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Reactivity and Synthetic Applications of Multicomponent Petasis Reactions

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ABSTRACT: The Petasis boron–Mannich reaction, simply referred to as the Petasis reaction, is a powerful multicomponent coupling reaction of a boronic acid, an amine, and a carbonyl derivative. Highly functionalized amines with multiple stereogenic centers can be efficiently accessed via the Petasis reaction with high levels of both diastereoselectivity and enantioselectivity. By drawing attention to examples reported in the past 8 years, this Review demonstrates the breadth of the reactivity and synthetic applications of Petasis reactions in several frontiers: the expansion of the substrate scope in the classic three-component process; nonclassic Petasis reactions with additional components; Petasis-type reactions with noncanonical substrates, mechanism, and products; new asymmetric versions assisted by chiral catalysts; combinations with a secondary or tertiary transformation in a cascade- or sequence-specific manner to access structurally complex, natural-product-like heterocycles; and the synthesis of polyhydroxy alkaloids and biologically interesting molecules.

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The PR has been developed as a powerful multicomponent transformation owing to several attractive features, such as a wide scope and relatively diverse variability for each of the three PR components, compatibility with various secondary transformations, and high stereoselectivity for the formation of functional amine products, together with other merits including mild and robust reaction conditions, ready availability of starting substrates, flexible scalability ranging from microscale to gram scale, and an atom-economical nature (Figure 1). In addition to the versatile synthetic utility, the biologically relevant properties of many products make the PR a powerful tool in probe compound development and drug development. The topic has been reviewed on several occasions in both book chapters and journal articles, either as a comprehensive summary, such as the chapter in 2005 by Petasis and coworkers, and the full compilation in 2010 by Candeias and coworkers, or a part of a broader topic, such as the nucleophilic addition of boronic acids and derivatives to imines, asymmetric MCRs, and stereocontrolled cascade reactions.

Although mechanistic understanding is still progressing, a boronate complex formed between the boronic acid and the in situ generated iminium species derived from the amine and carbonyl components is believed to be the key intermediate, which facilitates the nucleophilic addition of the boronate substituent to the electrophilic iminium ion. This assumption has been supported by a range of mechanistic studies performed, including density functional theory (DFT) analysis and nuclear magnetic resonance (NMR) analysis, as well as the characterization of crystal structures for boronate intermediates. The irreversible nature of the last step involving the cis-diastereoselective transfer of the boronate substituent with the simultaneous formation of a new carbon–carbon bond classifies the PR as a type-II MCR.

Developments reported in the past 8 years have significantly expanded the scope of the PR, leading to maturation of the reaction in five general directions. First, the reactivity and substrate scope of the classic type of three-component PR have been extensively explored through the application of masked or new carbonyl components, unconventional amines such as amides and aminophosphonates, as well as a wide range of boronic acid and boronate reagents, such as allenyloboronic acids and allenylboronates. Second, the classic three-component PR has been elaborated into a more complex four-component variant. Third, Petasis-type reactions based on preformed imine substrates in two-component types or with noncanonical substrates in three-component types have been developed. Fourth, the PR has been combined with secondary transformations in cascade- or sequence-dependent manners, such as subsequent Diels–Alder reactions to access polycyclic scaffolds with a high content of sp3-hybridized carbon atoms. Fifth, PRs have been applied for the synthesis of biologically active compounds, including the total synthesis of polyhydroxy alkaloids. In addition, PRs have been performed under various new reaction conditions in comparison with the traditional catalyst-free procedures, represented by the use of chiral or metal catalysts (Figure 1). The year of 2018 marked the 25th anniversary of the initial report on this versatile MCR. In this Review, we provide a comprehensive discussion of PRs with an emphasis on the reaction scope and synthetic application to access structurally diverse products, covering recent synthetic examples reported between 2011 and 2018. The synthetic examples listed in the following sections are classified...
according to the five general directions summarized above. Asymmetric PRs catalyzed by chiral catalysts or auxiliaries were incorporated into Sections 2 to 5. An applied first filtration rule is that examples are only being grouped into the second section of “three-component Petasis reactions” if they cannot be appropriately covered under other sections. It is noteworthy that PRs have been successfully demonstrated in the solid phase for the synthesis of both amino acids and peptides.43−46

Figure 1. Reactivity and synthetic applications of multicomponent petasis reactions. (A) Five overall directions for the PR covered in this Review, including asymmetric variants. (B) Representative examples of the three components typically used in PRs: carbonyls, amines, and boronic acids or other boronic components. (C) Common merits and limitations of PRs.
including the synthesis of fluorous-tagged N-alkylated amino acids using fluorous-tagged hydroxylamines,\textsuperscript{47,48} derivatization and stapling of peptides by an on-resin PR,\textsuperscript{49} and combinatorial synthesis of peptidomimetics employing PR-Ugi sequence reactions,\textsuperscript{50} but such solid-supported PRs are generally not covered in this Review.

## 2. THREE-COMPONENT PETASIS REACTIONS

### 2.1. Glyoxylic Acid and Derivatives as the Carbonyl Component

#### 2.1.1. Glyoxylic Acid.

Glyoxylic acid monohydrate has been widely used in PRs for the synthesis of phenylglycine derivatives as tissue factor/factor VIIa inhibitors (TF-FVIIa).\textsuperscript{24,51−54} A series of phenylpyrrolidine phenylglycinamides was synthesized and evaluated as TF-FVIIa inhibitors.\textsuperscript{24,51} The PR of glyoxylic acid, Boc-protected 1,6-diaminoisoquinoline, and phenylboronic acids led to the formation of phenylglycinamides 1 that were coupled to phenyl pyrrolidinyl and yielded a series of TF-FVIIa inhibitors. Enantiomerically pure compounds were obtained by chiral separation. The carboxypyrrolidinyl compound 2 showed a clean in vitro safety panel against receptors and enzymes, a moderate clearance, and a low distribution volume (Scheme 1).\textsuperscript{51}

On the basis of the structural information obtained through modeling of the TF-FVIIa active site, series of macrocyclic phenylglycinamides as TF-FVIIa inhibitors was designed and synthesized with the aim to improve the poor rodent metabolic stability and oral bioavailability of previously reported phenylglycinic inhibitors.\textsuperscript{19,52−54} Key intermediates 4 and 7 were obtained through PRs of glyoxylic acid monohydrate, Boc-protected 4-fluoro-1,6-aminoisoquinoline, and in-house synthesized requisite boronic acids 3 or 6 with a trimethylsilyloxy carbonyl protecting group. Macrocyclization of 4 via intramolecular amidation and subsequent chiral...
separation yielded 5, whereas the intramolecular urea formation of 7, followed by subsequent chiral HPLC separation, gave 8 (Scheme 2). Although this series of macrocyclic TF-FVIIa inhibitors showed improved potency and rodent metabolic stability, they suffered from poor tissue kallikrein selectivity and poor rat pharmacokinetic properties.19

PRs have been used for the synthesis of N-monomosaccharide-substituted α-amino acids.55 N-Glycosyl α-amino acids 9 were recently synthesized from tetraacetyl-D-glycosamine hydrochloride, alkenylboronic acids, and glyoxylic acid. Although chiral D-glycosamine substrate was used, the product was formed with a low diastereomeric excess (de) value (17%). In addition, the fact that the replacement of the glyoxylic acid with pyruvic acid afforded only 9% of the expected product 9c showed the limited scope of this reaction (Scheme 3).56

In addition to the use of CH2Cl2, MeCN, and MeOH as common solvents for the PR, the addition of other polar solvents, such as TFA, has been observed to accelerate the PR, as judged by the reduced reaction time. The PR of glyoxylic acid, 5-nitroindoline, and boronic acid was accelerated by TFA to give a series of 2-(5-nitroindolin-1-yl)-2-arylacetic acids 10 in moderate to good yield with reaction times ranging from 1 to 7 h. The reaction showed a good substrate scope for boronic acids, with the exception of the more electron-deficient 4-nitrophenylboronic acid. The obtained arylacetic acids 10 were studied as precursors for the synthesis of potential HDAC inhibitors (Scheme 4).57

The direct borylation of azulene gave azulen-1-ylboronic acid pinacol ester,58 which was used as the boronic component to react with glyoxylic acid monohydrate and various amines to afford azulenyglycine compounds 11 in good yields. Azulene was formed as a byproduct in this PR through the protodeboronation of the boronic acid pinacol ester (Scheme 5). As this PR proceeded, a significant color change from violet to blue, owing to the unique π-electron property of azulene, was observed.59

Helicenes are polycyclic aromatic screw-shaped nonplanar compounds that can be used as building components for chiral ligands.60 The fusion of more than five benzene or other aromatic rings leads to inherent helical chirality, distinguished by an enantiopure (P) or (M) configuration.61 Enantiopure carbol[6]helicenyl boronate (M)-12, synthesized via a key photocyclization step from a tetracyclic boronate substrate, was recently further functionalized to give several amino derivatives that were employed in a range of different steps, among which was an asymmetric PR using glyoxylic acid monohydrate and morpholine, followed by a TMS−diazomethane-mediated methylation to give morpholine 13 in modest stereoselectivity with a diastereomeric ratio (dr) value of 7:3 (Scheme 6). The stereochemistry of the minor (M,S) isomer of 13 was confirmed by X-ray crystal structure.62

Manolikakes and coworkers reported the use of sulfonamides as the amine component in both palladium-catalyzed and catalyst-free PRs.63,64 The PR of sulfonamides, glyoxylic acid monohydrate, and aryl- or alkenylboronic acids led to the formation of substituted α-aryl- or α-alkenylglycines 14−19. This method bears the common advantages of the classic PR, being both catalyst-free and air- and moisture-tolerant. A wide substrate scope in terms of both the sulfonamides and boronic acids was tested, and only electron-poor sulfonamides (quinoline-3-sulfonamide and 4-nitrobenzenesulfonamide) or boronic acid (pyridine-3-ylboronic acid) failed to react (Scheme 7).64

Kuroda and coworkers reported the application of a PR of glyoxylic acid, N-methylbutylamine, and 1-pyrenboronic acid for the synthesis of a fluorescent α-amino acid as a method to...
determine the glyoxylic acid concentration in urine. Recently, the same group reported the determination of glyoxylic acid in human serum as a potential diagnostic approach for diabetes by utilizing a PR. Glyoxylic acid as a target model analyte was demonstrated to react with 1-pyreneboronic acid, thus incorporating a measurable fluorescent moiety, and taurine as a smooth purification tag to a sulfonic acid, which can be easily purified using ion-exchange chromatography (Scheme 8).

Other previous examples of using glyoxylic acid as the carbonyl component in PRs include the synthesis of fused 1,2,5-triazepines and tetrahydrocarbazoles from N-Boc-hydrazines.

### 2.1.2. Sulfonamide as Chiral Auxiliary in an Asymmetric Petasis Reaction

Hutton and coworkers reported the preparation of βγ-dihydroxyamino acid derivatives through different PR-based strategies. In a synthetic approach aiming to access a key dihydroxymototyrosine fragment for the total synthesis of echinocandins, a series of βγ-dihydroxyamino acid derivatives were obtained through a PR asymmetric dihydroxylation sequence. It was observed that a higher concentration (0.33 M in CH2Cl2 in comparison with 0.2 M in CH2Cl2) led to the complete conversion of the Petasis product from glyoxylic acid, chiral tert-butylsulfonamide, and substituted (E)-styrylboronic acids in excellent yield ranging from 90 to 99% and good to high diastereoselectivity. The N-sulfonamido amino acids were subsequently treated with hydrochloric acid in methanol to give sulfonamide-cleaved and concomitantly esterified methyl esters, which were further Cbz-protected and asymmetrically dihydroxylated using pseudoenantiomeric ligand (DHQ)2-PHAL to yield the desired (S,S,S) isomer of βγ-dihydroxy amino acid ester (Scheme 9).

A series of βγ-unsaturated α-amino acids were synthesized through an enantioselective PR of glyoxylic acid, (S,)-2-methylpropane-2-sulfonamide, and vinylboronic acids promoted by InBr3 (Scheme 10). It was proposed that a five-membered ring chelate between the quaternary boronate complex and the Lewis acidic indium contributed to the re-face migration of the boronic vinyl group to afford an R-configured product.

The same type of InBr3-promoted PR of glyoxylic acid monohydrate and (S)-2-methylpropionate-sulfonamide was used for the asymmetric synthesis of Petasis product using either 2-benzofuryl or 2-benzothienylboronic acid. The further transformation of led to a series of oxadiazines that were evaluated as γ-secretase modulators with predicted favorable drug-like properties for treating CNS diseases, such as Alzheimer’s disease (Scheme 11).

### 2.1.3. Glyoxalates in the Palladium-Catalyzed Asymmetric Petasis Reaction

To improve the relatively limited scope of the classical PR, where electron-rich boronic acids typically are needed, transition-metal-catalyzed Petasis additions of boronic acids to in situ formed imine species from aldehyde and amine components have been explored. A palladium(II) trifluoroacetate-catalyzed PR of glyoxylic acid and sulfonamides employing chiral ligand (S,S)-iso-propyl-4,4′,5′,5′-tetrahydro-2,2′-bioxazole was reported by Manolikakes and coworkers for the synthesis of α-aryl glycines in moderate to good yield and with excellent enantioselectivity (>99:1). The scope of the reaction was evaluated with aryl and...
alkyl sulfonamides, glyoxalates, and arylboronic acids (Scheme 12). Subsequent amine protection using 2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-sulfonyl enabled the racemization-free removal of the sulfonyl group to give the corresponding free amines.74 Previously, the same research group reported the enantioselective synthesis of \( \alpha \)-arylamines using a palladium-catalyzed PR, using the chiral tetrahydrobioxazole ligand 26, of aldehydes, sulfonamides, and arylboronic acids.63 In addition to the previously mentioned examples of catalysis, ultrasound irradiation has also been used to promote the PR of glyoxylic acids in the synthesis of \( \alpha \)-arylglucines.75

### 2.2. Salicylaldehyde and Derivatives as the Carbonyl Component

#### 2.2.1. Salicylaldehyde

Tertiary phenolamines of general structure 28 can be obtained through PRs involving salicylaldehyde. This common product may be synthesized via PRs under a variety of conditions.76–79 The addition of molecular sieves (MSs) to remove water usually accelerates this PR variant,80–82 although PRs are reported to be water-compatible.83–85 Water removal from the reaction mixture presumably drives the equilibrium from a hemiaminal species formed between aldehyde and amine components to a synthetically active iminium species. A PR of salicylaldehyde derivatives was performed in the presence of MS, which made it possible to perform the reaction under milder conditions at room temperature and to eliminate side products. The reaction showed good tolerance toward different salicylaldehydes and arylboronic acids for the synthesis of target alkylaminophenols 28 in generally moderate to good yield. A few failed examples
included the use of the electron-deficient 3-nitrophenylboronic acid and the substitution of a second hydroxyl group on the salicylaldehyde (Scheme 13). The developed method was applied for the synthesis of the core scaffold of BIIB042, a γ-secretase modulator with potential applications in the treatment of Alzheimer’s disease. In addition to the arylboronic acids used in this study, a wide range of boronic acid components have also been employed in PRs with salicylaldehydes and secondary amines, such as boronobenzylphosphonates. Alkylaminophenols with core scaffold 28 could also be generated through cobalt ferrite nanoparticle-catalyzed PRs. Another series of similar diphenylmethanamines, generally containing a morpholino instead of a pyrrolidino alkyl moiety, was synthesized using a catalysis based on chitosan or trititanate nanotubes in high yield. The methodology could also be extended to a series of piperazine-substituted aminophenols. Other catalysts, including lanthanum(III) trifluoromethanesulfonate, Mg–Al mixed oxides, and 4 A supported copper catalysts, were also applied in the PR of salicylaldehyde, morpholine, and arylboronic acid. 2-(Aryl(piperidin-1-yl)methyl)phenols sharing the same or higher structural familiarity as 28 were recently used as substrates for the synthesis of 9-aryl-2,3,4,9-tetrahydro-1H-xanthen-1-ones in a FeCl₃-mediated approach involving nucleophilic substitution and intramolecular cyclization steps. A microwave-assisted PR catalyzed by CuO-nanoparticle-decorated reduced graphene oxide composite was recently reported for the synthesis of similar aminophenols. Additionally, Petasis products of the same scaffolds as that of 28 were obtained through a tetratornular Zn₂Dy₂ coordination cluster-catalyzed PR, featuring the low catalyst loading of the Zn₂Dy₂ coordination cluster. Diaminophenols 29, which can be classified as a double Petasis product involving two identical salicylaldehydes and two amines, were also obtained in good yield but with unknown diastereoselectivity in this Zn₂Dy₂-catalyzed method from benzene 1,4-diboronic acid (Scheme 14). A recent solvent-free protocol using ball milling was reported for the synthesis of alkyl- and arylaminophenols of the same scaffolds.

Tertiary phenolamines obtained through a one-step PR could be directly applied in biological studies without further functionalization. Candeias, Rijo, and coworkers reported the antibacterial activities of tertiary phenolamines synthesized by a three-component PR from salicylaldehyde. Testing against a panel of Gram-positive and Gram-negative bacteria, indoline-substituted aminophenols, such as compound 30, showed the most potent antibacterial activities. Additionally, indolines sharing the same scaffold as 30 were reported to have weak cytotoxicity against U2OS cells via apoptosis-induced cell death, and tertiary phenolamines of the scaffold of 30 have shown cytoxicities against osteosarcoma cells. Later, the Petasis product 31, which shares a high degree of structural similarity with 30 but differs by the nature of the para substituent of the phenyl group, was evaluated as a selective, potent antibacterial against multi-drug-resistant Gram-positive bacteria for nosocomial infections. The Petasis product 32 was recently released as a site-specific (Ser99) inhibitor of human BCL2-associated death promoter phosphorylation (Scheme 15).

The decarboxylation of proline has been previously reported as a modification strategy to give functionalized unnatural α-amino acid analogs. A decarboxylative PR of proline, salicylaldehyde, and arylboronic acids was employed for the synthesis of aminophenols 34. It was proposed that the condensation of proline with salicylaldehyde gave an iminium ion species comprising a tetracoordinated boronate intermediate 33, which led to pyrrolidine 34 upon the translocation of the aryl group from the boron to the iminium carbon (Scheme 16).

2.2.2. Thiourea-Catalyzed Asymmetric Petasis Reaction. A dual thiourea–INOL catalyst 35 was selected for the PR of salicylaldehyde after screening a series of chiral thiourea organocatalysts. The amine scope was tested for secondary
amines including morpholine, piperidine, and pyrrolidine, and both aryl and vinylboronic acids were employed for the synthesis of target compounds 36 in yields up to 92% and with ee values up to 95% (Scheme 17). It was proposed that a transient BINOL-derived boronate was formed by the aldehyde–amine iminium intermediate and the thiourea catalyst. Subsequent re-face attack of the boronic substituent to the iminium ion afforded the R-configured product preferentially.

2.3. α-Hydroxy Aldehydes

2.3.1. α-Hydroxy Aldehydes. A series of functionalized β-hydroxy hydrazides 37–46 with up to five variable substituents were obtained in low to excellent yield in a 1:1 mixture of MeOH and HFIP at 65 °C. A selection of substituted aromatic hydrazides and a few aliphatic hydrazides led to the expected yields. The variation of the boronic acid component showed that electron-rich boronic acids were significantly more efficient than electron-neutral phenylboronic acids, which failed to give the substituted hydrazido product. The obtained β-hydroxy hydrazides were subjected to triphosgene-mediated cyclization to give oxadiazolones 47 or oxazolidinones 48 selectively depending on the application of either mildly or strongly basic workup procedures, respectively (Scheme 18). Other sequential transformations using the obtained functionalized β-hydroxy hydrazides with carefully positioned substituents led to the synthesis of a selection of structurally diverse polycyclic scaffolds.

2.3.2. Lactols as Masked α-Hydroxy Aldehydes. Lactols, which are easier to synthesize and handle in comparison with corresponding α-hydroxy aldehydes, were used in several studies as alternative carbonyl components. A series of polyhydroxy trans-1,2-aminoalcohols 50 were synthesized in good yield from lactol substrates 49, obtained through the dual protection of D-araboascorbic acid using 3,3-dimethoxypentane and 2,2-dimethoxypropane, respectively (Scheme 19). 1,2-Aminoalcohols 50 with three contiguous stereogenic centers and functionalization handles were further tested in regioselective acetal cleavage, alcohol oxidation, and ozonolysis reactions in this study.

2.3.3. Lactols in the BINOL-Catalyzed Asymmetric Petasis Reaction. Schaus and coworkers have reported significant progress in the area of asymmetric Petasis allylation reactions. Pioneering asymmetric PRs catalyzed by chiral diols developed in the Schaus group had led to the synthesis of chiral α-amino esters from alkenyl boronates, secondary amines, and ethyl glyoxylate, the synthesis of chiral amides from the addition of aryl, vinyl, and alkynyl boronates to acyl imines, and the synthesis of diastereomerically pure anti- and syn-β-amino alcohols from boronates, α-hydroxy aldehydes, and amines.

The use of enantiopure α-hydroxy aldehydes in conventional PRs lead to the formation of enantiopure β-amino alcohols with exclusive anti-diastereoselectivity. To complement this process, Schaus and coworkers reported the syn-diastereoselective synthesis of β-amino alcohol 52 using 20 mol % BINOL-derived catalyst 51, thus overriding the intrinsic anti-diastereoselectivity. Starting from α-hydroxy aldehydes in the form of lactols, l-phenylalanine methyl ester, and diethylboronates, the corresponding syn products were usually obtained with high diastereoselectivity, whereas the use of amino acetals generally led to the poor diastereoselectivity of inseparable products. The use of an achiral amino ester led to compounds 52l,m with poor diastereoselectivity, and the use
of a D-amino ester favored the formation of the antiprod-

Scheme 18

* Compounds 40, 42-46 were tested using other aldehyde components instead of glycolaldehyde.

of a D-amino ester favored the formation of the antiproduct 52o (Scheme 20). It was concluded that S-confi-
grulated BINOL catalyst and L-amine led to the formation of the syn product, whereas the R-configured catalyst and D-amine usually enhanced the antiselectivity. It was noteworthy that the amine structure and configuration played a significant role in the diastereoselective formation of the product. In addition to $\alpha$-hydroxyl aldehydes masked as lactols, glycolaldehyde in the form of glycolaldehyde dimer was also successfully applied for this (S)-BINOL-catalyzed synthesis of $\beta$-amino alcohols.\(^{109}\)

A later enantioselective synthesis of alkylaminophenols by PRs of salicylaldehydes, secondary amines, and arylboronic acids catalyzed by BINOL was reported to give moderate to good yield with enantiomeric excess ($ee$) values up to 86%.\(^{111}\) Additionally, a study using 3,3'-Me2-BINOL as the catalyst, further accelerated by the presence of 4 Å MSs, has been reported. NMR analysis revealed a possible role of the secondary amine component in triggering the BINOL-involved catalytic sequence. The Petasis products were isolated in variable yields ranging from 39 to 94% with high $ee$ values up to 99%, which may be linked to the water-removal effect of the present MSs.\(^{81}\) In addition to lactols, carbohydrates constitute an attractive class of $\alpha$-hydroxy aldehydes amenable to PRs owing to their ready availability and high stability.\(^{20}\)
Norsikian, Beau, and coworkers reported the synthesis of a series of 1,2-trans-diamines 54 with multiple functionalizable handles from N-protected α-amino aldehydes 53, such as N-tosylated amino aldehyde derived from L-phenylalanine. A series of secondary amines, mainly allylamines, and boronic acids were tested in this reaction variant, and yields of up to 71% and ee values ranging from 3 to 98% were reported, together with exclusive antidiastereoselectivity. Molecular sieves were added to this PR, which improved both the yield and the enantiomeric purity. The protecting group on the amino aldehyde significantly affected the outcome of the reaction, both in terms of the yield and the enantiomeric purity. N-Tosylated and N-nosylated substrates were identified as optimal substrates, whereas several other conventional N-protecting groups, including trimethylsilylhexanoyl, showed limited reactivity. The protected α-amino aldehydes were subsequently transformed into a variety of secondary amines through reaction with boronic acids and thiols, with yields ranging from 43 to 90% and ee values from 43 to 90%.
acetyl, and Boc, led to lower yields and greatly reduced enantiomeric purity. N-Methyl-N-tosyl-disubstituted amino aldehydes failed to undergo the desired transformation (Scheme 21). The authors reported a follow-up study based on DFT calculations with a detailed mechanistic analysis of the influence of the N-protection group, which suggested an important coordination role of the protecting group to form a transient boronate intermediate and the existence of concurrent PR and racemization pathways. The PR was favored for sulfonated substrates, such as Ts- and Ns-protected aldehydes, whereas racemization became predominant for carbamate and acetamide substrates, thereby explaining the low yields and the erosion of ee values for the carbamate and acetamide products. It is noteworthy that in a recent first report of SN2-type substitution using arylboric acids as nucleophiles, α-aryl-α-mesylation acetamides were stereoselectively converted to α,α-diaryl acetamides with excellent ee values and good yield in the presence of a CONH group in the acetamide substrates.

2.5. Pyridinecarboxaldehyde and Derivative as the Carbonyl Component

An adjacent hydroxyl moiety is not the only functional group capable of coordinating boronates of the carbonyl component; PRs may also be successfully carried out with 2-pyridinecarboxaldehyde and 2-sulfamidobenzaldehyde, where embedded nitrogen atoms of carbonyl components act as potential directing moieties. 2-Pyridinecarboxaldehydes has been used as the carbonyl component in classic three-component PRs, notably with a broad amine scope. Optimized conditions with refluxing acetonitrile gave a diverse selection of 2-pyridyl-functionalized amines in variable yields, generally depending on the activity of the boronic acids. Electron-rich boronic acids, such as (E)-styrylboronic acid, furan-2-boronic acid, and 4-methoxyphenylboronic acid, gave the corresponding products in good yield, typically >70%, whereas phenylboronic acid and electron-deficient 3,5-bis(trifluoromethyl)phenylboronic acid failed to react effectively (Scheme 22). It is noteworthy that reactions of 4-(dimethylamino)-2-pyridinecarboxaldehyde and (E)-styrylboronic acid also led to the formation of a direct alkylation byproduct in addition to the expected Petasis product.

A range of allylic alcohols with three functionalized handles was synthesized through a HCl-promoted PR of 2-pyridinecarboxaldehydes, 4-substituted-1,2-oxaborol-2(5H)-ols, and secondary amines, including both cyclic and acyclic counterparts. 2-Pyridinecarboxaldehydes with electron-withdrawing or sterically hindering substituents gave medium to excellent product yield (Scheme 23).

2.6. Miscellaneous Carbonyl Components

2.6.1. Formaldehyde. Formaldehyde may react with aromatic amines and boronic acids to yield aromatic tertiary amines through a double PR pathway. The initial reaction of aniline, formaldehyde, and phenylboronic acid yielded 64a in

A range of allylic alcohols 60–63 with three functionalized handles was synthesized through a HCl-promoted PR of 2-pyridinecarboxaldehydes, 4-substituted-1,2-oxaborol-2(5H)-ols, and secondary amines, including both cyclic and acyclic counterparts. 2-Pyridinecarboxaldehydes with electron-withdrawing or sterically hindering substituents gave medium to excellent product yield (Scheme 23).

Scheme 23
89% yield when heating to 60 °C in toluene for 24 h. The reaction scope was tested by using both electron-rich and electron-deficient anilines and boronic acids. Reactions that failed to complete typically involved amines or boronic acids with strong electron-withdrawing groups, such as 4-trifluoromethylphenylboronic acid and 4-nitroaniline. Heteroaryl amines gave products 64g and 64h in lower yields as well as product 64j from a nonaromatic amine (Scheme 24).

The reaction process involves sequential PRs with two identical carbonyl and two identical boronic acid components.

2.6.2. Benzaldehydes. A dual-activation approach using a dual-catalyst system was employed for the synthesis of α-substituted amides 65−70 from amides, which are rarely used as amine components for the PR due to their low nucleophilicity. The optimal reaction conditions comprised the use of ytterbium(III) triflate in combination with palladium(II) trifluoroacetate and 2,2'-bipyridine (or 4,4'-dinitro-2,2'-bipyridine), and the scope of the reaction was tested for a wide range of amides, aryl aldehydes, and arylboronic acids, aiming for conditions with no need to exclude air or moisture. It was proposed that ytterbium(III) triflate functions as a Lewis acid that catalyzes condensation between the amide and the aldehyde, and the in situ generated trifluoromethanesulfonic acid functions as a Brønsted acid to further activate the acyliminium ion intermediate. Meanwhile, palladium(II) trifluoroacetate reacts with the arylboronic acid to form a nucleophilic arylpalladium(II) intermediate. The reaction between two such active intermediates led to the formation of target compounds 65−70 in variable yields, ranging from 34 to 93% (Scheme 25).

2.6.3. Aziridine Aldehyde Dimer. Yudin and coworkers reported a series of multicomponent transformations using aziridine aldehyde dimers for the diastereoselective synthesis of highly functionalized heterocycles. A series of readily available aziridine aldehyde dimers 71 were used as the carbonyl component for the synthesis of aziridine-containing diamines 73 and 74. It was proposed that the formation of an iminium N,O-chelate intermediate 72 progressed to give the target compounds 73 and 74 with the simultaneous release of an aziridine aldehyde monomer. A selection of secondary amines and para-substituted styrylboronic acids or benzofur-2-ylboronic acid was successfully tested in this process. Alkynyl pinacol boronic esters led to compounds of reduced diastereomeric excess. Primary amines led to mixtures of intractable compounds. The regioselective ring-opening of the aziridine ring by nucleophilic BzSH or BzOH led to functionalized 1,2- and 1,3-diamines depending on the R1 substituent of 73 and 74 (Scheme 26).

2.6.4. α-Imino Amides in the Thiourea-Catalyzed Asymmetric Petasis Reaction. Takemoto and coworkers reported the application of a thiourea catalyst in asymmetric Petasis-type reactions with quinolines as the amine component. A series of hydroxyl-containing thiourea catalysts were screened for an asymmetric PR of such α-imino amides, substituted anilines, and vinylboronic acids. N-Aryl amino acid derivatives 76 were obtained in yields of up to 86% and with ee values of up to 93% by the application of catalyst 75 (Scheme 27). Amino acid derivatives 76 were subjected to further transformation to a forth an oxazolidinone and a tricyclic dihydroquinoline. Additionally, this hydroxy thiourea-catalyzed PR was applied to the stereoselective synthesis of dipeptides and tripeptides.
Candeias and coworkers reported the use of glycerol as an effective solvent for the synthesis of both salicylaldehyde-derived and 2-pyridinecarboxaldehyde-derived products. The use of glycerol gave PR products in improved yields using salicylaldehyde substrates when compared with similar reactions performed in ethanol, whereas 2-pyridinecarboxaldehyde substrates gave comparative yields with PRs performed in acetonitrile (Scheme 28). DFT calculations suggested that the formation of cyclic five- and six-membered glycerol-derived boronic esters possibly disrupts the PR pathway. In addition to alkylaminophenols and pyridines obtained through this glycerol-mediated PR, a catalytic amount of dibenzylamine was used for the condensation between salicylaldehydes and (E)-styrylboronic acid to give 2H-chromenes in glycerol.

Pyne and coworkers reported the first examples of allenyl pinacolboronate as the boronic component for the selective formation of either allenylamine or alkynylamine products depending on the choice of aldehyde and amine components. The reaction of salicylaldehyde, allenyl pinacolboronate, and various amines led to α-allenyl products from secondary amine components and propargyl product 79 from primary amine components. The reaction using glycoaldehyde and

Scheme 26

Scheme 27

Scheme 28

2.7. Multiple Carbonyl Components

The reaction of salicylaldehyde, allenyl pinacolboronate, and various amines led to α-allenyl products 78 from secondary amine components and propargyl product 79 from primary amine components. The reaction using glycoaldehyde and...
chiral α-hydroxy aldehyde afforded exclusively anti-β-amin-β-
alleny]l alcohols 80–82, regardless of the primary or secondary amines involved (Scheme 29). The selective formation of alkenyl and allenyl products was explained by either an intramolecular γ-addition or α-addition pathway of the tetracoordinated boronate transition intermediate.42

Petasis and coworkers originally reported the first examples of allenylboronate reactions, thus yielding α-allenyl and α-propargyl α-amino acids and anti-β-amino alcohols selectively depending on the applied components. The Pyne and Petasis reports on allenyl pinacolboronate revealed consistent selectivity and product formation with di

amines involved (Scheme 29). The selective formation of allenyl alcohols α-chiral α of allenylboronate reactions, thus yielding tetracoordinated boronate transition intermediate.42

amines exclusively led to α-examples, formed as the carbonyl component, the primary aliphatic amines of aldehyde and amine components. When using glyoxylic acid as the carbonyl component, the primary aliphatic amines formed α-propargyl α-amino acids 83, whereas secondary amines exclusively led to α-allenyl α-amino acids 84. In other examples, α-hydroxy aldehydes and primary amines led to either allenyl or allenyl products 85 and 86. Secondary amines, α-hydroxy aldehydes, and carbohydrate afforded allenyl anti-β-α-amino alcohol products 86 with high stereoselectivity. This variant was also applied to substituted allenylboronic acids or pinacolboronates, where reactions based on boronic acids gave reduced yields, albeit with improved diastereoselectivity in comparison with those involving pinacolboronates (Scheme 30). Owing to the presence of multiple functional handles, the obtained allenyl and allenyl Petasis products serve as versatile substrates for further diversification transformations.44

A copper-catalyzed PR was developed for the synthesis of tertiary amines and amino esters using 2-pyridinedicarboxaldehyde and ethyl glyoxalate. The reaction was tested for a limited selection of secondary amines, such as pyrrolidine, piperidine, and diethylamine, which typically gave the desired products 87 and 88 in moderate to good yield, whereas the use of dicyclohexylamine was unsuccessful (Scheme 31). Steric hindrance could explain why the use of ortho-substituted phenylboronic acid lead to only trace amounts of product (<5%). NMR-based mechanistic studies suggested a boron to copper transmetalation pathway and the necessity of a coordinating functionality on the carbonyl component.45

3. FOUR-COMPONENT PETASIS REACTIONS

A few PR variations that involve four components have been reported in recent years. On the basis of the chemical nature and discovery path, four-component PRs can be classified as two types. The first type is reactions that were originally designed to be performed in a traditional three-component manner, where either the solvent or an additional boronic acid component has been identified as a feasible fourth component to be predictably integrated into the PR product. The second relates to reactions that include a nontypical PR building block as the fourth component.

3.1. Solvent as the Fourth Component

A three-component PR of amino acids (L-proline or N-methyl-

i-alanine), phenylboronic acids, and glycoaldehyde dimer performed in methanol led to the formation of a dioxazaboronate product, which incorporated the solvent methanol as a fourth component.127 L-Proline led to the corresponding dioxazaboronate products 89 and 90 in good to excellent yield with excellent diastereoselectivities, typically ranging from 90 to >95%. An evaluation of the substrate scope revealed a wide range of substrates tolerance toward boronic acids being aryl, heteroaryl, or alkyl types and alcohols including both aliphatic and unsaturated alcohols such as ethanol, isopropanol, benzyl alcohol, allyl alcohol, and propargyl alcohol (alcohol as the solvent or 10 equiv of alcohol in tetrahydrofuran) (Scheme 32). The DFT-based mechanism study indicated that the alcohol component was involved in the formation of a key enol intermediate in addition to its crucial role in proton-transfer steps.

3.2. Boronic Acid as the Fourth Component

A four-component PR was developed by adding orthogonally reactive boronic acids to three-component PR mixtures of α-hydroxy aldehydes, hydrazides, and boronic acids.101,128 The reaction proceeded with an initial three-component PR step, relying on the first, more electron-rich and reactive boronic acid to act as carbon nucleophile to form an α-hydrazone alcoholic, which condensed with the boron moiety from the second boronic acid, thus functioning as a boron electrophile to form the bicyclic dioxadiazaborocines 91–106. A wide selection of boron substrates including substituted phenyl, heteroaromatic, vinyl, and aliphatic boronic acids was successfully used in the reaction, including sterically hindered 1-pyreneboronic acid, 2-methylboronic acid, and a BINOL-derived bis(boronic) acid, whereas 2,6-dimethylphenylboronic acid failed to give the corresponding condensation product.
Scheme 30

\[
\begin{align*}
\text{Scheme 31}
\end{align*}
\]
It is noteworthy that two boronic acids of similar electronic nature can be used for this four-component transformation, but this requires sequential additions.128

3.3. Noncanonical Building Block as the Fourth Component

A four-component Cu(II)-catalyzed Petasis-like reaction of amines, formaldehyde, boronic acids, and alkyne was reported to yield tertiary propargylamines.129 Replacing the alkyne component with a propiolic acid increased the reactivity of the carbon nucleophile, making it possible to attack the iminium species of the Petasis three-component product without a Cu(II) catalyst. This type of metal-free four-component PR was independently reported by two groups for the synthesis of N-benzyl propargylamines108−111.130,131 It is noteworthy that two components of formaldehyde are involved in this transformation to form the initial benzyl hemiaminal intermediate107, and thus it can also be classified as a five-component reaction (Scheme 34). Substituted propargylamines are versatile substrates for the synthesis of diverse heterocycles via a variety of synthetic transformations, such as RCM, ROM, and enyne cyclization reactions.132,133 The PR of benzylamines, formaldehyde, boronic acid, and propiolic acids constitutes an alternative metal-free approach for the synthesis of functionalized propargylamines through A3-coupling of amines, aldehydes, and alkynes.134 A more recent study reported the synthesis of propargylamines of the same scaffold of 108−111 through a four-component reaction of aliphatic amines, formaldehyde, arylboronic acids, and alkynyl carboxylic acids catalyzed by magnetic CuFe2O4 nanoparticles.135

A related four-component transformation for the enantioselective synthesis of chiral α,γ-substituted γ-lactones was achieved by an intramolecular Passerini reaction using 5-hydroxyfuran-2(5H)-one, boronic acids, isocyanides, and a secondary amine catalyst. Although an “intramolecular boronate−iminium complex” is proposed by the condensation among 5-hydroxyfuran-2(5H)-one, boronic acids, and secondary amine as the initial step of the reaction, the boronic acid substituent is likely migrated via a Michael addition instead of a PR.136

4. PETASIS-TYPE REACTIONS

4.1. Two-Component Petasis-Type Reactions

N-Acyliminium ions are reactive species that have been widely explored for the synthesis of heterocyclic compounds with diverse scaffolds.137 Baty initially reported the cis-diastereoselective addition of aryl and alkenyl boronates to cyclic N-acyliminium ion species derived from hemiaminal substrates.138 Pyne and coworkers then reported the diastereoselective addition of boronic acids to both five- and six-membered cyclic N-acyliminium ions.139 Doyle and coworkers reported the Ni(0)-catalyzed Petasis-type addition of π-neutral or π-deficient arylboronic acids to N-acyliminium ions derived from isoquinoline and quinolines.140 Later, the Petasis-type addition of aryl and alkenylboronic acids to Cbz-protected piperidinium ions derived from 3-hydroxy-2-methoxy-N,O-acetal112 was reported for the diastereoselective synthesis of 2,3-disubstituted piperidine113, which was further treated with 3,5-bis(trifluoromethyl)benzyl bromide to give the neurokinin-1 antagonist114 (Scheme 35).141

Nielsen and coworkers reported an efficient reductive cyclization approach for the synthesis of N-substituted β,γ-dihydropyridyl-γ-lactams115, which were used as precursors to generate cyclic N-acyliminium ions in the presence of boron.
Cyclic N-acyliminium ions derived from β,γ-dihydroxy-γ-lactams reacted with electron-deficient boronic acids in this two-component PR to give substituted γ-lactams with high cis-diastereoselectivity, albeit in low yield, probably through the chelation-controlled addition via the hydroxyl moiety similar to that of canonical PRs. In contrast, the use of electron-rich boronic acids resulted in γ-lactams with no or poor diastereoselectivity owing to a possible pathway of the direct addition of boronic acids to cyclic N-acyliminium ions (Scheme 36).

A metal-free carbon–hydrogen-bond functionalization for the regioselective synthesis of 2-substituted quinolines was performed in a Petasis-like manner by reacting quinoline N-oxides with boronic acids. The coordination of the boronic acid at the quinoline N-oxide oxygen was followed by the migration of the boronate substituent, and a final rearomatization before the elimination of boronic acid led to the formation of quinolines in moderate to good yield. The reaction was tolerated for a range of substituted quinoline N-oxide substrates; the ones with electron-deficient substituents usually led to a better yield. Quinoxaline N-oxide was also successfully applied to give quinoxaline in this reaction, but the analogous isoquinoline, pyridine, and quinazoline N-oxides failed to undergo similar reactions (Scheme 37).

Petasis-type reactions with organotrifluoroborate salts as activated nucleophiles for the direct addition to imine and enamine substrates do not necessitate the presence of a directing group for the intramolecular transfer of the boronate substituent. In the presence of TFA, both potassium vinyl trifluoroborate and aryl trifluoroborate were successfully used as boron nucleophiles in the reaction with carbamate-protected imines or enamines to give products in moderate to excellent yield (Scheme 38). The reaction was also tested for imine electrophiles containing chiral auxiliaries, but no diastereoselectivity could be observed.

A series of 1-alkyl-2,3-dicyano-5-arylpyrazinium salts was used as imine species for two-component Petasis-type...
reactions with electron-rich boronic acids including thienyl, furyl, benzothienyl, and styrylboronic acids to afford 5,6-diaryl-1,6-dihydropyrazines \(133\) in moderate to good yield (Scheme 39). The absolute configurations were determined by X-ray crystal structures of enantiomers isolated by chiral HPLC. The synthesized dihydropyrazines were tested for their antifungal and antimycobacterial activities.\(^{22,146}\)

Scheme 35

Scheme 36

* Isolated yield of the cis-isomer only
4.2. Three-Component Petasis-Type Reactions

Aryl-substituted 2,5-dihydrofurans 136 were synthesized from alkenyl boronic acid and salicylaldehydes promoted by amines in a Petasis-type transformation. A series of substituted alkenylboronic acids synthesized from propargyl alcohol were used as an uncommon boronic component. Among a series of secondary amines tested, morpholine was identified as the optimal amine, whereas bulky amines, such as diisopropylamine, diphenylamine, and benzhydrylamine, failed to give the expected products. An iminium intermediate derived from salicylaldehyde and morpholine is proposed to form a tetracoordinate boronate intermediate 134, which undergoes an intramolecular transfer of the alkenyl carbanion moiety from boronic acid to the iminium ion species and yields boronate 135. Following hydration steps under weak basic conditions, an intramolecular substitution reaction and a final hydrolysis release the target compound 136 (Scheme 40). An imine allylation of glyoxylic acid with chiral tert-butanesulfinamide and allylboronic acid pinacol esters was reported for the synthesis of optically active γδ-unsaturated α- amino acids with excellent diastereoselectivity. More recently, an efficient three-component Petasis-type reaction using pinacol gem-difluoroallylboronates and commercially available β-chiral amino alcohols was reported for the diastereoselective synthesis of chiral gem-difluorohomoallyl-morpholine 144−147 in good to excellent yield with high diastereoselectivity. A broad scope of aldehydes, including heteroaromatic, cinnamyl, aliphatic aldehydes and benzaldehydes, was applicable to this transformation (Scheme 42). The formation of a reactive gem-difluoroallylboronate intermediate undergoing intramolecular imine allylation was proposed to explain the observed region- and stereoselectivity. Another Petasis-type allylation with dimethylamine adducts of triallyl-, triprenyl-, and cinnamyl-dipropylboranes was recently reported for the homoauxiliary of primary amine substrates with formaldehyde. In a recent study from the Schaus group, chiral 3,3'-Ph2-BINOL 148 was used to activate allylboronates and were obtained in moderate to good yield. Other secondary amines led to the formation of Mannich bases 140 and 141. In the case of primary amines, ortho-alkylaminomethyl-substituted phenol intermediate 142 proceeded to couple to another component of formaldehyde and was converted to benzoxazine 143 in moderate to good yield in the presence of K2CO3 (Scheme 41). It is noteworthy that the use of either benzothienylboronic acid or thienylboronic acid under the same TBHP conditions failed to give the phenol analogs via oxidation, whereas the classic PR products 142 and 143 were isolated.

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Another type of amine-promoted nucleophilic addition to iminium ion species was later reported for the synthesis of 1,2-diones. A three-component Petasis-type intermediate is proposed to undergo self-deamination via in situ protonation and aerobic oxidation to give a wide range of aryl 1,2-diones.149

A three-component reaction of paraformaldehyde, amines, and phenylboronic acids was applied for the synthesis of Mannich bases 137−139 and benzoxazines 141 under an oxidation condition using tert-butyl hydroperoxide (TBHP). It is proposed that the boronic acid was oxidized by TBHP and hydrolyzed to generate a phenol intermediate, which reacts with imine species derived from paraformaldehyde and amines to regioselectively form the ortho-substituted phenols. Using morpholine as the amine substrate, the Mannich bases 139 were obtained in moderate to good yield. Other secondary amines led to the formation of Mannich bases 140 and 141. In the case of primary amines, ortho-alkylaminomethyl-substituted phenol intermediate 142 proceeded to couple to another component of formaldehyde and was converted to benzoxazine 143 in moderate to good yield in the presence of K2CO3 (Scheme 41). It is noteworthy that the use of either benzothienylboronic acid or thienylboronic acid under the same TBHP conditions failed to give the phenol analogs via oxidation, whereas the classic PR products 142 and 143 were isolated.150

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crotvylboronates for nucleophilic addition to imines derived from aldehyde and amine building blocks of diverse structural and electrophilic properties. Chiral homoallylic amines were obtained in good to excellent yield and with good to excellent enantioselectivity (Scheme 43). Both syn- and anti-diastereomers of allylic amines with two vicinal stereogenic centers were accessible with (Z)- and (E)-crotvylboronates, respectively (Scheme 44). A catalyst-free Petasis-allylboration of 1,2-amino alcohol, aldehyde, and pinacolallylboronate was recently reported for the synthesis of both racemic and chiral homoallyl amines at room temperature.

A copper-catalyzed Petasis-type reaction was developed for the synthesis of functionalized α-substituted amides from preformed imines, tetraarylboranes, and acid chlorides. The reaction was applied to N-benzyl, N-aryl, and N-alkyl imines and aryl- and alkyl-substituted acid chlorides, all leading to the expected product in moderate to good yield. The proposed mechanism involved the formation of a stabilized pyridinium intermediate, which reacted with the in situ formed organocopper complex derived from copper catalyst CuCl and NaBPh₄ to give amides (Scheme 45).

4.3. Traceless Petasis Reactions

Thomson and coworkers reported a Petasis-type coupling of α-hydroxy aldehydes or ketones with alkynyl trifluoroborate salts and an arylsulfonylhydrazine to obtain allenes, a process referred to as a "traceless" PR. Lewis acids, such as Sc(OTf)₃ and La(OTf)₃, were screened to promote hydrazone formation, prior to addition of the alkylnyl component to form the propargyl hydrazide, from which the loss of sulfonic acid yielded diazine. A subsequent nitrogen extrusion step gave the desired allenes. 2-Nitrobenzenesulfonylhydrazide was successfully applied in this reaction, whereas 4-tosylhydrazide led only to the corresponding propargyl hydrazide intermediate. A series of alkylnyl trifluoroborates were tolerated in this reaction, leading to the corresponding hydroxyallenes in good to high yield. A range of carbonyl components, ranging from protected aldehyde, (D)-(−)-glyceraldehyde, α-hydroxyacetone, 1-hydroxyhexan-2-one, 2-hydroxycyclohexanone, to even a β-hydroxy aldehyde, were successfully evaluated in this reaction, yielding allenes, respectively (Scheme 46). It is noteworthy how benzyloxyacetaldehyde, which lacks an α-hydroxy group, led to the allene product in 23% yield. A subsequent high-throughput optimization of the traceless PR was performed by invoking a self-assembled monolayer/matrix-assisted laser desorption–ionization mass spectrometry platform. The most effective condition, using BF₃·OEt₂ as the Lewis acid, was identified through simultaneous conduction of more than 1800 reactions on self-assembled monolayers of alkanethiolates on gold. The traceless PR promoted by BF₃·OEt₂ was then successfully performed under solution-phase conditions to give substituted allenes using aldehyde substrates without a hydroxyl activating group (Scheme 47).

4.4. Asymmetric Traceless Petasis Reactions

More recently, Thomson and Schaus reported an enantioselective version of the traceless PR for the synthesis of enantioenriched allenes from achiral substrates catalyzed by chiral biphenols via two approaches. In the first approach,
alkynyl boronates were added to glycolaldehyde-derived imines to generate allylic hydroxyl allenes. A 2D evaluation of the sulfonyl hydrazide to make the hydrazone and the chiral biphenol to catalyze the traceless PRs revealed optimal reaction conditions with 2,5-dibromophenylsulfonyl hydrazide and 3,3′,6,6′-(CF₃)₄-BINOL (177) in a toluene/mesitylene solvent system. A range of arylalkynyl boronates of diverse electronic nature, aliphatic and unsaturated boronates, and a silylalkynyl boronate were applied in this traceless PR under the optimized condition to give chiral allenes. Addition-ally, α-hydroxyacetone was used as the electrophile to give trisubstituted allene. Chiral bicyclic alkynyl boronates were used for the diastereoselective synthesis of allenes using (S)-BINOL catalyst 177 and (R)-BINOL catalyst 178, respectively. However, a follow-up investigation on the diastereoselective traceless PR with 2,2-dimethyl-1,3-dioxolan-4-ol as the α-hydroxy carbonyl component gave mixed results. (S)-BINOL 177 led to the formation of the anticipated anti-allenes with enhanced selectivity, whereas (R)-BINOL 178 was ineffective in increasing the formation of syn-allenes (Scheme 48).

In the second approach, allyl boronates were added to alkynyl hydrazones to afford 1,3-alkenyl allenes. A similar 2D evaluation of the sulfonyl hydrazide to make the alkynyl hydrazone and the chiral biphenol to catalyze the traceless PRs revealed an optimal condition using 2-nitro-4-trifluoromethylphenylsulfonyl hydrazide and 3,3′-Ph₂-BINOL (148) to give the highest yields and best enantioselectivities. A collection of electron-rich and electron-poor arylpropiolaldehydes, silylpropiolaldehyde, propionic aldehydes containing heteroatom substituents, and aliphatic propionic aldehydes was effectively converted to the corresponding allenes with excellent enantioselectivity. When a protected chiral 1,2-diol-containing propionaldehyde was used, allene was obtained with excellent diastereoselectivity (Scheme 49).

Very recently, the Schaus group reported an asymmetric traceless PR of enals, sulfonylhydrazines, and allylboronates for the synthesis of acyclic 1,4-dienes via a reductive transposition pathway of the in situ generated allylic diazene intermediates. The scope of the reaction was initially evaluated by using β-methyl enals to afford the rearranged allylated products containing benzyllic stereocenters in high yield and with excellent enantioselectivity. As
an exception, β-alkyl-β-methyl enal led to the formation of product 190g probably due to the facile isomerization of the intermediate hydrazone. The crotylation of nonbranched enal under this traceless PR condition using BINOL 148 also afforded the corresponding 1,4-diienes 191 containing methyl-substituted stereocenters with excellent enantioselectivity. For β/β-disubstituted enal substrates with substituents bulkier than a methyl group, 2-nitro-benzenesulfonyl hydrazide and BINOL catalyst 51 were used to access the allylated products 193. Catalyst 51 was also used for the crotylation of the β-alkyl enal substrate to give diene product 192 with excellent enantioselectivity, albeit in modest yield. Diene products of both 1,4-syn and 1,4-anti-types and two methyl-substituted tertiary stereocenters could be obtained by using (E)- and (Z)-crotlyboronates, catalyzed by BINOL ent-51 (Scheme 50).161 One significant advantage of this BINOL-catalyzed traceless PR is that up to two stereocenters could be installed in the desired acyclic 1,4-diienes from achiral substrates.

5. PETASIS CASCADE AND SEQUENCE REACTIONS

5.1. PR/Intramolecular Diels–Alder (PR/IMDA) Cascade

The PR of furan-2-boronic acids, allylamine and its derivatives, and a wide range of carbonyl components including glycolaldehyde, glyoxylic acid, salicylaldehyde, and α-hydroxypent-4-enal in PRs may provide a smooth crossroad to advanced precursors for complex polycyclic scaffolds. Multiple chiral centers and scaffolds with high contents of sp3 hybridized carbon atoms can be obtained by the PR with intramolecular Diels–Alder (IMDA) cascade reactions. The bicyclic hexahydroepoxyisoindole scaffold formed via Diels–Alder cyclization between the furan ring and the allylamine is a distinct structure feature for the direct products formed through this type of PR/IMDA reaction. Sequential strategies combining other types of ring-opening and ring-closing reactions led to the construction of diverse scaffolds, as illustrated in the following examples.

A PR/IMDA cascade reaction was recently reported for the synthesis of the tricyclic hexahydroepoxyisoindole 195 as a single diastereomer from allylamines, glycolaldehyde dimer, and furan-2-boronic acids. The Petasis products were isolable, but the cascade may also be performed in one single reaction step. The replacement of allylamines with N′-allylated hydrazides in this PR/IMDA cascade led to the desired hexahydroepoxyisoindoles 196 diastereoselectively in comparable yields. A cascade using α-hydroxylated aldehydes, Bn-protected allyl amine, and S-Boc-amine-substituted furyl-2-ylobonic acids gave the PR/IMDA products 197, which were applied for small-molecule library synthesis (Scheme 51).163 Nielsen and coworkers developed a PR/IMDA oxidative cleavage sequence starting from salicylaldehyde, Bn-protected allyl amine, and furan-2-boronic acid to give phenol 198 as the PR/IMDA cascade product. Following the oxidative cleavage of phenol 198 using catalytic K2OsO4 and NMO as the oxidants with the subsequent treatment of NaIO4 yielded key dialdehyde intermediates 199, which were reduced to give the diols 200 in the presence of NaBH4. An additional Mitsunobu reaction mediated by di-tert-butyl azodicarboxylate (DBAD) and PPh3 transformed diols 200 to the cyclized products 201 in nearly quantitative yields. Alternatively, dialdehydes 199 were subject to reductive amination using NaBH(OAc)3 to give cyclized epoxypyrrolo[3,4-c]azepines 202 (Scheme 52).164 A PR/IMDA/amidation/oxidative cleavage sequence was performed using glyoxalic acid instead of salicylaldehydes as the carbonyl component to first obtain amide 203 via the PR/IMDA/amidation sequence and then form diols 204 via the subsequent oxidative cleavage/reduction sequence. Diols 204 could be further cyclized to yield tryicly pyrrolidinones 205 and 206 with a diversified handle at the 2-position of the octahydro-6H-furo[2,3-c]pyrrolo[3,4-b]pyrrol-6-one core scaffold (Scheme 53).165 A second allyl group can be incorporated into the PR/IMDA product by choosing the corresponding substrates to achieve a PR/IMDA−ROM/RCM sequence. In the PR/IMDA cascade, the replacement of the glycolaldehyde dimer with a masked α-hydroxypent-4-enal as the carbonyl component led to the formation of the hexahydroepoxyisoindole 207 with an allyl handle. The treatment of 207 with Grubbs II catalyst gave the hydroxyfurindole 208, which featured five stereogenic centers and multiple appended substituents suitable for further structural diversification. The PR/IMDA allyl product 209 obtained via the PR/IMDA cascade using an allyl-substituted furan-2-boronic acid was subjected to a ROM/RCM sequence to give the tricyclic tetrahydropyridine 210 (Scheme 54).166 The obtained compounds 201, 202, 205, 206, and 208−210 all shared a densely functionalized polycyclic core structure bearing at least three stereogenic centers as well as at least three handles for further derivatization and are attractive scaffolds for the establishment of natural-product-like small-molecule libraries.165−166

A PR−acyrloylation/Diels−Alder sequence was employed to access the tetrahydroepoxyisoindolones 213−217 in moderate yields using the furyl-containing hydrazido Petasis three-component products 211 via the formation of the PR intermediate 212 (Scheme 55).102

Strategical positioning of allyl and furan moieties in the bicyclic boronate resulting from a four-component PR involving hydrazide enabled the synthesis of PR/IMDA cascades in a simple operation to give pentacyclic scaffold
Beau and coworkers reported a PR/IMDA cascade in combination with an RCM/Michael addition cascade to access hexahydroisoindoles with up to five newly formed stereogenic centers. The PR/IMDA cascade was initially tested in the reaction of \((E)-(3\text{-}\text{methylbutal}-1,3\text{-diien}-1\text{-yl})\)-boronic acid, diallylamine, and \((S)-2\text{-}\text{hydroxyheptanal}, which was obtained by regioselective oxidation of the corresponding \((S)-1,2\text{-}\text{diol} to give hexahydroisoindole as a single isomer with complete stereocontrol at all three newly formed stereogenic centers. The stereochemical configuration of was indirectly confirmed by the X-ray crystal structure of a \(p\text{-}\text{nitrobenzoylated} analog. The aldehyde scope of the PR/
IMDA cascade was later expanded to include different optically pure α-hydroxyaldehydes and carbohydrates under the optimal condition of microwave irradiation at 120 °C for 30 min. The allyl appendage of the PR/IMPDA product 221 then underwent a ruthenium-catalyzed cross metathesis with methyl vinyl ketone to form enone intermediate 222, which yielded the tricyclic or tetracyclic octahydrooxazinoisoindole 223 as an enantiopure isomer (Scheme 57). A follow-up study from the same group expanded the scope for the three substrates in this PR/IMPDA − metathesis/Michael addiction sequence. DFT calculations for the stereoselective formation of the target compounds in the PR/IMPDA cascade revealed the preorganization of favorable transition structures stabilized by intramolecular hydrogen bonds.

Scheme 45

Scheme 46

Scheme 47
5.2. Petasis Reaction–Ring-Closing Metathesis Sequences

Schreiber and coworkers reported early examples of applying the PR for the synthesis of skeletal and stereochemically diverse small molecules. More recently, Nielsen and coworkers reported the synthesis of diverse scaffolds using a PR–RCM sequence. The functionalized α-hydroxy-hydrazone scaffolds were subjected to RCM using Grubbs II catalyst. Different scaffolds ranging from five-membered to seven-membered ring systems were obtained in moderate to good yield ranging from 58 to 80% (Scheme S8).

The four-component hydrazido–PR using trans-2-phenylvinylboronic acids as both boronic acid components was used to synthesize two different tricyclic dioxadiazaborocine scaffolds depending on the RCM sequence strategy. The allyl substrate 234, which was obtained through a three-component hydrazido–PR, was first treated with Grubbs II catalyst to form RCM product 235 and then with (E)-styrylboronic acid to give pyrrolooxadiazaborole 236. Alternatively, the four-component hydrazido–PR product 237 was formed prior to treatment with the Grubbs II catalyst, thus providing RCM product 238 (Scheme S9).

A PR–RCM sequence was employed for the synthesis of highly functionalized pyrrolinols 240 featuring a Grubbs-II-catalyzed ring-closing metathesis reaction of the Petasis products 239 synthesized from tert-butyl diphenylsilyl-protected α-hydroxyl aldehydes, substituted allylamines, and...
(E)-styrylboronic acid with excellent diastereoselectivity and retained enantiomeric purity. A sequential ring expansion step of the pyrrolinol 240 through aziridinium intermediate 241 provided mono-, di-, or trisubstituted piperidines 242 in excellent enantiomeric purity and good to excellent yield of up to 99% (Scheme 60).\textsuperscript{166}

Enantiomerically pure cyclic amino esters were obtained by the allylation of Petasis products 243, which were obtained in high diastereoselectivity from the PR of glyoxylic acid, (S)-1-phenylethylamine, and allylboronic acid. The pure diasteroisomer could be isolated after esterification and then allylated, albeit with partial epimerization occurring to give inseparable diastereoisomers 244, lowering the de value to ≈60%. RCM of 244 catalyzed by Grubbs second-generation catalyst in the presence of 0.5 equiv of Ti(OEt)\textsubscript{4} as the Lewis acid to suppress “poisoning effect” toward the Grubbs catalyst by the nucleophilic nitrogen of 244 gave the chromatographically separable cyclic amino esters 245 (Scheme 61).\textsuperscript{167}

### 5.3. Petasis Reaction–Intramolecular Cyclization Cascade and Sequence

A three-component PR of glyoxal, arylboronic acids, and cyclic amino alcohols including (S)-pyrrolidin-2-ylmethanol and piperidin-2-ymethanol was reported for the synthesis of bicyclic pyrrolo[2,1-c][1,4]oxazin-3-ols 246 with good yields.
but low $dr$ values. When thien-2-ylboronic acid and 3-pyridylboronic acid were applied, none of the expected products were isolated, but electron-poor 3,5-difluorophenylboronic acid did lead to a 37% yield of the desired material $246h$ (Scheme 62). The synthesized compounds were tested for their insecticidal activity against armyworm and their nematicidal activity.\(^{168}\) A series of secondary amines, 2-(benzylamino)phenols $247$, obtained via the condensation of 2-aminophenols and benzaldehydes were used as the amine component in a PR involving glyoxal and phenylboronic acids. Bicyclic compounds $248$, with the trans-2-hydroxy-1,4-benzoxazine products being the major isomer, were obtained in variable yields and with variable $dr$ values (Scheme 63).\(^ {169}\) The same type of trans-2-hydroxy-1,4-benzoxazines was obtained through a pyridinium
A three-component PR was used for the synthesis of imidazo[1,2-α]pyridine-3-ols using 2-aminopyridine, glyoxylic acid, and arylboronic acid with microwave irradiation at 160 °C. This transformation involved the formation of the Petasis product as an intermediate undergoing intramolecular nucleophilic cyclization, followed by dihydroxylation and aromatization to yield the imidazo[1,2-α]pyridine-3-ols in moderate to good yield (Scheme 64). The Petasis product could also be successfully isolated in good yield following an alternative method relying on heating at 80 °C in DMF for 1 h.171

A Petasis/lactamization cascade reaction of 2-aminobenzamides was reported for the synthesis of 1,4-benzodiazepine-3,5-diones, thus constituting an alternative synthesis of compounds of the similar scaffold from 2-aminobenzamides via the Passerini reaction.2-3-Aminobenzamides, formed from isatoic anhydride and amines, were reacted with glyoxylic acid to form an imine intermediate that was coordinated with an arylboronic acid to facilitate a rate-limiting transfer of the boronate substituent to provide the Petasis product, which underwent intramolecular amidation to give cyclized compound in yields ranging from 60 to 78% (Scheme 65). The presence of MSs accelerated the reaction attributed to the facile formation of the imine intermediate.173

Rozwadowska and coworkers reported the synthesis of tetrahydroisoquinolines through a PR−Pomeranz−Fritsch−Bobbitt cyclization sequence.174,175 Petasis products were synthesized from glyoxylic acid, aminoacetaldehyde acetal, and...
3,4-dimethoxyphenylboronic acid. The solvent and reaction temperature were observed to affect the diastereoselective outcome of the reaction. Both the Petasis products and the N-deprotected products could be subjected to the acidic conditions required for the Pomeranz–Fritsch–Bobbitt cyclization, thus generating tetrahydroisoquinoline acids in generally excellent yield. The use of chiral amino-acetaldehyde acetals led to enantiomerically pure isoquinoline acids (Scheme 66). Hulme and coworkers reported a PR–nucleophilic cyclization sequence to synthesize quinoxalines from substituted glyoxaldehydes. Using mainly the mono-Boc-protected benzene-1,2-diamine, the PR revealed a broad scope by using a diverse set of glycolaldehyde and boronic acids with diverse electronic and steric properties. However, the highly hindered 2,4,6-trimethylphenyl glycoaldehyde failed to yield the expected products. The obtained Petasis products were subject to acid-mediated Boc deprotection and intramolecular nucleophilic cyclization to give quinoxalines in mostly good to excellent yield (Scheme 66).

Trabocchi and coworkers reported a PR–intramolecular acetalization/lactonization cascade reaction to access a series of highly functionalized morpholines using glycolaldehyde, styrylboronic acid, and either glycine-derived amino acetaldehydes or benzylated threonine derivatives. The use of dimethoxy ethylamino derivative of threonine led to diastereoselective synthesis of PR product 257b, which was used to exploit the following cyclization steps. Acetalization under different conditions led to morpholine acetals and lactone, which could be further acetalized to give a bicyclic morpholine (Scheme 68).

Norsikian and Beau reported a PR for the synthesis of amino alcohol from diallylamine, α-hydroxy aldehyde, and boronic acid. Amino alcohol 263 was deallylated and acetyl-protected to give amide, which was cyclized to give oxazoline catalyzed by FeCl₃. The ring opening of oxazoline in the presence of trimethylsilyl azide, followed by saponification and amino-iminomethanesulfonic acid...
substitution gave the guanidine 266 as a zanamivir analog (Scheme 69). A PR using 1-alkene-1,2-diboronic esters was reported in a PR−Suzuki coupling sequence. The Petasis product obtained from (Z)-1-alkene-1,2-diboronic esters, secondary amines, and glyoxylic acid was directly esterified to form the product (E)-γ-boronated amino esters 267 by treating with diazomethane solution in diethyl ether. The reactions with secondary amines all led to the methylated Petasis product in moderate to good yield with high diastereoselectivity, whereas the sterically hindered (S)-N-benzyl-α-methylbenzylamine led to the corresponding product with poor diastereoselectivity. Benzylamine failed to give the expected product. Suzuki coupling reactions were tested with the second boronate moiety of the obtained amino esters 267 to give further substituted α,β-unsaturated amino esters 268 (Scheme 70). The same group recently reported a Suzuki coupling−intramolecular PR sequence together with a Suzuki coupling−intramolecular PR sequence using the same type of 1-alkene-1,2-diboronic esters. The Suzuki coupling led to the regioselective formation of a single (E)-stereoisomer of boronate 269, which reacted with secondary amines to give the Petasis product 270. Boronate 269 with an appropriately positioned aldehyde moiety, that is, at the 2-position of the phenyl group, was used as the dual aldehyde and boronic component for the Petasis cyclization reaction to give 1-amino-1H-indenes 271 in good yield ranging from 66 to 92% (Scheme 71). These two studies illustrated the divergent synthesis of the same substituted α,β-unsaturated amino esters from common 1,2-bis(boronates) substrates via two reverse-combinations of the PR and the Suzuki coupling reaction.

5.4. PR−Suzuki Sequence and Suzuki−PR Sequence

Carboni and coworkers reported several studies using alkyl boronic esters or 1,2-diboronic esters for the synthesis of functionalized heterocycles. A PR using 1-alkene-1,2-diboronic esters was reported in a PR−Suzuki coupling sequence. The Petasis product obtained from (Z)-1-alkene-1,2-diboronic esters, secondary amines, and glyoxylic acid was directly esterified to form the product (E)-γ-boronated amino esters 267 by treating with diazomethane solution in diethyl ether. The reactions with secondary amines all led to the methylated Petasis product in moderate to good yield with high diastereoselectivity, whereas the sterically hindered (S)-N-benzyl-α-methylbenzylamine led to the corresponding product with poor diastereoselectivity. Benzylamine failed to give the expected product. Suzuki coupling reactions were tested with the second boronate moiety of the obtained amino esters 267 to give further substituted α,β-unsaturated amino esters 268 (Scheme 70). The same group recently reported a Suzuki coupling−intramolecular PR sequence together with a Suzuki coupling−intramolecular PR sequence using the same type of 1-alkene-1,2-diboronic esters. The Suzuki coupling led to the regioselective formation of a single (E)-stereoisomer of boronate 269, which reacted with secondary amines to give the Petasis product 270. Boronate 269 with an appropriately positioned aldehyde moiety, that is, at the 2-position of the phenyl group, was used as the dual aldehyde and boronic component for the Petasis cyclization reaction to give 1-amino-1H-indenes 271 in good yield ranging from 66 to 92% (Scheme 71). These two studies illustrated the divergent synthesis of the same substituted α,β-unsaturated amino esters from common 1,2-bis(boronates) substrates via two reverse-combinations of the PR and the Suzuki coupling reaction.

5.5. Other Petasis Cascade or Sequence Reactions

Inspired by previous studies on amine-promoted aldehyde functionalization and single-electron-transfer (SET)-promoted formylation, Wang and coworkers reported a transition-metal-free formylation of boronic acids via a Petasis-type addition between glyoxylic acid, arylboronic acids, and secondary amines following by SET-promoted decarboxylation and hydrolysis. On the basis of the proposed rapid exergonic process of SET from tetrahydroquinoline and indoline to oxygen, in situ formed Petasis products 272 underwent oxygen-promoted oxidative decarboxylation to form the iminium ion species 273, and hydrolysis hereof yielded aldehydes 274−279 with the concomitant release of the tetrahydroquinoline as a catalyst. The substrate test revealed the wide scope toward boronic acids of different electron-density properties. Arylaldehydes and biologically relevant heteroaromatic aldehydes were obtained in moderate to good yield. This Petasis oxidation cascade reaction poses as an orthogonal formylation approach to palladium-catalyzed formylation that employs aryl bromides and iodides as substrates, such as 276 and 277 (Scheme 72). Using indoline as the amine component and styrylboronic acid as the boronic component, enals 280−283 were obtained in comparative yields (Scheme 73). A PR−Ugi sequence reactions was performed on an automated continuous-flow microreactor system. An individual PR using either glyoxylic acid or salicylaldehyde was performed in a silicon microreactor first before being combined with the Ugi reaction in serially connected microreactors using glyoxylic acid under optimized conditions to give amide 284 (Scheme 74). Kinetic analysis was...
performed to determine rate-limiting steps and activation energies and to evaluate the proposed mechanism based on data collected through this continuous-flow PR–Ugi sequence reaction.

6. APPLICATION IN THE SYNTHESIS OF NATURAL PRODUCTS

One of the earliest and most widely used applications of the PR was for the synthesis of \( \alpha \)-amino acids or \( \beta \)-amino alcohols as building blocks for further synthetic or biological studies,\(^{190,191} \) as demonstrated by many early examples for the synthesis of iminocyclitols,\(^{192} \) sialic acids,\(^{55} \) and pyrrolizidine alkaloids.\(^{36,193−196} \)

6.1. Polyhydroxy Alkaloids

Pyne and coworkers reported the PR-based synthesis of diverse polyhydroxylated alkaloids,\(^{197} \) among which was a 10-step total synthesis of calystegine B4 alkaloids.\(^{198} \) Different from a previous zinc-mediated tandem reaction with a RCM–hydroboration–oxidation sequence,\(^{199} \) a PR of benzylamine, (E)-styrylboronic acid, and (−)-D-lyxose was used for the synthesis of aminotetrol\(^{285} \), which was converted to the RCM substrate\(^{286} \) to give oxidation–RCM or RCM–oxidation.
product 287, and the remaining steps of deprotection and cyclization gave calystegine B4 288 with an overall yield of 3.4 or 4.7% (Scheme 75). This study exemplifies the synthesis of calystegine alkaloids starting from monosaccharides.

Conduramine oligomers, aminocyclohexenetriols in which an amino group is present, are common fragments included in several natural products. The synthesis of conduramines has been achieved via different approaches. Norsikian, Beau, and coworkers reported the synthesis of conduramine A1 292 and C4 296 using a PR of biallylamine and in-house-prepared highly functionalized boronic acids. Starting from multiple protected D-ribofuranose 299, the boronic acid 300 was prepared and used as the dual aldehyde and boronic component for the lengthy PR. An acidic treatment to remove all protecting groups was needed to proceed to the PR with diallylamine to give Petasis product 291 as a single diastereomer in 72% yield. A final palladium-catalyzed deallylation step yielded ent-conduramine A1 292. Comparatively, starting from multiple protected D-ribofuranoside 293, boronic acid 294 was used as the dual aldehyde and boronic

Scheme 60

Scheme 61

Scheme 62

Scheme 63
component for the PR with diallylamine to yield allyl-protected conduramine 295 as a single diastereoisomer in 60%. Conduramine C4 was obtained after a final palladium-catalyzed deallylation step. It was proposed that the six-membered transition state of tetracoordinated borate intermediates involving the β-hydroxyl group of the aldehyde contributed to the exclusive anti-stereoselectivity of β-amino alcohol products formed in this PR. A separate PR−RCM sequence was applied for the synthesis of both enantiomers of conduramine E300 and 304. D-Galactose and D-mannose were used for the synthesis of the corresponding carbonyl components 297 and 301 for a following three-component PR with (E)-styrlyboronic acid and tert-butylamine to form Petasis products 298 and 302, respectively. A subsequent Boc protection and intramolecular oxazolidinone-ring formation and a following RCM gave key oxazolidinone intermediates 299 and 303, which were hydrolyzed and tert-butyl-deprotected to yield conduramine E300 and 304, respectively (Scheme 76).

Pyne and coworkers reported various synthetic studies for the synthesis of polyhydroxylated monocylic alkaloids as well as their application as starting materials to access more complex alkaloids. Polyhydroxylated pyrrolidine alkaloids dihydroxymethyl−dihydroxy pyrrolidine
and 1,4-dideoxy-1,4-imino-D-arabinitol (DAB) were found in diverse plant species. Bouillon and Pyne reported a synthesis of DMDP and DAB from L-xylose over seven and eight steps with an overall yield of 35 and 22%, respectively. The PR was used as a key step for the synthesis of the amino diol from benzyl-protected L-xylofuranose, benzylamine, and (E)-styrylboronic acid as a single diastereomer in 76% yield. Subsequent transformations including intramolecular $S_{N}2$ cyclization yielded the pyrrolidine, and ozonolysis of the styryl double bond afforded DMDP. The synthesis of DAB was achieved by the serendipitous loss of the C-5 substituent via fragmentation during the ozonolysis step and final hydrogenolysis to remove all benzyl protecting groups (Scheme 77). Pyne and coworkers reported several synthetic studies using the PR as a key step to obtain α-amino alcohols for the

(DMDP) 307 and 1,4-dideoxy-1,4-imino-α-arabinitol (DAB) 308 were found in diverse plant species. Bouillon and Pyne reported a synthesis of DMDP and DAB from L-xylose over seven and eight steps with an overall yield of 35 and 22%, respectively. The PR was used as a key step for the synthesis of the amino diol 305 from benzyl-protected L-xylofuranose, benzylamine, and (E)-styrylboronic acid as a single diastereomer in 76% yield. Subsequent transformations including intramolecular $S_{N}2$ cyclization yielded the pyrrolidine 306, and ozonolysis of the styryl double bond afforded DMDP 307. The synthesis of DAB 308 was achieved by the serendipitous loss of the C-5 substituent via fragmentation during the ozonolysis step and final hydrogenolysis to remove all benzyl protecting groups (Scheme 77). Pyne and coworkers reported several synthetic studies using the PR as a key step to obtain α-amino alcohols for the
synthesis of different types of polyhydroxylated alkaloids. A PR of α-hydroxy aldehyde 309, enantiomerically pure allylamine 310, and (E)-styrylboronic acid gave the amino alcohol 311, which was used as a key step for the total synthesis of hyacinthacine C5 and 318 with a bicyclic hexahydro-1H-pyrrolizine core (Scheme 79). A disparity of chirality at the 5-, 6-, and 7-positions on the B-ring of the core was revealed between previously reported hyacinthacines and ones synthesized in this study, judged by spectroscopic analysis and crystal structures of

![Scheme 70](image1)

![Scheme 71](image2)

![Scheme 72](image3)
key precursors. Seven obtained hyacinthacine C₅ compounds were then evaluated as weak to moderate α-glycosidase inhibitors (9.9 to 130 μM).

6.2. Loline Alkaloid

The loline alkaloids, which incorporate a tricyclic ring system with a strained ethereal bridge, four contiguous stereogenic centers, and two basic nitrogen atoms (including one heterocyclic nitrogen atom), have been the subject of many synthetic works. A two-component Petasis-like step was used to synthesize the loline alkaloid scaffold. The diastereoselective addition of tetramethylpentanediol boronates to the N-acyliminium ion species, which was derived from dihydroxypyrrolidine, gave vinylpyrrolidinol. Six following steps, including a tethered aminohydroxylation, led to the formation of pyrrolooxazinone, from which the N-Boc norlodine was obtained as the loline alkaloid scaffold in another five steps (Scheme 80).

6.3. Sialic Acid

Legionaminic acids, analogs of N-acetylneuraminic acid, are diamino monosaccharides belonging to the family of nonulosonic acids and are key virulence factors in Legionnaires’ disease. Seeberger and coworkers reported a stereoselective synthesis of orthogonally protected legionaminic acids via chelation-controlled organometallic additions and the PR starting from D-threonine, which was used as the precursor for the synthesis of the aldehyde compound. The PR of α-hydroxyl aldehyde, (E)-styrlyboronic acid, and monoallylamine gave aminol in 76% yield and with high antidiastereoselectivity (dr > 19:1). Pd-catalyzed deallylation and chemoselective acetylation gave an N-acetate compound that was used for the subsequent synthesis of orthogonally protected legionaminic acid, which was used for the further synthesis of a linker-equipped legionaminic acid (Scheme 81). A recent study reported the total biosynthesis of the same type of legionaminic acid acetylated at the 5- and 7-positions.

7. CONCLUSIONS

The PR has proved to be a powerful MCR to achieve synthetically interesting transformations and access biologically interesting molecules. The year 2018 marks the 25th anniversary of the initial report of this three-component condensation of carbonyls, amines, and boronates. This Review revealed the breadth of the synthetic application and the recent progress in employing the PR through a systematic overview of examples published in the past 8 years.

The two common limitations of the PR, especially in early examples, were usually that only activated aldehydes or aldehydes bearing a suitable boron-directing group could be successfully applied and only reactive boronic acids, such as electron-rich heteroaryl or vinylboronic acids, could lead to...
Scheme 76

Scheme 77

Scheme 78

* 2-Step yield including a metathesis reaction to obtain a vinyl sultone as the precursor of 309.
desired Petasis products in satisfactory yield. The reactivity of the PR has been greatly explored in different frontiers, as demonstrated by illustrated recent examples, which not only addressed the two limitations but also significantly expanded the utility of the PR in organic synthesis, medicinal chemistry, and chemical biology. Carbonyl components with or without a directing group, amines of both high and poor nucleophilicities, and boronic acid or boronates of aryl, allyl, alkynyl, and allenyl nature have all been successfully applied for the production of desired Petasis products, mostly being substituted amino acids, β-amino alcohols, and aminophenols; Although being catalyst-free is a valued feature of the classic type of PR, the presence of chiral catalyst leads to the formation of functionalized Petasis products with excellent diastereoselectivity and enantioselectivity. The four-component PR, usually discovered through serendipitous manners, enabled the equipping of an additional functional handle. Petasis-type reactions including not only the common two-component type but also the newly reported traceless type greatly diversified the chemotypes accessible through PRs. More excitingly, the combination of the PR with the Diels–Alder reaction, ROM/RCM reaction, metal-catalyzed coupling, or other types of intramolecular cyclization in either a cascade or sequence manner made it possible to furnish a wide range of natural-product-like compounds that have a high content of sp³-hybridized carbon atoms and a rich count of stereogenic centers. Not surprisingly, PRs have been successfully applied for the synthesis of polyhydroxy alkaloids and biologically active compounds that showed varied biological activities.

The authors declare no competing financial interest.

Biographies

Dr. Peng Wu received his doctoral degree in medicinal chemistry working with Professor Yongzhou Hu at Zhejiang University in 2012. He then performed postdoctoral research with Professor Thomas E. Nielsen at the Technical University of Denmark and the University of Copenhagen. In 2016, he moved to Massachusetts, working as a Research Fellow in Chemical Biology at Harvard University, Broad Institute, Brigham and Women’s Hospital, and the Massachusetts Institute of Technology. In 2018, he was appointed as Assistant
Professor in Medicinal Chemistry Research in the Department of Drug Design and Pharmacology at the University of Copenhagen and Group Leader at the Chemical Genomics Centre of the Max Planck Institute of Molecular Physiology in Dortmund. His general research interests include structure-diverse synthesis, small-molecule probes in chemical biology, and drug discovery. One of his current research areas is the modulation of protein–RNA interactions using small molecules.

Professor Michael Givskov received his M.Sc. in cell biology from the University of Southern Denmark 1983 and his Ph.D. in Microbiology in 1987 from the University of Copenhagen (UCPH). He did postdoctoral research at the Technical University of Denmark (DTU) with Professor Søren Molin as a supervisor, and in 1996, he was appointed Associate Professor in Microbiology, where he developed his skills and interest in chemical biology. Subsequently, in 2004, he was appointed Professor of Biomedical Microbiology and head of the Centre of Biomedical Microbiology, DTU. He became the founder and research director of the spin-out company QSI-Pharma in 2002. He received the degree Doctor of Technical Sciences in 2006 from DTU, and in 2008, he was headhunted for a professorship in biomedical microbiology at the Medical Faculty of UCPH. In 2010, he became one of the founders of the Singapore Center for Environmental Life Sciences Engineering (SCELSE) and was appointed Professor of Biomedical Microbiology and head of the Centre of Biomedical Microbiology, DTU. He became the twin positions in Copenhagen and Singapore. His interests are biofilm biology, cell signaling, and chemical biology approaches to develop antimicrobials with novel modes of action.

Professor Thomas E. Nielsen received his Ph.D. from the Technical University of Denmark for work in the field of natural product total synthesis under the supervision of Professor David Tanner. He then carried out postdoctoral studies at the Carlsberg Laboratory (with Professor Morten Meldal, 2003–2005) and Harvard University and the Broad Institute of Harvard and MIT (with Professor Stuart L. Schreiber, 2006–2007), working within various areas of chemical biology research. In 2008, he returned to the DTU Chemistry and cofounded the Center for Antimicrobial Research (CAR), heading the development of new synthesis methodology, bioactive materials, and assay technologies, and joined SCELSE, Nanyang Technological University in 2010 as a visiting professor. In 2014, he became the director of Protein & Peptide Chemistry, Novo Nordisk A/S, and was affiliated as a professor in the Department of Immunology and Microbiology, University of Copenhagen. A central theme in his research is the chemical synthesis of small molecules, peptides, and modified proteins to probe biological phenomena and ultimately provide the basis for the development of new medicines to treat cancer, haemophilia, diabetes, obesity, and antimicrobial infectious disease. He has received several national and international scientific awards and is the coauthor of more than 100 journal publications and patents.

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ABBREVIATIONS USED

| Ac | acetyl |
| BINOL | 1,1′-bi-2-naphthol |
| Bpin | boronic acid pinacol ester |
| Bn | benzyl |
| Bt | benztiazole |
| i-Bu | iso-butyl |
| Bz | benzoyl |
| Boc | tert-butyloxycarbonyl |
| CBz | carboxybenzyl |
| DFT | density functional theory |
| de | diastereomeric excess |
| dr | diastereomeric ratio |
| ee | enantiomeric excess |
| Et | ethyl |
| HFIP | 1,1,1,3,3,3-hexafluoroisopropanol |
| IMDA | intramolecular Diels–Alder reaction |
| Me | methyl |
| Ms | methanesulfonyl |
| MS | molecular sieves |
| MW | microwave |
| NMR | nuclear magnetic resonance |
| Na | p-nitrobenzenesulfonyl |
| Ph | phenyl |
| i-Pr | iso-propyl |
| PFB | Pomeranz–Fritsch–Bobbitt cyclization |
| PR | Petasis reaction |
| RCM | ring-closing metathesis |
| ROM | ring-opening metathesis |
| SET | single electron transfer |
| S_N | nucleophilic substitution |
| TBHP | tert-butyl hydroperoxide |
| TFA | trifluoroacetic acid |
| TF-FVIa | tissue factor/factor VIIa |

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