considerable redistribution of electron density in the unsaturated acid upon formation of an adduct of this type.

5. ACTIVATION OF HYDROXYL AS A LEAVING GROUP: CATALYSIS OF SUBSTITUTION, REARRANGEMENT AND ELIMINATION REACTIONS

Catalytic activation of alcohols toward nucleophilic displacement or elimination by ionization of the C–O bond is an appealing alternative to traditional approaches requiring stoichiometric activating reagents.[93] Transition metal complexes, Lewis acids derived from main group elements, and Brønsted acids have been identified as useful catalysts, most often using π-activated (benzylic, allylic, or propargylic) alcohols as substrates.[94] Organoboron acids are well-suited for such approaches, given their ability to engage in reversible covalent interactions with alcohols and their tolerance of water, the byproduct of direct substitution or elimination processes.

5.1. Direct Nucleophilic Substitution Reactions of Alcohols. In 2010, McCubbin's group reported that electron-deficient arylboronic acids catalyze the Friedel–Crafts alkylation of electron-rich aromatics and heteroaromatics with allylic alcohols.[95] In the presence of pentafluorophenylboronic acid and 4 Å molecular sieves, 2-methylfuran and activated allylic alcohol **30** underwent efficient condensation at room temperature (Scheme 30, eq 1). In a representative Friedel–Crafts dehydration, $C_6F_5B(OH)_2$ provided a higher yield than TsOH, $BF_3{\cdot}OEt_2$, and $FeCl_3$ and efficiency comparable to that of $AuCl_3$. Regio- and stereochemical outcomes, as well as trends in substrate reactivity, were consistent with the involvement of a

Scheme 29. Boronic Acid-Catalyzed Cycloadditions of 2-Alkynoic Acids



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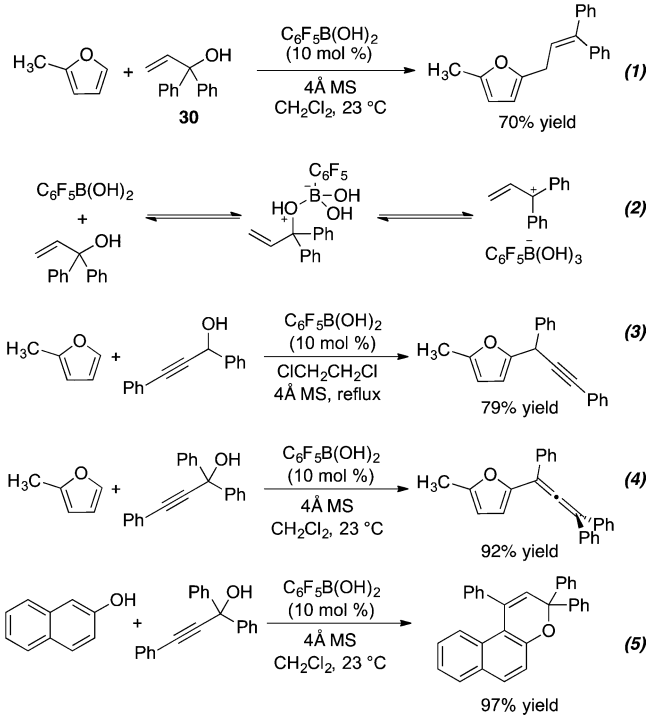
Scheme 30. Boronic Acid-Catalyzed Friedel–Crafts Alkylations Employing Allylic and Propargylic Alcohols

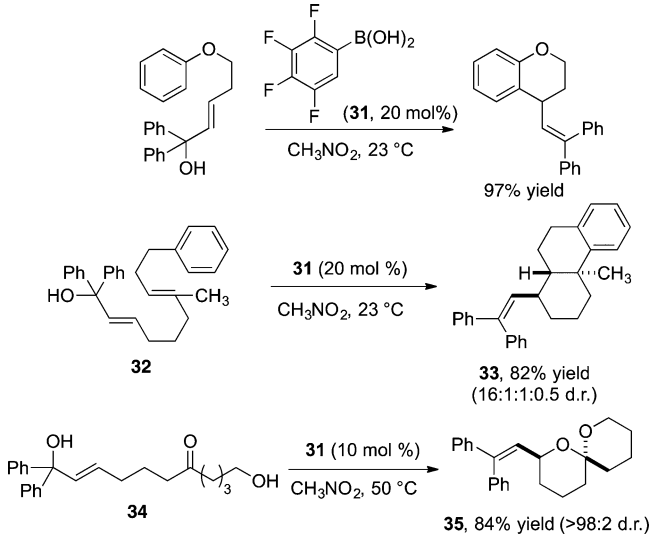


carbocation intermediate, presumably generated by ionization of an ate complex, as shown in eq 2. Subsequent reports from the group extended this mode of reactivity to benzylic[96] and propargylic alcohol substrates.[97] Reactions of benzylic alcohols proceeded efficiently, provided that a carbocation-stabilizing group was present either at the benzylic position (e.g., diarylmethanol substrates) or as an ortho or para substituent on the arene moiety. Friedel–Crafts reactions of propargylic alcohols provided access to substituted propargylmethyl or, in the case of more sterically hindered alcohol starting materials, allene products (eqs 3 and 4). A cascade reaction using 2-naphthol with a tertiary propargylic alcohol resulted in the formation of a substituted naphthopyran (eq 5).

Hall and co-workers have applied boronic acid catalysis to intramolecular displacements of alcohols by carbon- and oxygen-centered nucleophiles (Scheme 31).[98] Tetrafluorophenylboronic acid **31** provided yields superior to $C_6F_5B(OH)_2$: either reduced steric effects or a stabilizing CH···O hydrogen bonding interaction when employing **31** could contribute to this difference in catalytic activity. Under optimized conditions (nitromethane solvent, in the absence of dehydrating agent), reactions generally proceeded efficiently at room temperature or with mild heating (50 °C), and a near-quantitative recovery of boronic acid **31** was demonstrated. Tricyclization of **32** generated benzo-fused *trans*-decalin **33**, whereas **34** resulted in the spiroketal **35**, with both products being formed in high diastereomeric ratios. The substrate scope and reactivity trends suggested the involvement of a carbocation intermediate.

In the absence of an external nucleophile, allylic alcohols underwent boronic-acid 1,3-transposition reactions, driven by the formation of a conjugated or more highly substituted alkene product (Scheme 32).[99] Propargylic alcohols underwent the related Meyer–Schuster rearrangement, generating enone products. Evaluation of eight electron-deficient boronic acid catalysts revealed that tetrafluorophenylboronic acid **31** provided

Scheme 31. Intramolecular Boronic Acid-Catalyzed Nucleophilic Substitution Reactions of Allylic Alcohols



useful results for the majority of substrates, with hexafluoronaphthaleneboronic acid **36** being preferred for challenging cases. Both exogenous water and 4 Å molecular sieves impaired the catalytic reactivity, consistent with previous observations on boronic acid-catalyzed cycloaddition reactions.[84] Optically enriched substrates **37a** (96% ee) and **37b** (99% ee) underwent 1,3-transposition to generate products **38a** and **38b** in 23% and 87% ee, respectively, suggesting a substrate-dependent, borderline S_N1'/S_N2' mechanism. To further elucidate the extent of ionization, ^{18}O-labeling studies were carried out using a stoichiometric quantity of boronic acid **31**. In an isomerization proceeding through a solvent-separated ion pair, a statistical distribution of the labeled oxygen would be expected, leading to allylic alcohol product with 33% ^{18}O incorporation. Conversely, essentially no retention of the ^{18}O label in the allylic alcohol product would be expected for a reaction proceeding through a closed transition state. Enone with 33% ^{18}O content was generated from propargyl alcohol **39**, consistent with an ionization-based mechanism: geometrical constraints of the propargylic system likely preclude a closed transition state. Allylic alcohol **40**, a better candidate for a chairlike transition state, resulted in only 10% ^{18}O transfer to the product, suggesting significant S_N2' character.

5.2. Organoboron Acid-Catalyzed Dehydrations. In addition to nucleophilic substitutions, elimination reactions of hydroxyl groups are catalyzed by organoboron acids. In the course of their efforts to develop borinic acid-catalyzed Mukaiyama aldol reactions, the group of Yamamoto observed that $(C_6F_5)_2BOH$ efficiently promoted the dehydration of β-hydroxyketones to *E*-configured α,β-enones (Scheme 33).[59] *Anti*-aldol products underwent borinic acid-catalyzed elimination more rapidly than their syn diastereomers. This observation was consistent with a mechanistic proposal involving two-point binding of the hydroxy ketone to the borinic acid: the anti-configured product allows for the pseudoequatorial placement of the R^1 and R^3 substituents while orienting the α-proton in the pseudoaxial position (thus meeting the stereoelectronic requirement for the deprotonation step). While somewhat distinct from the reactivity described in this section, the electron-rich borinic acid $(C_6F_5)_2BOH$ also activates alcohols toward Oppenauer oxidations (trimethylacetaldehyde, $MgSO_4$, toluene, 23 °C); hydride transfer from a boron alkoxide to

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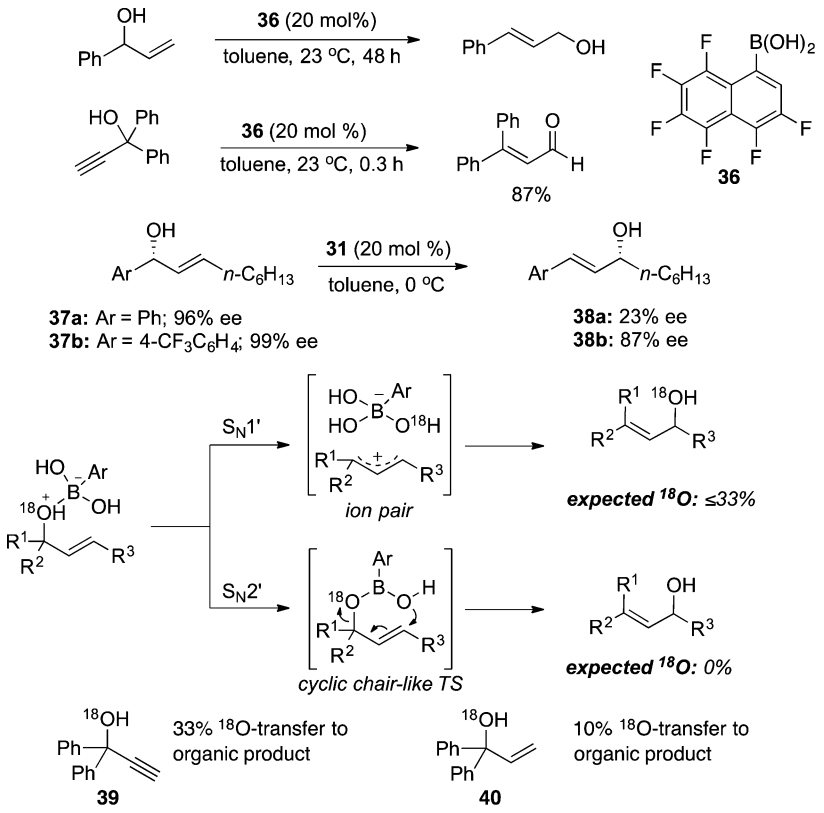
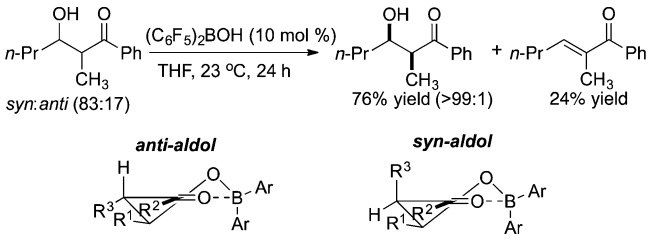
Scheme 32. Rearrangements of Allylic and Propargylic Alcohols Catalyzed by Electron-Deficient Boronic Acid 36; Stereochemical Studies and ^{18}O Labeling Experiments



Scheme 33. Borinic Acid-Catalyzed Dehydration of β-Hydroxy Ketones



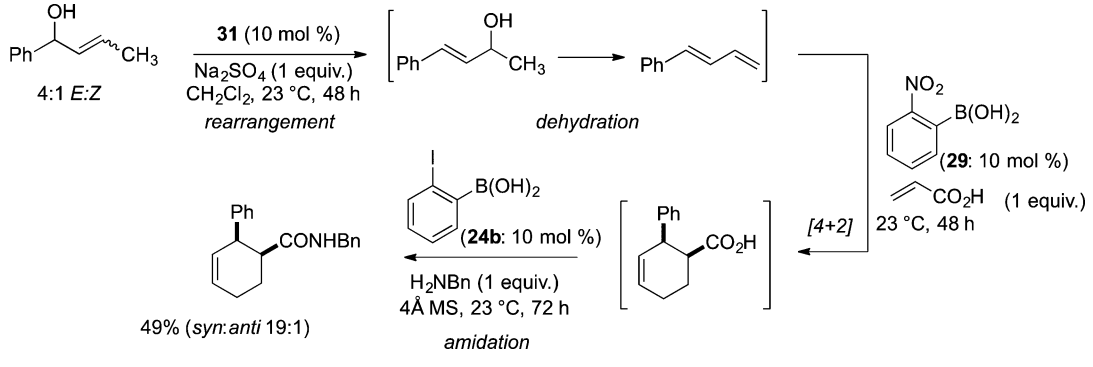
a coordinated aldehyde group is a likely mechanism for this process.[100]

Hall and co-workers observed that certain products of allylic alcohol 1,3-transposition reactions underwent boronic acid-catalyzed elimination to generate butadienes. Taking advantage of the versatile catalytic reactivity of boronic acids, a one-pot 1,3-transposition/elimination/cycloaddition/amidation sequence was carried out using three distinct catalysts (Scheme 34).

6. ACTIVATION OF HYDROXYL GROUPS AS PRO-NUCLEOPHILES

The preceding section indicates that binding of a hydroxyl group to an electron-deficient boronic acid can promote ionization, leading to enhanced electrophilic reactivity. On the other hand, the condensation of organoboron acids with alcohols has also proved to be a useful method for catalytic generation of activated, oxygen-centered nucleophiles, enabling regioselective manipulations of di- and polyols. The blueprint for this reactivity pattern was established by Aoyama and co-workers, who showed that the boronate ester **41** derived from $PhB(OH)_2$ and methyl α-fucopyranoside could be activated toward regioselective

Scheme 34. One Pot, Tandem Reaction Sequence Employing Multiple Boronic Acid Catalysts



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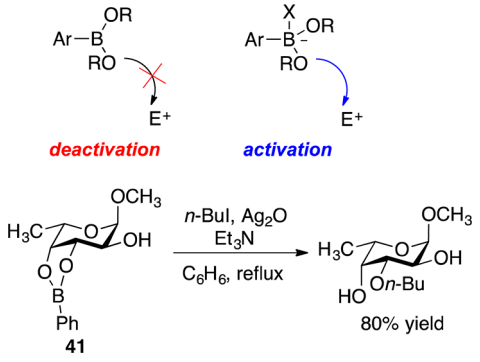
alkylation by addition of the Lewis base Et_3N (Scheme 35).[101] This chemistry was extended to selective glycosylations, also via a

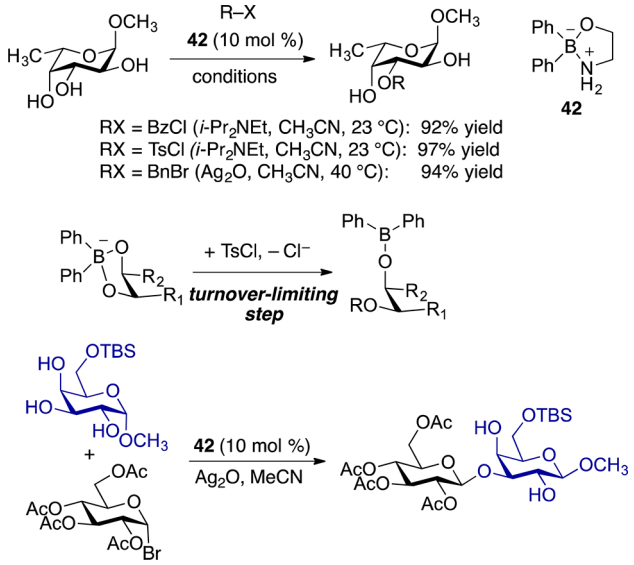
Scheme 35. Protection versus Activation in Tri- And Tetracoordinate Boron Alkoxides; Regioselective Alkylation through Lewis Base Activation of Boronic Ester 41



proposed tetracoordinate boronate intermediate.[101b] These observations indicated that whereas boronic esters display attenuated nucleophilicity at oxygen (a feature that enables their applications as protective groups for 1,2- and 1,3-diols[2a]), formation of a tetracoordinate adduct can trigger their reactivity toward electrophiles. The nucleophilic reactivity of tetracoordinate complexes has also been invoked to explain the rate accelerations of salicylaldimine hydrolysis reactions by arylboronic acids.[102]

Our group has pursued activation of di- and polyols using borinic acids, on the basis of the hypothesis that this class of organoboron acids would provide access to nucleophilic, tetracoordinate diolate adducts under anhydrous conditions and in the absence of a Lewis base. Our earlier work on direct aldol reactions of pyruvic acids[62] (Section 3.1) hinted at the feasibility of this proposal. (The recent work of Saito on bifunctional catalysts for imide alcoholysis (Section 4.2) provides another instance in which tetracoordinate borinate esters are proposed to act as O-centered nucleophiles.[89]) Indeed, the commercially available ethanolamine ester of diphenylborinic acid (**42**) was identified as a catalyst capable of activating pyranoside-derived triol substrates as well as a range of diols, toward regioselective reactions with acyl, sulfonyl, and alkyl halide electrophiles (Scheme 36).[103] For carbohydrate-derived substrates, selective activation of *cis*-1,2-diol groups was observed, with delivery of the electrophile to the equatorial OH group. The preferential interaction of the catalyst with *cis*-1,2-diol moieties was consistent with patterns of carbohydrate binding by organoboron compounds that are apparent from the molecular recognition literature:[104] the selectivity for the equatorial OH group could reflect a steric effect, although calculated Fukui indices pointed to electronic differences between the two boron-bound alkoxide groups. Studies of the O-tosylation of *cis*-1,2-cyclohexanediol suggested that **42** acts as a precatalyst, with displacement of the ethanolamine ligand being facilitated by N,O-bis(tosylation); first-order kinetics in catalyst and TsCl, zero-order kinetics in *i*-Pr_2NEt, and pseudo-zero-order (saturation) kinetics in diol substrate were consistent with sulfonylation of the cyclic borinate ester being turnover-limiting, a proposal that was further supported by catalyst substituent effect studies. It should be noted that arylboronic acids have also been shown to catalyze the monoalkylation of symmetrical 1,2- and 1,3-diols, such as (±)-hydrobenzoin and *cis*-cyclohexanediol, with 4-fluorophenylboronic acid being identified as optimal for several substrates.[105] The selective activation of *cis*-cyclohexanediol over cyclohexanol indicated the importance of two-point binding to the

Scheme 36. Borinic Acid-Catalyzed Acylation, Sulfonylation, Alkylation, and Glycosylation of Pyranoside Substrates



boronic acid catalyst, although the precise nature of the activated species is not completely clear.

Borinic acid catalysis was successfully extended to regioselective activation of glycosyl acceptors, using glycosyl halide electrophiles in conjunction with Ag_2O as a halide abstracting reagent (Scheme 36).[106] Limitations to this process clearly exist; as described above, it is restricted to glycosyl acceptors bearing *cis*-1,2-diol moieties. Furthermore, only glycosidic linkages having the 1,2-trans configuration could be generated, apparently reflecting an S_N2-type displacement of the axially configured halide leaving group. From this perspective, further study of small-molecule (nonenzyme) catalysts capable of influencing the regiochemical outcome of glycosylation reactions would be of great interest, with potential applications in the synthesis and study of oligosaccharides and glycosylated natural products.

7. CONCLUSIONS AND OUTLOOK

Organoboron acids were used as components of some of the first chiral Lewis acids to be developed, and it is clear that their application in catalysis remains an active and highly relevant field. Brønsted- and Lewis-assisted organoboron Lewis acids that have been discovered in recent years are remarkable for both their catalytic activity and their generality, and their emergence has led to a dramatic expansion in the scope of stereoselective cycloaddition methodologies. Bifunctional and assisted catalysis involving boronic acids has gained significant momentum; as new modes of catalytic reactivity involving boronic acids are discovered, opportunities to develop such bifunctional catalysts will continue to expand. Furthermore, the ability to use boronic ester formation as a simple method for catalyst fine-tuning is likely to be applicable to many catalyst classes. Organoboron acids appear to possess unique properties as catalysts for dehydration reactions (acyl transfer reactions of carboxylic acids and nucleophilic substitutions of alcohols), and there are many appealing prospects for future work in this area, ranging from applications in peptide coupling to enantioselective catalysis. Understanding the mechanistic intricacies of these superficially simple transformations will likely accelerate developments of this type. The ability to take advantage of the reversible covalent interactions between carbohydrates and organoboron acids in

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catalysis is a relatively new direction, and numerous applications in stereoselective catalysis and target-oriented synthesis can be envisioned. Improvements in catalyst activity or alterations in selectivity, perhaps through the development of bifunctional catalysts equipped with substrate-binding or -activating groups, would also be of interest.

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

Ala,alanine; Phe,phenylalanine; SDS,sodium dodecyl sulfate; TIPS,triisopropylsilyl; TMS,trimethylsilyl; Ts,*para*-toluenesulfonyl

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