CHEMICAL REVIEWS

Review

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Reactivity and Synthetic Applications of Multicomponent Petasis Reactions

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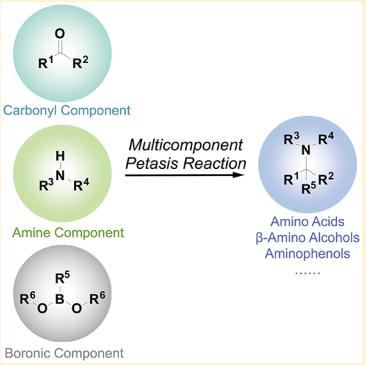
ABSTRACT: The Petasis boron−Mannich reaction, simply referred to as the Petasis reaction, is a powerful multicomponent coupling reaction of a boronic acid, an amine, and a carbonyl derivative. Highly functionalized amines with multiple stereogenic centers can be efficiently accessed via the Petasis reaction 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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1. INTRODUCTION

Multicomponent reactions (MCRs),[1−3] such as those that bear the name of their discoverers, Biginelli,[4] Hantzsch,[5] Mannich,[6] Passerini,[7] Povarov,[8] Strecker,[9] and Ugi,[10,11] have been widely used as complexity-generating reactions to rapidly access diverse scaffolds of both synthetic and biological interest. Synthetic small molecules developed based on MCR-derived scaffolds have served as valuable chemical probes, mimics of natural products, and leads in drug discovery.[1,2]

In 1993, Petasis and coworker reported a new type of MCR involving a secondary amine, paraformaldehyde, and (*E*)-vinylboronic acid to access allylamines,[12] which is an archetype of the widely used three-component reaction, nowadays known as the Petasis borono–Mannich reaction, or simply the Petasis reaction (PR). In this Review, we define the PR as a multicomponent transformation of a boronic acid, an amine, and a carbonyl derivative. The term "Petasis borono–Mannich reaction" may not accurately describe the nature of this boron-based MCR, because a mechanism different from that of conventional Mannich reactions has been proposed.[13] The "borono–Mannich reaction" notation incorrectly indicates that boronic acids can directly react with electrophilic iminium ion species. The "Petasis" notation has been applied to several other transformations, such as the Petasis olefination reaction reported in 1990[14] and the Petasis–Ferrier rearrangement reported in 1996.[15] The former is a ketone or aldehyde olefination via a four-membered titanium intermediate using dimethyl titanocene as the Petasis reagent,[14] and the latter is a transformation of cyclic enol acetals to tetrahydrofurans or tetrahydropyrans via a Lewis-acid-promoted oxygen-to-carbon transposition pathway.[15] Although the original PR did not employ any catalyst, variants relying on either chiral organocatalysts or metal complexes are now widely abundant, together with reactions where the original three components, amine, aldehyde, and boronic acid, have been expanded to include many other functionalities. In this Review, the abbreviation "PR" refers to boron-based reactions as well as the above-mentioned variants.

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,[16] compatibility with various secondary transformations,[17] 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.[18−24] The topic has been reviewed on several occasions in both book chapters[25−29] and journal articles,[16,30,31] either as a comprehensive summary, such as the chapter in 2005 by Petasis[25] and the full compilation in 2010 by Candeias and coworkers,[16] or a part of a broader topic, such as the nucleophilic addition of boronic acids and derivatives to imines,[26] asymmetric MCRs,[31] and stereocontrolled cascade reactions.[32]

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 carbon. This assumption has been supported by a range of mechanistic studies performed, including density functional theory (DFT) analysis[33−35] and nuclear magnetic resonance (NMR) analysis,[36,37] as well as the characterization of crystal structures for boronate intermediates.[38] 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.[11]

Developments reported in the past 8 years have significantly expanded the scope of the PR,[17] 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,[39,40] as well as a wide range of boronic acid and boronate reagents, such as allenylboronic acids and allenylboronates.[41,42] 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 sp^3-hybridized carbon atoms.[18] 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

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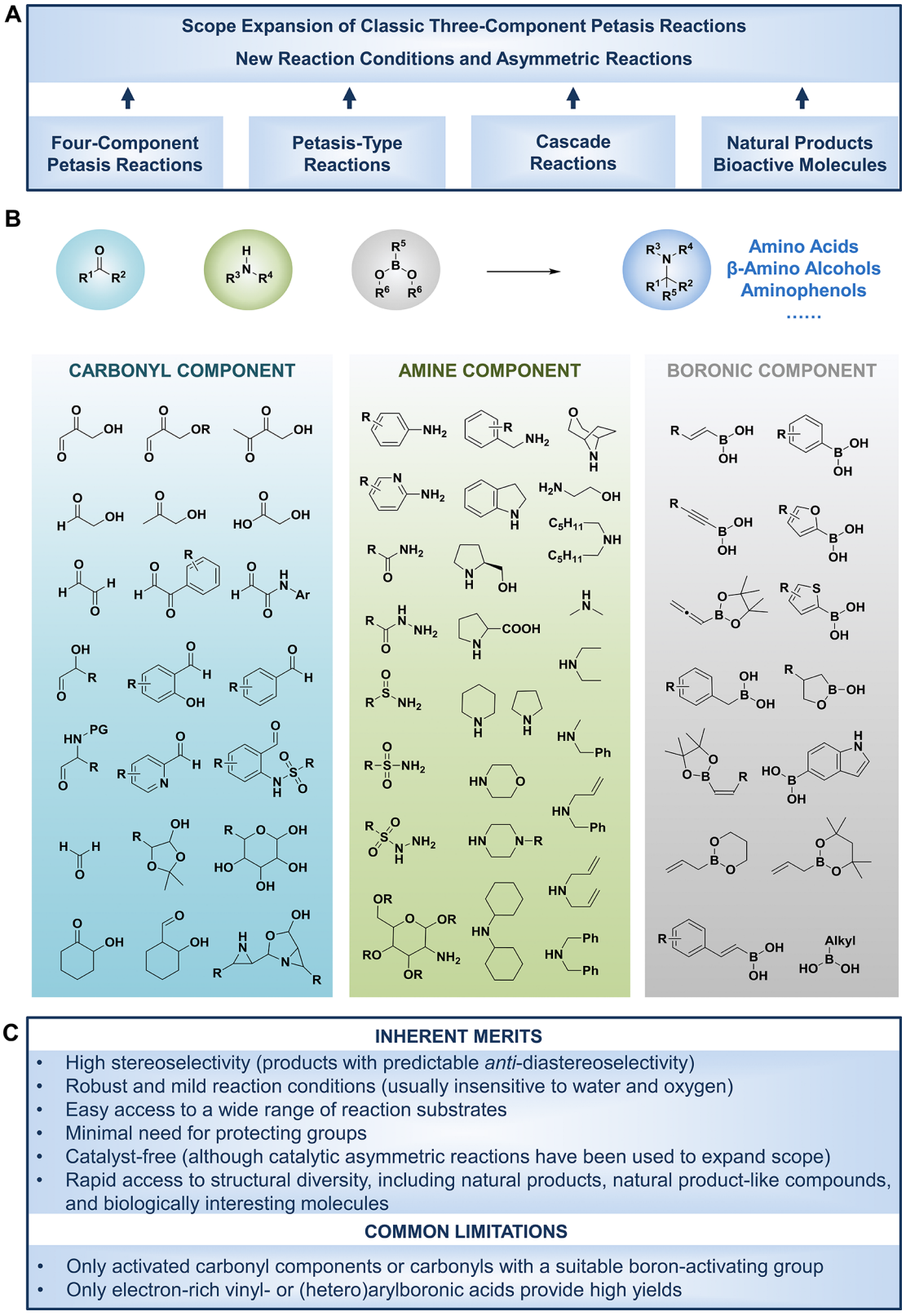

Figure 1. Reactivity and synthetic applications of multicomponent petasis reactions. (A) Five overall directions for the PR covered in this Review, including asymmetric variants. (B) Representative examples of the three components typically used in PRs: carbonyls, amines, and boronic acids or other boronic components. (C) Common merits and limitations of PRs.

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]

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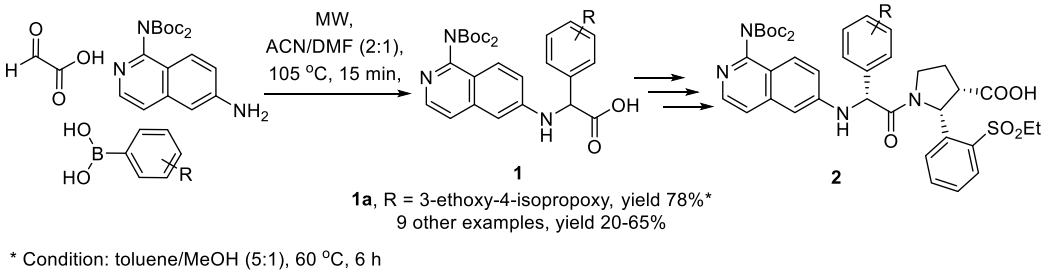
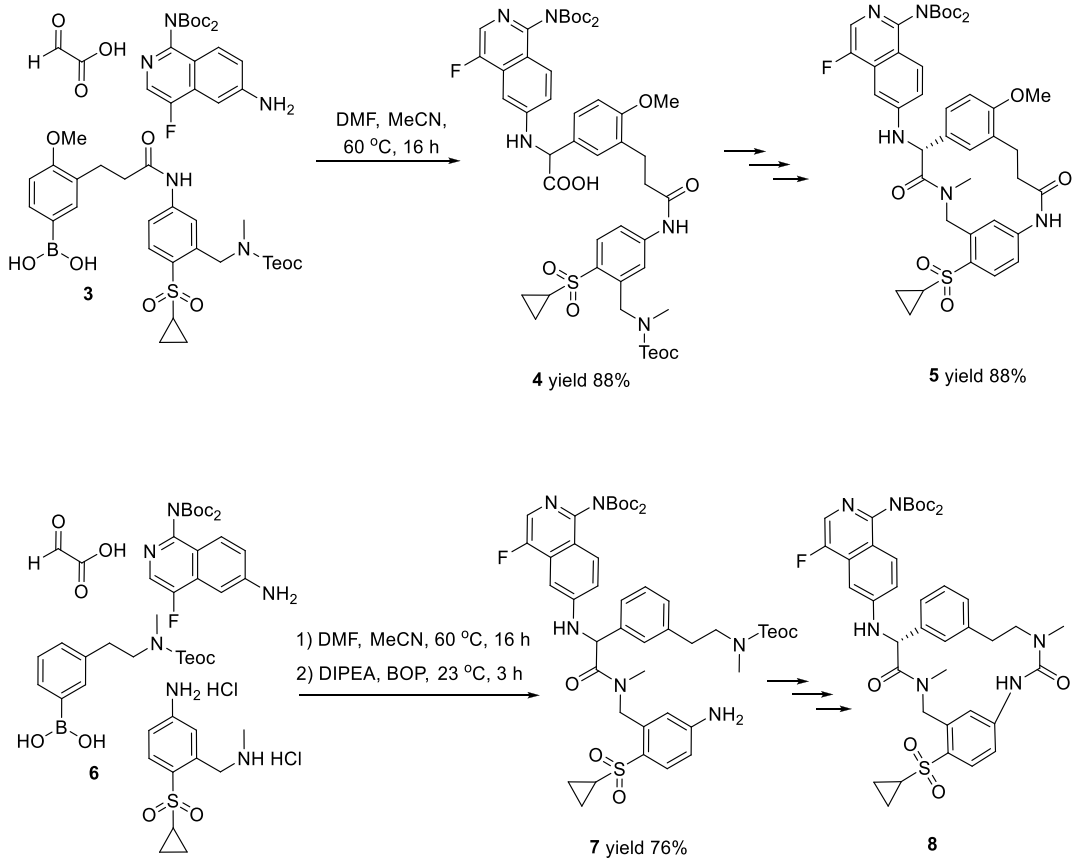
Scheme 1



Scheme 2



including the synthesis of fluorous-tagged *N*-alkylated amino acids using fluorous-tagged hydroxylamines,[47,48] derivatization and stapling of peptides by an on-resin PR,[49] and combinatorial synthesis of peptidomimetics employing PR-Ugi sequence reactions,[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).[24,51−54] A series of phenylpyrrolidine phenylglycinamides was synthesized and evaluated as TF-FVIIa inhibitors with promising oral bioavailability and a favorable in vitro safety profile for the potential treatment of thromboembolic disorders.[24,51] The PR of glyoxylic acid, Boc-protected 1,6-diaminoisoquinoline, and phenylboronic acids led to the formation of phenylglycines **1** that were coupled to phenyl pyrrolidine to yield a series of TF-FVIIa inhibitors. Enantiomerically pure compounds were obtained by chiral separation. The carboxypyrrolidine compound **2** showed a clean in vitro safety panel against receptors and enzymes, a moderate clearance, and a low distribution volume (Scheme 1).[51]

On the basis of the structural information obtained through modeling of the TF-FVIIa active site, series of macrocyclic phenylglycines as TF-FVIIa inhibitors was designed and synthesized with the aim to improve the poor rodent metabolic stability and oral bioavailability of previously reported phenylglycine inhibitors.[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 trimethylsilylethoxycarbonyl protecting group. Macrocyclization of **4** via intramolecular amidation and subsequent chiral

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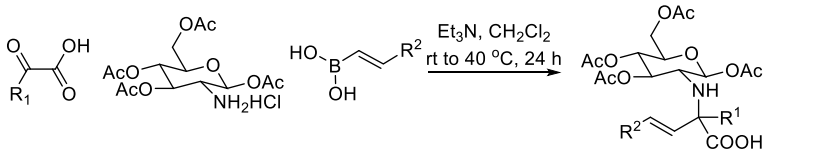
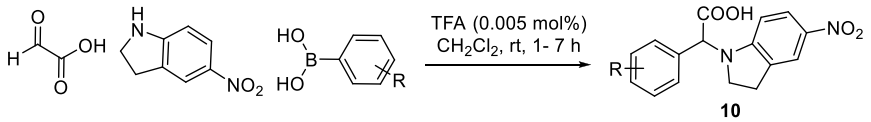
Scheme 3



9a, R^1 = H, R^2 = Ph, yield 81%
9b, R^1 = H, R^2 = propyl, yield 88%
9c, R^1 = methyl, R^2 = Ph, yield 9%

Scheme 4



10
21 examples, yields 65-94%

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]

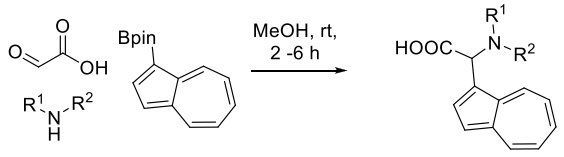
PRs have been used for the synthesis of *N*-monosaccharide-substituted α-amino acids.[55] *N*-Glycosyl α-amino acids **9** were recently synthesized from tetraacetyl-D-glycosamine hydrochloride, alkenylboronic acids, and glyoxylic acid. Although chiral D-glycosamine substrate was used, the product was 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 CH_2Cl_2, 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 azulenylglycine 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]

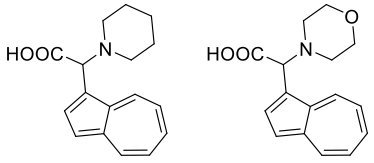
Helicenes are polycyclic aromatic screw-shaped nonplanar compounds that can be used as building components for chiral ligands.[60] The fusion of more than five benzene or other aromatic rings leads to inherent helical chirality, distinguished by an enantiopure (P) or (M) configuration.[61] Enantiopure carbo[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

Scheme 5



11

11a, R^1 = H, R^2 = Bn, yield 83%
11b, R^1 = H, R^2 = 4-methoxybenzyl, yield 87%
11c, R^1 = H, R^2 = allyl, yield 85%
11d, R^1 = H, R^2 = hexyl, yield 82%
11e, R^1 = H, R^2 = 2-hydroxyethyl, yield 92%
11f, R^1 = ethyl, R^2 = ethyl, yield 73%
11g, R^1 = hexyl, R^2 = hexyl, yield 62%



11h yield 91% **11i** yield 77%

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

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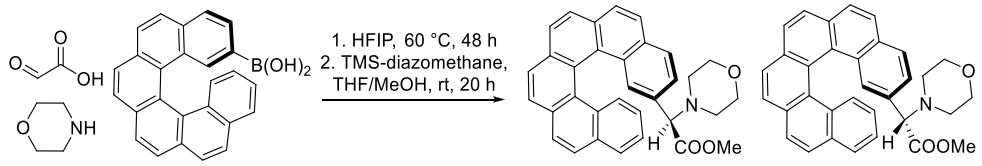
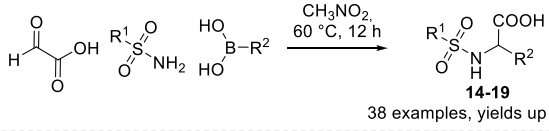
Scheme 6



(*M*)-**12** (*M,R*)-**13** major (*M,S*)-**13** minor

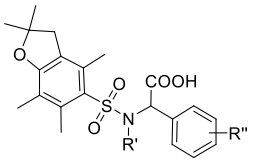
two-step total yield 84%, dr 7:3

Scheme 7

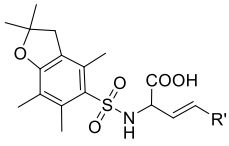


14-19

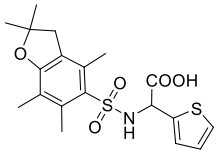
38 examples, yields up to 98%



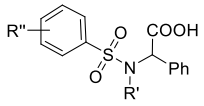
14a, R' = H, R" = H, yield 90%
14b, R' = methyl, R" = H, yield 92%
14c, R' = H, R" = 4-bromo, yield 62%
14d, R' = H, R" = 4-fluoro, yield 81%
14e, R' = H, R" = 4-methoxy, yield 98%
14f, R' = H, R" = 4-ethoxycarbonyl, yield 49%
14g, R' = H, R" = 2-chloro, yield 85%
14h, R' = H, R" = 3-chloro, yield 80%
14i, R' = H, R" = 4-chloro, yield 89%
14j, R' = H, R" = 3-trifluoromethyl, yield 61%
14k, R' = H, R" = 2-methyl, yield 87%
14l, R' = H, R" = 4-methyl, yield 90%



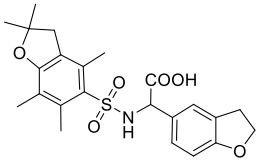
16a, R' = propyl, yield 69%
16b, R' = chloromethyl, yield 90%
16c, R' = Ph, yield 95%



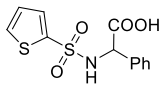
17 yield 82%



15a, R' = H, R" = H, yield 90%
15b, R' = H, R" = 4-methyl, yield 84%
15c, R' = H, R" = 4-*tert*-butyl, yield 81%
15d, R' = H, R" = 4-methoxy, yield 96%
15e, R' = H, R" = 4-methoxy, yield 98%
15f, R' = H, R" = 4-fluoro, yield 60%
15g, R' = H, R" = 4-bromo, yield 62%
15h, R' = H, R" = 4-trifluoromethyl, yield 56%
15i, R' = H, R" = 4-nitro, yield 0%
15j, R' = methyl, R" = H, yield 89%
15i, R' = Bn, R" = H, yield 90%
15j, R' = methyl, R" = 4-trifluoromethyl, yield 90%

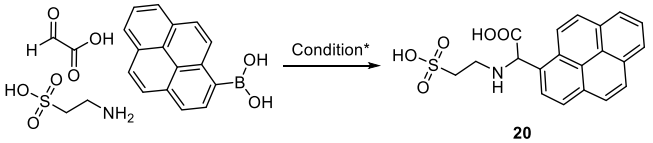


18 yield 60%



19 yield 95%

Scheme 8



20

* Reaction condition and yield not provided in the original report.

determine the glyoxylic acid concentration in urine.[65] 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 afford sulfonic acid **20**, which can be easily purified using ion-exchange chromatography (Scheme 8).[66]

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.[67,68]

2.1.2. Sulfinamide as Chiral Auxiliary in an Asymmetric Petasis Reaction. Hutton and coworkers reported the preparation of β,γ-dihydroxyamino acid derivatives through different PR-based strategies.[69−71] In a synthetic approach aiming to access a key dihydroxyhomotyrosine fragment for the total synthesis of echinocandins, a series of β,γ-dihydroxyamino acid derivatives were obtained through a PR asymmetric dihydroxylation sequence. It was observed that a higher concentration (0.33 M in CH_2Cl_2 in comparison with 0.2 M in CH_2Cl_2) led to the complete conversion of the Petasis product **21** from glyoxylic acid, chiral *tert*-butylsulfinamide, and substituted (*E*)-styrylboronic acids in excellent yield ranging from 90 to 99% and good to high diastereoselectivity. The *N*-sulfinyl amino acids **21** were subsequently treated with hydrochloric acid in methanol to give sulfinamde-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 β,γ-dihydroxy amino acid ester **22** (Scheme 9).[71]

A series of β,γ-unsaturated α-amino acids **23** were synthesized through an enantioselective PR of glyoxylic acid, (*S*)-2-methylpropane-2-sulfinamide, and vinylboronic acids promoted by $InBr_3$ (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.[72]

The same type of $InBr_3$-promoted PR of glyoxylic acid monohydrate and (*S*)-2-methylpropane-2-sulfinamide was used for the asymmetric synthesis of Petasis product **24** using either 2-benzofuryl or 2-benzothienylboronic acid. The further transformation of **24** led to a series of oxadiazines **25** that were evaluated as γ-secretase modulators with predicted favorable drug-like properties for treating CNS diseases, such as Alzheimer's disease (Scheme 11).[20]

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.[73] 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 **26** was reported by Manolikakes and coworkers for the synthesis of α-arylglycines **27** in moderate to good yield and with excellent enantioselectivity (>99:1). The scope of the reaction was evaluated with aryl and

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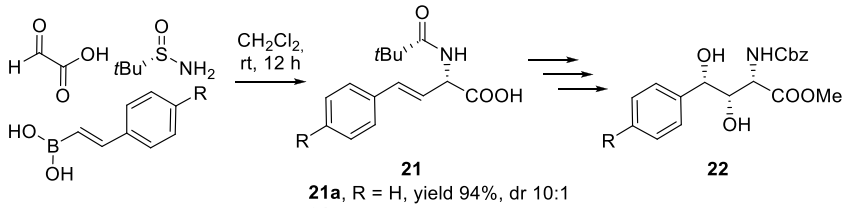
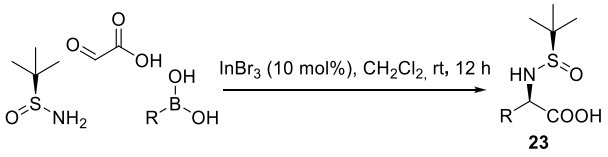
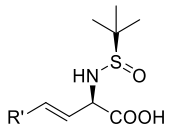
Scheme 9



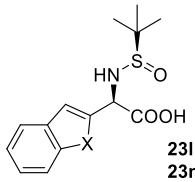
21a, R = H, yield 94%, dr 10:1
21b, R = methyl, yield 99%, dr 20:1
21c, R = Ph, yield 90%, dr 20:1
21d, R = acetoxy, yield 99%, dr 18:1
21e, R = methoxy, yield 99%, dr >20:1
21f, R = chloro, yield 95%, dr 13:1
21g, R = fluoro, yield 90%, dr >20:1

Scheme 10



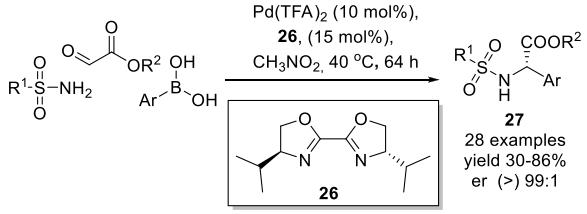


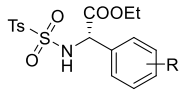
23a, R' = Ph, yield 65%, de 98%
23b, R' = 4-methylphenyl, yield 70%, de 98%
23c, R' = 4methoxyphenyl, yield 71%, de 99%
23d, R' = 4-fluorophenyl, yield 67%, de 98%
23e, R' = 4-chlorophenyl, yield 69%, de 98%
23f, R' = 3-chlorophenyl, yield 67%, de 98%
23g, R' = 4-trifluoromethylphenyl, yield 58%, de 93
23h, R' = 4-PhPh, yield 56%, de 96%
23i, R' = propyl, yield 62%, de 97%
23j, R' = hexyl, yield 60%, de 99%
23k, R' = Bn, yield 57%, de 98



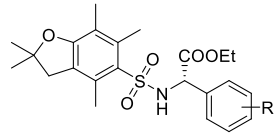
23l, X = O, yield 78%, de 99%
23m, X = S, yield 60%, de 96%

Scheme 12





27a, R = 3-trifluoromethyl, yield 45%, er 99:1
27b, R = 4-fluoro, yield 77%, er >99:1
27c, R = 4-bromo, yield 66%, er >99:1
27d, R = 4-chloro, yield 73%, er >99:1
27e, R = 3-chloro, yield 81%, dr >99:1
27f, R = 2-chloro, yield 67%, er 99:1



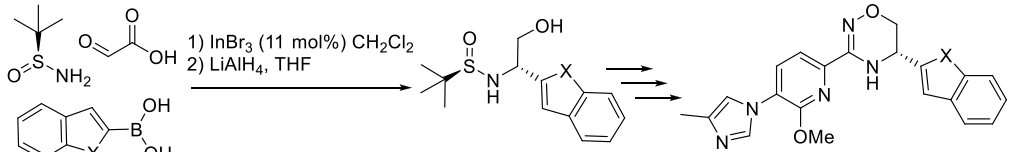
27g, R = H, yield 82%, er >99:1
27h, R = 4-methoxy, yield 82%, er >99:1
27i, R = 4-chloro, yield 87%, er 99:1
27j, R = 3-trifluoromethyl, yield 60%, er 99:1

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 α-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 α-arylglycines.[75]

2.2. Salicylaldeyde 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

Scheme 11



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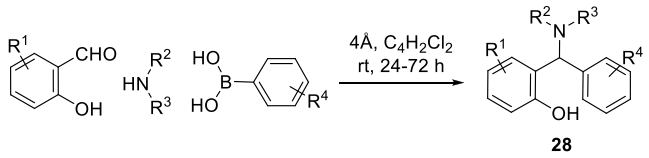
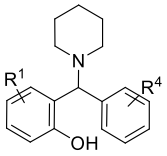
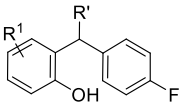
included the use of the electron-deficient 3-nitrophenylboronic acid and the substitution of a second hydroxyl group on the salicylaldehyde (Scheme 13).[80] The developed method was

Scheme 13





28a, R^1 = H, R^4 = 4-fluoro, yield 88%
28b, R^1 = 4-methoxy, R^4 = 4-fluoro, yield 80%
28c, R^1 = 4-bromo, R^4 = 4-fluoro, yield 84%
28d, R^1 = H, R^4 = methoxy, yield 91%
28e, R^1 = H, R^4 = 4-cyano, yield 42%
28f, R^1 = H, R^4 = 4-fluoro, yield 95%
28g, R^1 = H, R^4 = 2-methoxy, yield 65%
28h, R^1 = H, R^4 = 3-ethoxy, yield 72%
28i, R^1 = H, R^4 = H, yield 58%
28j, R^1 = H, R^4 = 4-chloro, yield 40%
28k, R^1 = 5-nitro, R^4 = 4-fluoro, yield 90%
28l, R^1 = H, R^4 = 3-nitro, yield 0%
28m, R^1 = 4-hydroxy, R^4 = 4-fluoro, yield 0%



28n, R^1 = H, R' = diallylamino, yield 95%
28n, R^1 = H, R' = diethylamino, yield 89%
28o, R^1 = H, R' = pyrrolidin-1-yl, yield 91%
28p, R^1 = (*R*)-1-carboxyethyl,
R' = methylpiperidin-1-yl, yield 85-90%

applied for the synthesis of the core scaffold of BIIB042, a γ-secretase modulator with potential applications in the treatment of Alzheimer's disease.[86] 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.[87]

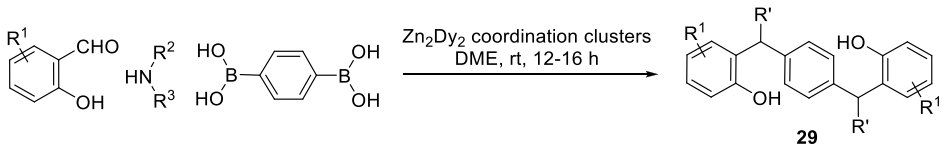
Alkylaminophenols with core scaffold **28** could also be generated through cobalt ferrite nanoparticle-catalyzed PRs.[76] Another series of similar diphenylmethanamines, generally containing a morpholino instead of a pyrrolidino alkyl moiety, was synthesized using a catalysis based on chitosan or trititanate nanotubes in high yield. The methodology could also be extended to a series of piperazine-substituted aminophenols.[43,77] Other catalysts, including lanthanum(III) trifluoromethanesulfonate, Mg−Al mixed oxides, and 4 Å supported copper catalysts, were also applied in the PR of salicylaldehyde, morpholine, and arylboronic acid.[88,89] 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-1*H*-xanthen-1-ones in a $FeCl_3$-mediated approach involving nucleophilic substitution and intramolecular cyclization steps.[90] A microwave-assisted PR catalyzed by CuO-nanoparticle-decorated reduced graphene oxide composite was recently reported for the synthesis of similar aminophenols.[91] Additionally, Petasis products of the same scaffolds as that of **28** were obtained through a tetranuclear Zn_2Dy_2 coordination cluster-catalyzed PR, featuring the low catalyst loading of the Zn_2Dy_2 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 Zn_2Dy_2-catalyzed method from benzene 1,4-diboronic acid (Scheme 14).[78] A recent solvent-free protocol using ball milling was reported for the synthesis of alkyl- and arylaminophenols of the same scaffolds.[92]

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.[21] Additionally, indolines sharing the same scaffold as **30** were reported to have weak cytotoxicity against U2OS cells via apoptosis-induced cell death,[79] and tertiary phenolamines of the scaffold of **30** have shown cytotoxicities against osteosarcoma cells.[93] 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.[94] The Petasis product **32** was recently released as a site-specific (Ser99) inhibitor of human BCL2-associated death promoter phosphorylation (Scheme 15).[95]

The decarboxylation of proline has been previously reported as a modification strategy to give functionalized unnatural α-amino acid analogs.[96−98] 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).[99]

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

Scheme 14



29a, R^1 = H, R' = indolin-1-yl, yield 92%
29b, R^1 = 3-methoxy, R' = indolin-1-yl, yield 95%
29c, R^1 = H, R' = diallylamino, yield 86%
29d, R^1 = 3-methoxy, R' = diallylamino, yield 88%

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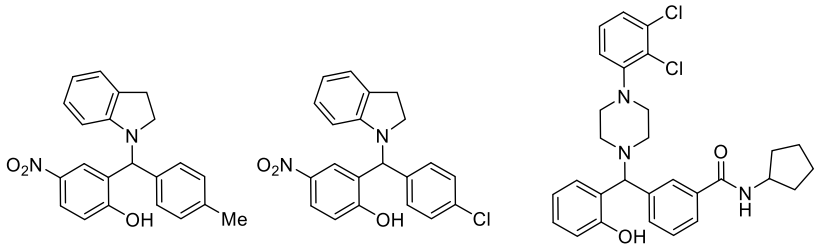
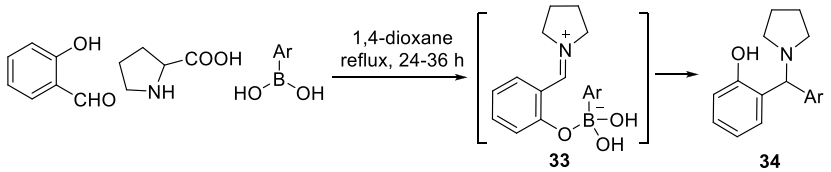
Scheme 15



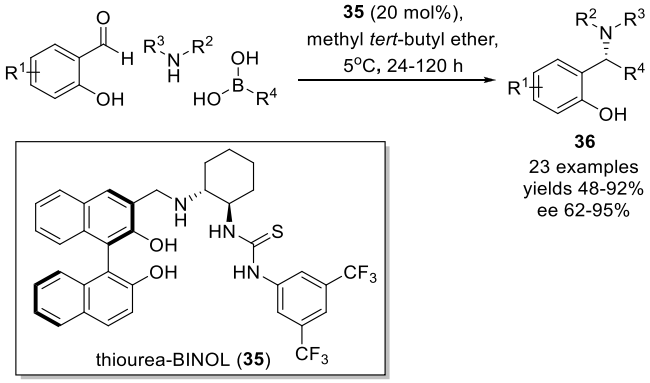
30 31 32

Scheme 16



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.[100]

Scheme 17



2.3. α-Hydroxy Aldehyde and Equivalent

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 products, and the N′-alkylated secondary hydrazides gave the highest 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).[101] 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.[102]

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.[103,104] 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.[105]

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,[106] the synthesis of chiral amides from the addition of aryl, vinyl, and alkynyl boronates to acyl imines,[107,108] and the synthesis of diastereomerically pure *anti*- and *syn*-β-amino alcohols from boronates, α-hydroxy aldehydes, and amines.[109]

The use of enantiopure α-hydroxy aldehydes in conventional PRs lead to the formation of enantiopure β-amino alcohols with exclusive anti-diastereoselectivity.[110] 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.[109] Starting from α-hydroxyl 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

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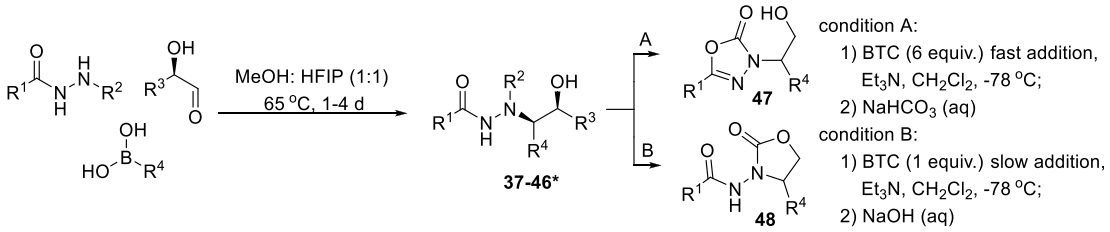
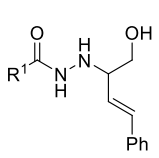
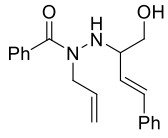
Scheme 18



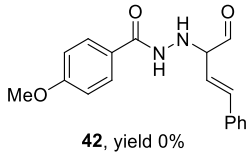
* Compounds **40, 42-46** were tested using other aldehyde components instead of glycoaldehyde



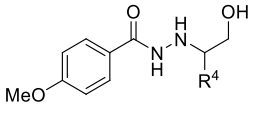
37a, R^1 = Ph, yield 52%
37b, R^1 = 4-HOC_6H_4, yield 56%
37c, R^1 = 4-$NO_2C_6H_4$, yield 49%
37d, R^1 = 4-ClC_6H_4,yield 80%
37e, R^1 = pyridin-3-yl, yield 64%
37f, R^1 = fur-2-yl, yield 0%
37g, R^1 = Bn, yield 37%
37h, R^1 = 4-heptyl, yield 31%
37i, R^1 = ethyl, yield 53%
37j, R^1 = methoxy, yield 31%



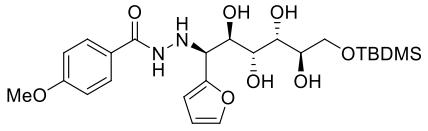
41, yield 0%



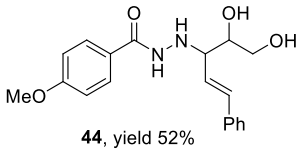
42, yield 0%



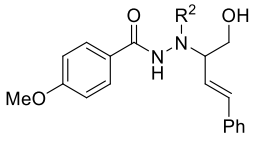
38a, R^4 = prop-1-en-1-yl, yield 26%
38b, R^4 = 1*H*-indol-5-yl, yield 39%
38c, R^4 = 2,4-dimethoxyphenyl, yield 48%
38d, R^4 = benzo[*b*]thiophen-2-yl,yield 55%
38e, R^4 = thien-2-yl, yield 64%
38f, R^4 = thien-3-yl, yield 45%
38g, R^4 = fur-2-yl, yield 95%
38h, R^4 = Ph, yield 0%
38i, R^4 = ethyl, yield 53%
38j, R^4 = methoxy, yield 31%



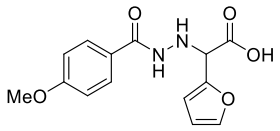
43, yield 81%



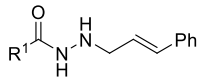
44, yield 52%



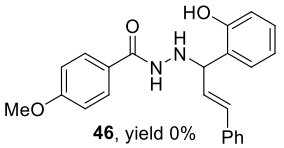
39a, R^2 = H, yield 63%
39b, R^2 = cyclohexylmethyl, yield 64%
39c, R^2 = allyl, yield 71%
39d, R^2 = Bn, yield 84%



45, yield 77%

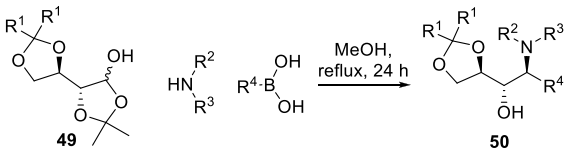


40a, R^1 = H, yield 0%
40b, R^1 = cyclohexylmethyl, yield 75%
40c, R^1 = Bn, yield 51%



46, yield 0%

Scheme 19



50a, R^1 = ethyl, R^2 = H, R^3 = benzhydryl, R^4 = (*E*)-styryl, yield 93%
50b, R^1 = ethyl, R^2 = H, R^3 = allyl, R^4 = (*E*)-styryl, yield 69%
50c, R^1 = ethyl, R^2 = Bn, R^3 = Bn, R^4 = (*E*)-styryl, yield 65%
50d, R^1 = ethyl, R^2 = allyl, R^3 = Bn, R^4 = (*E*)-styryl, yield 89%
50e, R^1 = ethyl, R^2 = allyl, R^3 = allyl, R^4 = (*E*)-styryl, yield 81%
50f, R^1 = ethyl, R^2 = H, R^3 = benzhydryl, R^4 = 4-methoxyphenyl, yield 80%
50g, R^1 = methyl, R^2 = H, R^3 = benzydryl, R^4 = (*E*)-styryl, yield 66%

of a D-amino ester favored the formation of the antiproduct **52o** (Scheme 20). It was concluded that *S*-configured 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 α-hydroxyl aldehydes masked as lactols, glycolaldehyde in the form of glycolaldehyde dimer was also successfully applied for this (*S*)-BINO- catalyzed synthesis of β-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′-Me_2-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 α-hydroxy aldehydes amenable to PRs owing to their ready availability and high stability.[36]

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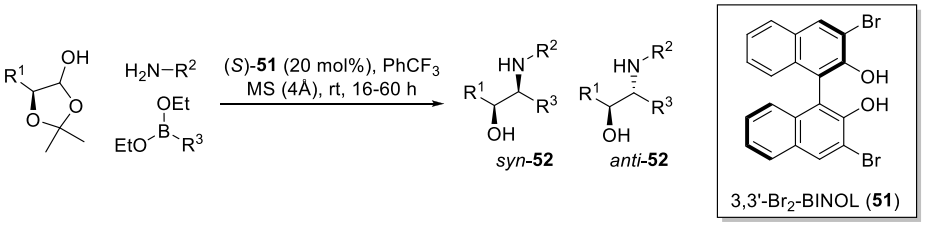
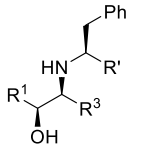
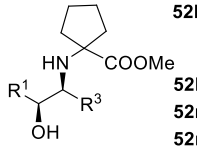
Scheme 20





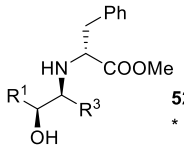
syn-**52a-k**

52a, R^1 = Ph, R^3 = (*E*)-styryl, R' = COOMe, yield 95%*, dr (*syn*/*anti*) 5.5:1
52b, R^1 = CbzNH$(CH_2)_2$, R^3 = (*E*)-styryl, R' = COOMe, yield 84%*, dr (*syn*/*anti*) 2:1
52c, R^1 = Ph, R^3 = (*E*)-styryl, R' = $CH(OCH_3)_2$, yield 96%*, dr (*syn*/*anti*) 7:1
52d, R^1 = Ph, R^3 = (*E*)-styryl, R' = $CH(OCH_3)_2$, yield 77%*, dr (*syn*/*anti*) 1.5:1
52e, R^1 = Bn, R^3 = 4-methoxyphenyl, R' = COOMe, yield 62%*, dr (*syn*/*anti*) 5:1
52f, R^1 = Ph, R^3 = 4-methoxyphenyl, R' = COOMe, yield 75%*, dr (*syn*/*anti*) 4:1
52g, R^1 = CbzNH$(CH_2)_2$, R^3 = 4-methoxyphenyl, R' = COOMe, yield 73%*, dr (*syn*/*anti*) 2:1
52h, R^1 = Bn, R^3 = 4-methoxyphenyl, R' = $CH(OCH_3)_2$, yield 65%*, dr (*syn*/*anti*) 1:1
52i, R^1 = Ph, R^3 = 4-methoxyphenyl, R' = $CH(OCH_3)_2$, yield 70%*, dr (*syn*/*anti*) 1:10
52j, R^1 = CbzNH$(CH_2)_2$, R^3 = 4-methoxyphenyl, R' = $CH(OCH_3)_2$, yield 71%*, dr (*syn*/*anti*) 1:4
52k, R^1 = Bn, R^3 = phenylethynyl, R' = COOMe, yield 77%*, dr (*syn*/*anti*) 5:1



syn-**52l-n**

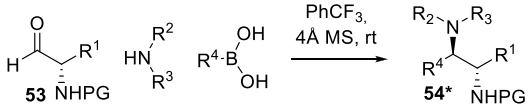
52l, R^1 = Bn, R^3 = (*E*)-styryl, yield 70%*, dr (*syn*/*anti*) 2:1
52m, R^1 = Ph, R^3 = (*E*)-styryl, yield 71%*, dr (*syn*/*anti*) 1.5:1
52n, R^1 = CbzNH$(CH_2)_2$, R^3 = (*E*)-styryl, yield 69%*, dr (*syn*/*anti*) 1:1

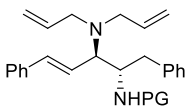


syn-**52o**

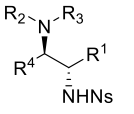
52o, R^1 = Bn, R^3 = (*E*)-styryl, yield 61%*, dr (*syn*/*anti*) 1:3
* *syn*- and *anti*- product combined yield

Scheme 21





54a, PG = nitrobenzenesulfonyl, yield 71%, ee 94%
54b, PG = 4-methoxy-2,3,6-trimethylphenylsulfonyl, yield 28%, ee 20%
54c, PG = 2-(trimethylsilyl)ethanesulfonyl, yield 39%, ee 71%
54d, PG = acetyl, yield 23%, ee 3%
54e, PG = *tert*-butyloxycarbonyl, yield 21%, ee 15%



54f, R^1 = Bn, R^2 = allyl, R^3 = benzyl, R^4 = (*E*)-styryl, yield 64%, ee 98%
54g, R^1 = Bn, R^2 = benzyl, R^3 = benzyl, R^4 = (*E*)-styryl, yield 72%, ee 96%
54h, R^1 = Bn, R^2 = methyl, R^3 = benzyl, R^4 = (*E*)-styryl, yield 48%, ee 71%
54i, R^1 = Bn, R^2 = allyl, R^3 = allyl, R^4 = (*E*)-2-cyclohexylvinyl, yield 48%, ee 82%
54j, R^1 = Bn, R^2 = allyl, R^3 = allyl, R^4 = vinyl, yield 51%, ee 86%
54k, R^1 = Bn, R^2 = benzyl, R^3 = benzyl, R^4 = furan-2-yl, yield 63%, ee 93%
54l, R^1 = Bn, R^2 = allyl, R^3 = allyl, R^4 = 4-methoxyphenyl, yield 38%, ee 82%
54m, R^1 = *iso*-propyl, R^2 = allyl, R^3 = allyl, R^4 = (*E*)-styryl, yield 53%, ee 87%
54n, R^1 = *iso*-butyl, R^2 = allyl, R^3 = allyl, R^4 = (*E*)-styryl, yield 51%, ee 83%
54o, R^1 = ((*tert*-butyldimethylsilyl)oxy)methyl, R^2 = benzyl, R^3 = benzyl, R^4 = (*E*)-styryl, yield 63%, ee 82%
* Exclusive *anti*-diastereoselectivity

2.4. Protected α-Amino Aldehydes

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 trimethylsilylethanesulfonamide,

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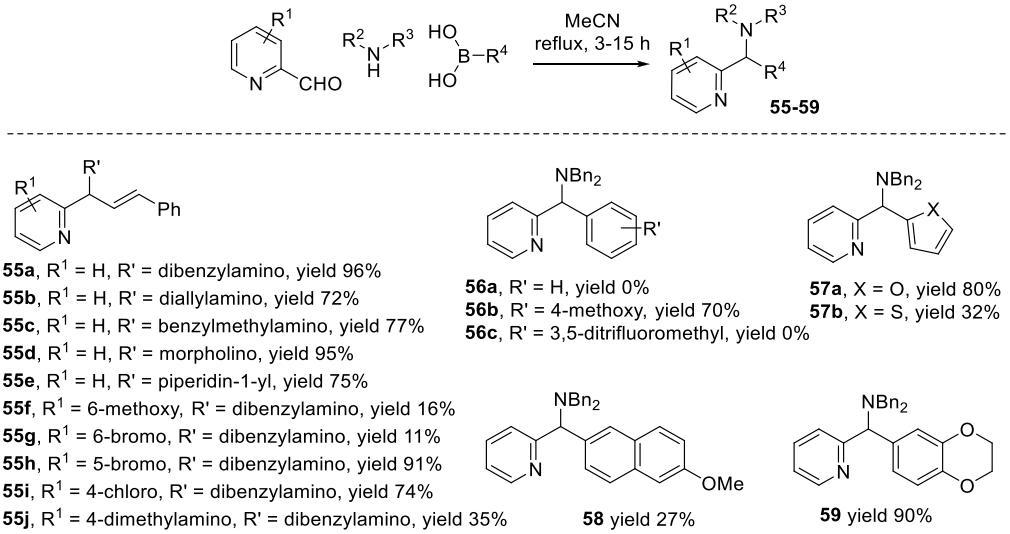
Scheme 22



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).[82] 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 sulfonylated 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.[35,82] It is noteworthy that in a recent first report of S_N2-type substitution using arylboronic acids as nucleophiles, α-aryl-α-mesylate 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.[112]

2.5. Pyridinecarboxaldehyde and Derivative as the Carbonyl Component

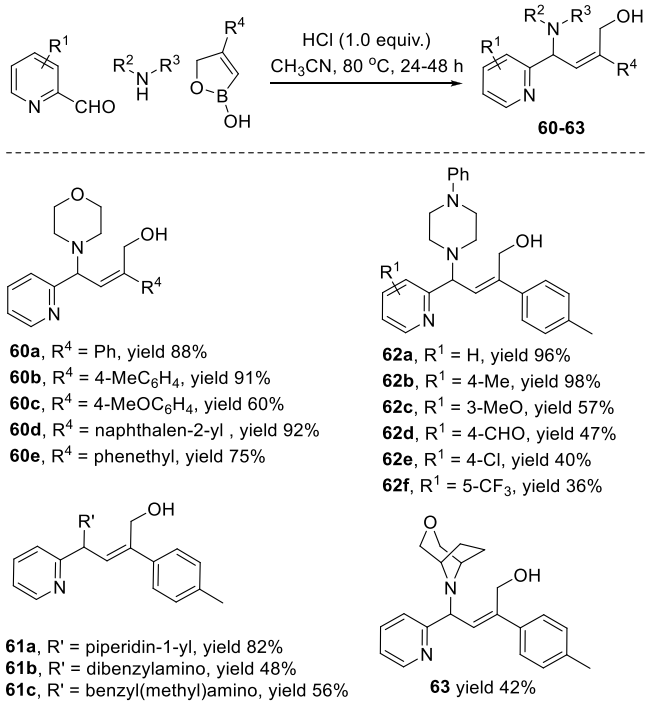
An adjacent hydroxyl moiety is not the only functional group capable of coordinating boronates of the carbonyl component; PRs may also be successfully carried out with 2-pyridinecarboxaldehyde and 2-sulfamidobenzaldehyde, where embedded nitrogen atoms of carbonyl components act as potential directing moieties.[113] 2-Pyridinecarboxaldehyde 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 **55**–**59** 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.[114,115]

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(5*H*)-ols, and secondary amines, including both cyclic and acyclic counterparts. 2-Pyridinecarboxaldehydes with electron-withdrawing or sterically hindering substituents led to products in low to medium yield, whereas unsubstituted and 4-methyl-2-pyridinecarboxaldehydes gave medium to excellent product yield (Scheme 23).[116]

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

Scheme 23



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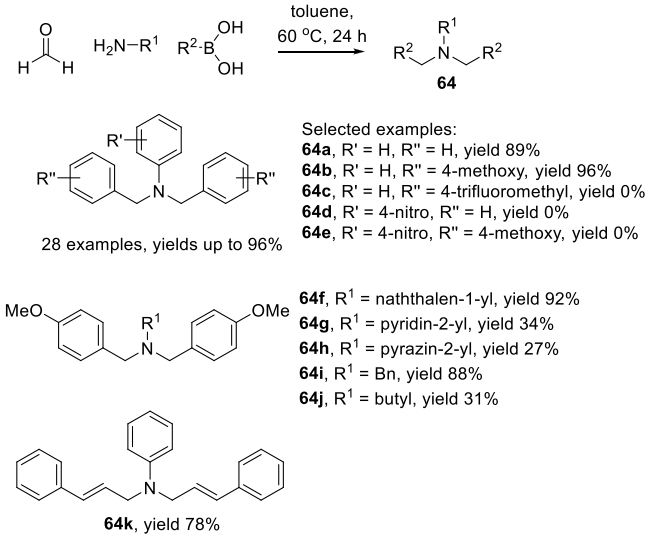
89% yield when heating to 60 °C in toluene for 24 h. The reaction scope was tested by using both electron-rich and electron-deficient anilines and boronic acids. Reactions that failed to complete typically involved amines or boronic acids with strong electron-withdrawing groups, such as 4-trifluoromethylphenylboronic 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).[117] The reaction process involves sequential PRs with two identical carbonyl and two identical boronic acid components.

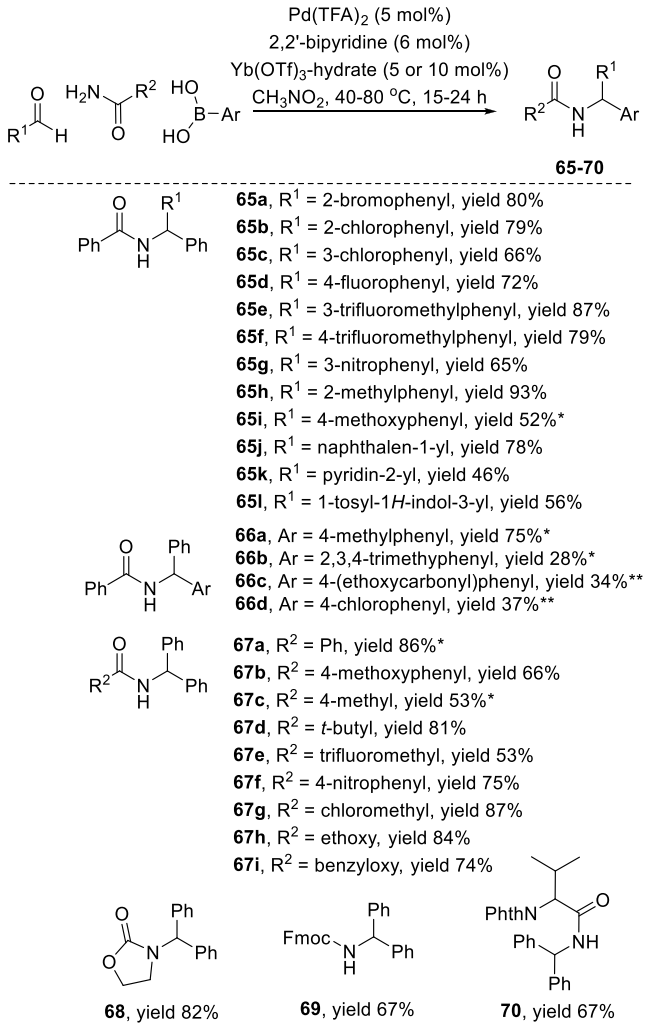
Scheme 24



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).[118]

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.[119−122] 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**.[123] 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-

Scheme 25



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 R^1 substituent of **73** and **74** (Scheme 26).[123]

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.[124] 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 afford an oxazolidinone and a tricyclic dihydroquinoline. Additionally, this hydroxy thiourea-catalyzed PR was applied to the stereoselective synthesis of dipeptides and tripeptides.[125]

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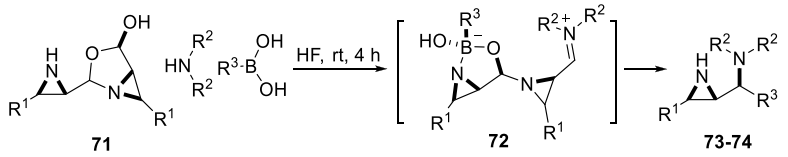
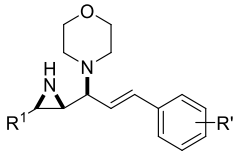
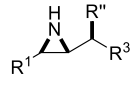
Scheme 26



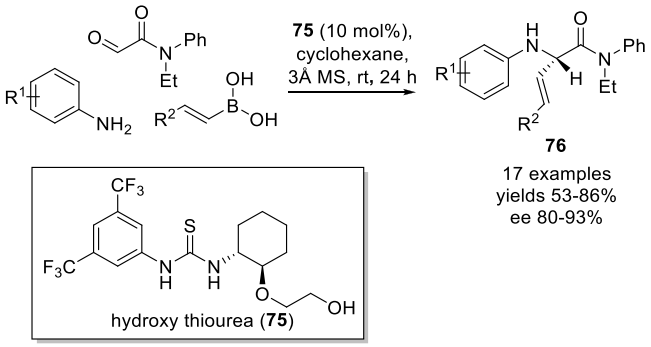


73a, R^1 = phenethyl, R' = H, yield 43%, syn: anti >19:1
73b, R^1 = *iso*-butyl, R' = H, yield 72%, syn: anti >19:1
73c, R^1 = H, R' = H, yield 39%, syn: anti > 19:1
73d, R^1 = *iso*-butyl, R' = 4-methoxy, yield 29%, syn: anti > 19:1
73e, R^1 = *iso*-butyl, R' = 4-fluoro, yield 57%, syn: anti > 19:1
73f, R^1 = *iso*-butyl, R' = 4-methyl, yield 58%, syn: anti > 19:1



74a, R^1 = *iso*-butyl, R^3 = (*E*)-styryl, R'' = pyrrolidin-1-yl, yield 53%, syn: anti >19:1
74b, R^1 = phenethyl, R^3 = (*E*)-styryl, R'' = dibenzylamino, yield 24%, syn: anti >19:1
74c, R^1 = *iso*-butyl, R^3 = (*E*)-styryl, R'' = diallylamino, yield 28%, syn: anti >19:1
74d, R^1 = *iso*-butyl, R^3 = benzofuran-2-yl, R'' = morpholino, yield 71%, syn: anti >19:1
74e, R^1 = *iso*-butyl, R^3 = phenylethynyl, R'' = morpholino, yield 36%, syn: anti 63:37*
74f, R^1 = *iso*-butyl, R^3 = ethynyl, R'' = morpholino, yield 38%, syn: anti 91:9*
* alkynyl pinacol boronic ester was used as the boronic component.

Scheme 27

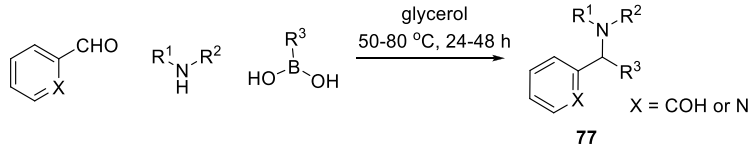


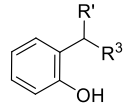
2.7. Multiple Carbonyl Components

Candeias and coworkers reported the use of glycerol as an effective solvent for the synthesis of both salicylaldehyde-derived and 2-pyridinecarboxaldehyde-derived products **77**. 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 **77a–i** and pyridines **77j** and **77k** obtained through this glycerol-mediated PR, a catalytic amount of dibenzylamine was used for the condensation between salicylaldehydes and (*E*)-styrylboronic acid to give 2*H*-chromenes in glycerol.[126]

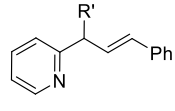
Pyne and coworkers reported the first examples of allenyl pinacolboronate as the boronic component for the selective formation of either allenylamine or alkynylamine products depending on the choice of aldehyde and amine components. The reaction of salicylaldehyde, allenyl pinacolboronate, and various amines led to α-allenyl products **78** from secondary amine components and propargyl product **79** from primary amine components. The reaction using glycoaldehyde and

Scheme 28





77a, R' = indolin-1-yl, R^3 = 4-methoxyphenyl, yield 90%
77b, R' = indolin-1-yl, R^3 = 4-vinylphenyl, yield 97%
77c, R' = indolin-1-yl, R^3 = phenyl, yield 94%
77d, R' = indolin-1-yl, R^3 = 2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl, yield 95%
77e, R' = dibenzylamino, R^3 = 4-methoxyphenyl, yield 75%
77f, R' = dibenzylamino, R^3 = 4-vinylphenyl, yield 76%
77g, R' = dibenzylamino, R^3 = (*E*)-styryl, yield 70%
77h, R' = benzylmethylamino, R^3 = 4-vinylphenyl, yield 70%
77i, R' = benzylmethylamino, R^3 = phenyl, yield 76%



77j, R' = morpholino, yield 82%
77k, R' = dibenzylamino, yield 86%

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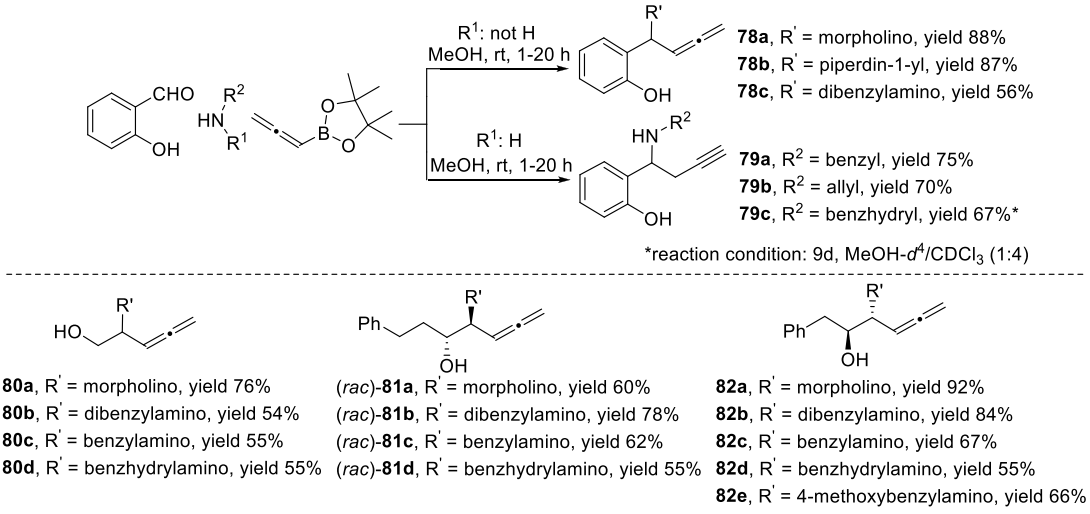
Scheme 29



chiral α-hydroxy aldehyde afforded exclusively *anti*-β-amin-β-allenyl alcohols **80**−**82**, regardless of the primary or secondary amines involved (Scheme 29). The selective formation of alkynyl 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 different combinations 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 alkynyl products **85** and **86**. Secondary amines, α-hydroxy aldehydes, and carbohydrate afforded allenyl *anti*-β-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 alkynyl Petasis products serve as versatile substrates for further diversification transformations.[41]

A copper-catalyzed PR was developed for the synthesis of tertiary amines and amino esters using 2-pyridinecarboxaldehyde 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.[37]

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-L-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-hydrazido alcohol, 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

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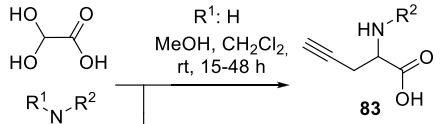
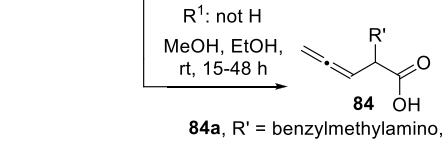
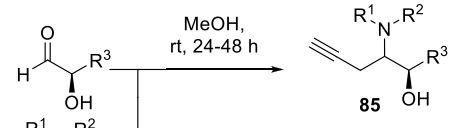
Scheme 30



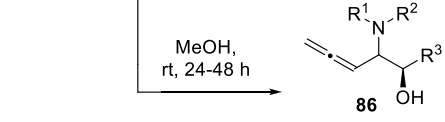
83a, R^2 = H, yield 72%, (**83**: **84** >99:1)
83b, R^2 = Bn, yield 81%, (**83**: **84** >99:1)
83c, R^2 = benzhydryl, yield 66%, (**83**: **84** >68:32)
83d, R^2 = allyl, yield 64%, (**83**: **84** >99:1)
83e, R^2 = (*R*)-2-hydroxy-1-phenylethyl, yield 34%, (**83**: **84** >99:1) de 27%



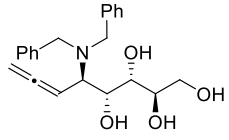
84a, R' = benzylmethylamino, yield 65%, (**84**: **83** >99:1)
84b, R' = diallylamino, yield 66%, (**84**: **83** >99:1)
84c, R' = morpholino, yield 70%, (**84**: **83** >99:1)
84d, R' = (*S*)-2-carboxypyrrolidin-1-yl, yield 32%, (**84**: **83** >99:1) de 44%



85a, R^1 =H, R^2 = 4-methoxyphenyl, R^3 = H, yield 78%, (**85**: **86** 1:1)
85b, R^1 = H, R^2 = (*R*)-2-hydroxy-1-phenylethyl, R^3 = H, yield 61%, (**85**: **86** >99:1) de 63%
85c, R^1 = H, R^2 = (*S*)-(1-carboxy-2-phenylethyl), R^3 = H, yield 68%, (**85**: **86** > 99:1) de 67%
(3*S*)-**85d**, R^1 = H, R^2 = Bn, R^3 = hydroxymethyl, yield 30%, (**85**: **86** > 99:1) de 23%

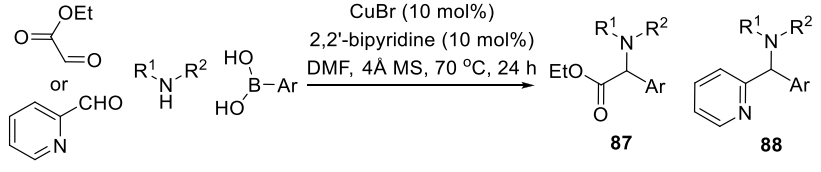


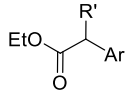
86a, R^1 = H, R^2 = Bn, R^3 = H, yield 46%, (**86**: **85** >99:1)
86b, R^1 = R^2 = Bn, R^3 = H, yield 90%, (**86**: **85** >99:1)
(3*S*)-**86c**, R^1 = R^2 = allyl, R^3 = hydroxymethyl, yield 70%, (**86**: **85** >99:1) de >99%
(3*S*)-**86d**, R^1 = R^2 = Bn, R^3 = hydroxymethyl, yield 65%, (**86**: **85** >99:1) de >99%



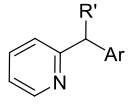
86e, yield 21% (**86**:**85** >99:1) de > 99%

Scheme 31





87a, R' = pyrrolidin-1-yl, Ar = phenyl, yield 90%
87b, R' = pyrrolidin-1-yl, Ar = furan-2-yl, yield 79%
87c, R' = piperidin-1-yl, Ar = phenyl, yield 51%
87d, R' = piperidin-1-yl, Ar = 4-fluorophenyl, yield 57%



88a, R' = dimethylamino, Ar = phenyl, yield 43%
88b, R' = dicyclohexylamino, Ar = phenyl, yield 0%
88c, R' = piperidin-1-yl, Ar = phenyl, yield 76%
88d, R' = piperidin-1-yl, Ar = 4-methylphenyl, yield 74%
88e, R' = pyrrolidin-1-yl, Ar = 2-methylphenyl, yield <5%

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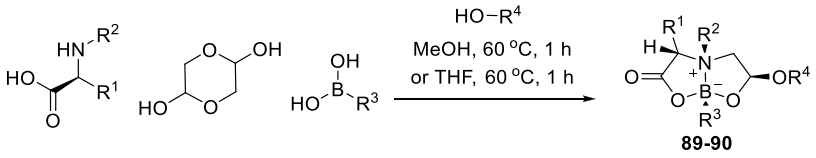
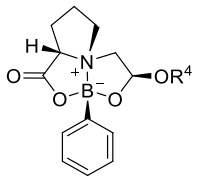
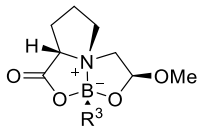
Chem. Rev. 2019, 119, 11245−11290

Scheme 32





89a, R^4 = ethyl, yield 89%, dr 93%
89b, R^4 = Bn, yield 60%, dr 89%
89c, R^4 = allyl, yield 78%, dr 97%
89d, R^4 = prop-2-yn-1-yl, yield 72%, dr 97%
89e, R^4 = thien-3-yl, yield 70%, er 92:8
89f, R^4 = *iso*-propyl, yield 85%, dr 72%
89g, R^4 = butyl, yield 60%, dr 96%
89h, R^4 = 2,2,2-trifluoroethyl, yield 73%, dr 92%
89i, R^4 = 3-phenylprop-2-yn-1-yl, yield 54%, dr 95%



90a, R^3 = 4-MeC_6H_4, yield 88%, dr >97%
90b, R^3 = 4-*n*-ButylC_6H_4, yield 75%, dr 95%
90c, R^3 = naphthalen-1-yl, yield 83%, dr 96%
90d, R^3 = thien-3-yl, yield 71%, dr 91%
90e, R^3 = 4-$MeOC_6H_4$, yield 57%, dr 97%
90f, R^3 = 4-FC_6H_4, yield 94%, dr 96%
90g, R^3 = 4-BrC_6H_4, yield 78%, dr 90%
90h, R^3 = 2-BrC_6H_4, yield 78%, dr >97%
90i, R^3 = 2,4-$Cl_2C_6H_4$, yield 70%, dr >97%
90j, R^3 = 4-$MeCOC_6H_4$, yield 65%, dr 95%
90k, R^3 = 2-Me,4-CNC_6H_4, yield 65%, dr 96%
90l, R^3 = cyclohexyl, yield 52%, dr >97%

(Scheme 33). 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 propargylamines **108**−**111**.[130,131] It is noteworthy that two components of formaldehyde are involved in this transformation to form the initial benzyl hemiaminal intermediate **107**, 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 A^3-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 $CuFe_2O_4$ 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(5*H*)-one, boronic acids, isocyanides, and a secondary amine catalyst. Although an "intramolecular boronate−iminium complex" is proposed by the condensation among 5-hydroxyfuran-2(5*H*)-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] Batey 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-hydroxyl-2-methoxy-*N*,*O*-acetal **112** was reported for the diastereoselective synthesis of 2,3-disubstituted piperidine **113**, which was further treated with 3,5-bis(trifluoromethyl)benzyl bromide to give the neurokinin-1 antagonist **114** (Scheme 35).[141]

Nielsen and coworkers reported an efficient reductive cyclization approach for the synthesis of N-substituted β,γ-dihydroxy-γ-lactams **115**, which were used as precursors to generate cyclic *N*-acyliminium ions in the presence of boron

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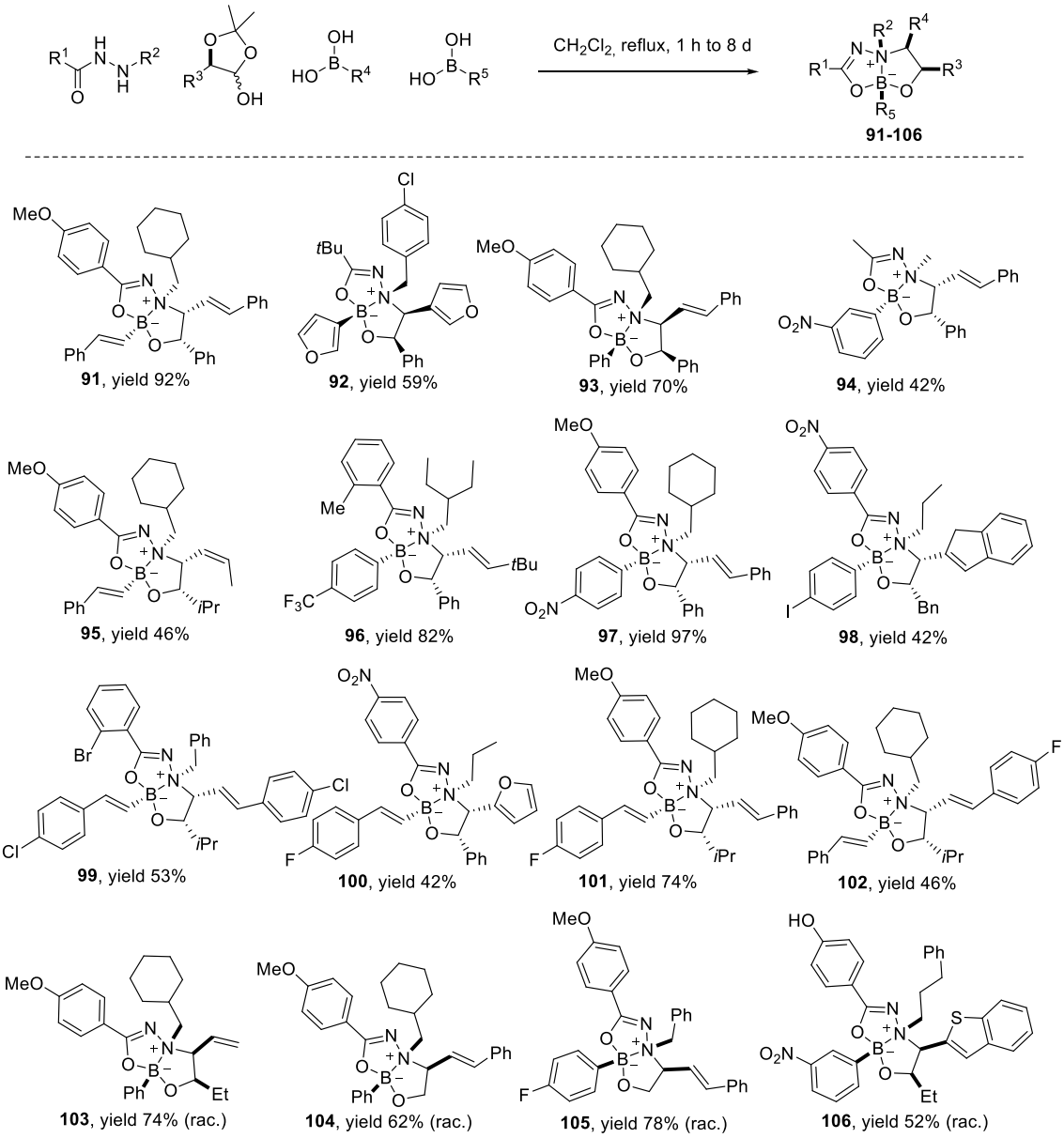
Scheme 33



trifluoride-diethyl ether.[142,143] Cyclic *N*-acyliminium ions derived from *β*,*γ*-dihydroxy-*γ*-lactams **115** reacted with electron-deficient boronic acids in this two-component PR to give substituted *γ*-lactams **116** 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 **117** with no or poor diastereoselectivity owing to a possible pathway of the direct addition of boronic acids to cyclic *N*-acyliminium ions (Scheme 36).[142]

A metal-free carbon−hydrogen-bond functionalization for the regioselective synthesis of 2-substituted quinolines **119**−**125** was performed in a Petasis-like manner by reacting quinoline *N*-oxides **118** 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 **119**−**124** 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 **125** in this reaction, but the analogous isoquinoline, pyridine, and quinazoline *N*-oxides failed to undergo similar reactions (Scheme 37).[144]

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 **126**−**131** in moderate to excellent yield (Scheme 38). The reaction was also tested for imine electrophiles containing chiral auxiliaries, but no diastereoselectivity could be observed.[145]

A series of 1-alkyl-2,3-dicyano-5-arylpyrazinium salts **132** was used as imine species for two-component Petasis-type

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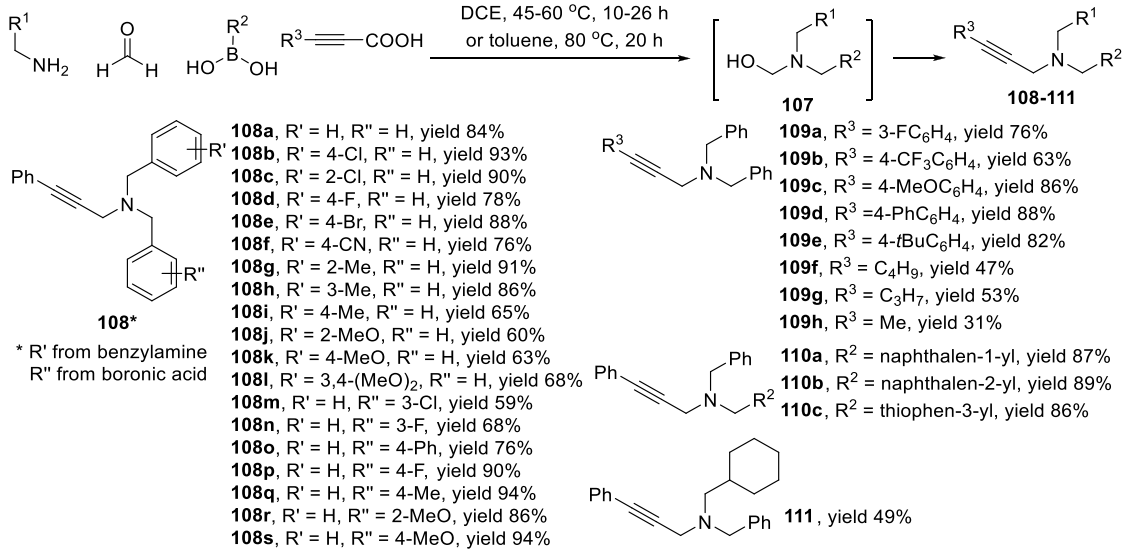
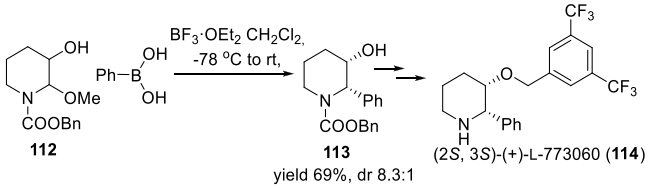
Scheme 34

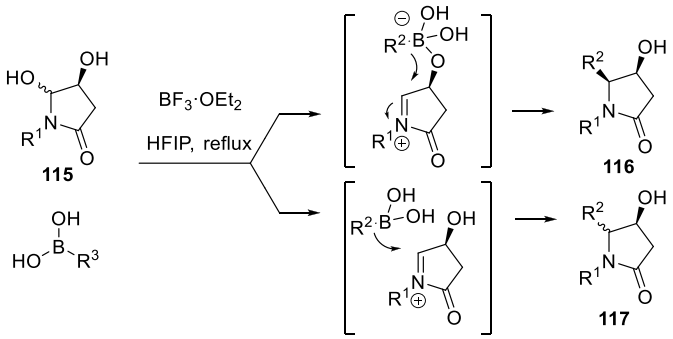


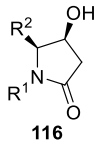
Scheme 35



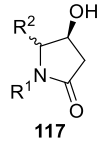
reactions with electron-rich boronic acids including thienyl, furyl, benzothienyl, and styrylboronic acids to afford 5,6-diaryl-1,6-dihydropyrazines **133** in moderate to good yield (Scheme 39). The absolute configurations were determined by X-ray crystal structures of enantiomers isolated by chiral HPLC. The synthesized dihydropyrazines were tested for their antifungal and antimycobacterial activities.[22,146]

Scheme 36





116a, R1 = Bn, R2 = prop-1-en-1-yl, yield 31%, dr > 20:1
116b, R1 = Bn, R2 = 3-chloroprop-1-en-1-yl, yield 46%, dr > 20:1
116c, R1 = Bn, R2 = vinyl, yield 50%, dr > 20:1
116d, R1 = Bn, R2 = phenyl, yield 13%, dr > 20:1
116e, R1 = Bn, R2 = 4-BrC6H4, yield 23%, dr > 20:1
116f, R1 = allyl, R2 = 3-chloroprop-1-en-1yl, yield 17%, dr > 20:1
116g, R1 = prop-2-yn-1-yl, R2 = 3-chloroprop-1-en-1yl, yield 17%, dr > 20:1
116h, R1 = prop-2-yn-1-yl, R2 = vinyl, yield 50%, dr > 20:1



117a, R1 = Bn, R2 = 3,4-(MeO)2C6H3, yield 72%, dr 1:1
117b, R1 = Bn, R2 = 2,4-(MeO)2C6H3, yield 48%, dr 1:1
117c, R1 = allyl, R2 = benzo[*b*]thiophen-3-yl, yield 39%, dr 3:2
117d, R1 = Bn, R2 = benzo[*b*]thiophen-2-yl, yield 90%, dr 3:2
117e, R1 = 2,4-(MeO)2C6H3, R2 = thiophen-2-yl, yield 11%*, dr 7:3
117f, R1 = 2,3-dihydro-1*H*-inden-2-yl, R2 = furan-2-yl, yield 72%, dr 3:2
117g, R1 = 5-methylfuran-2-yl, R2 = fuan-2-yl, yield 20%, dr 3:2
117h, R1 = phenethyl, R2 = benzofuran-2-yl, yield 56%, dr 3:2
*Isolated yield of the *cis*-isomer only

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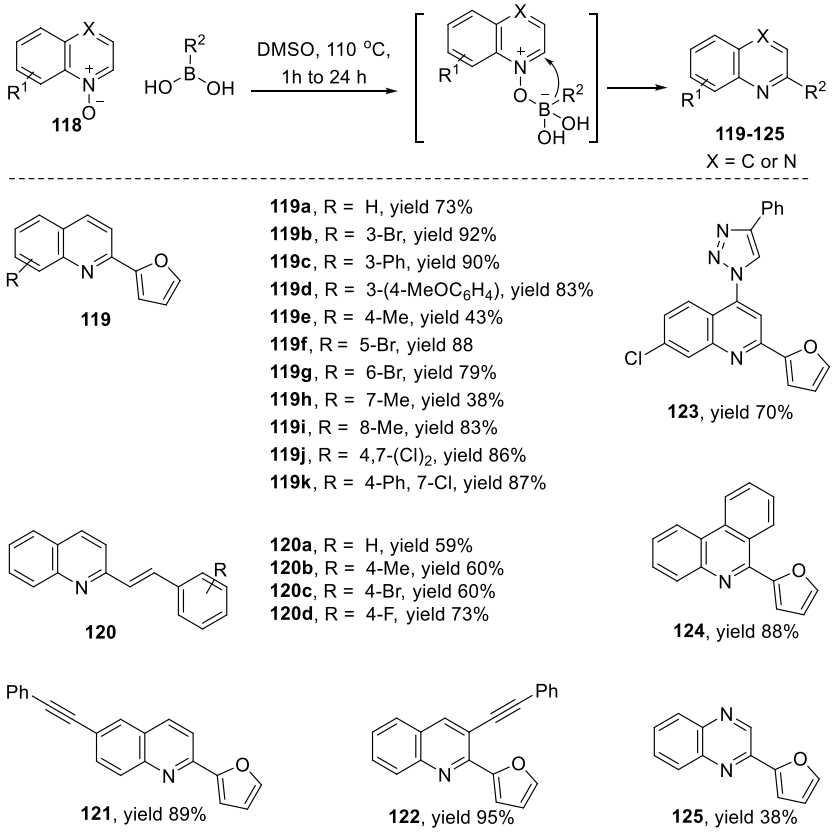
Scheme 37



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.[147] 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).[148] 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 susbtrate, 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 K_2CO_3 (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]

An imine allylation of glyoxylic acid with chiral *tert*-butanesulfinamide and allylboronic acid pinacol esters was reported for the synthesis of optically active γ,δ-unsaturated α-amino acids with excellent diastereoselectivity.[151] 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*-difluorohomoallylamines **144**−**147** in good to excellent yield with high diastereoselectivitiy. 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 allylboration was proposed to explain the observed region- and stereoselectivity.[152] Another Petasis-type allylation with dimethylamine adducts of triallyl-, triprenyl-, and cinnamyl-dipropylboranes was recently reported for the homoallylation of primary amine substrates with formaldehyde.[153]

In a recent study from the Schaus group, chiral 3,3′-Ph_2-BINOL **148** was used to activate allylboronates and

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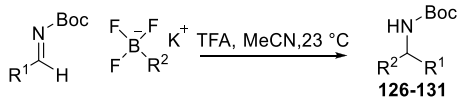
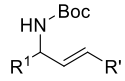
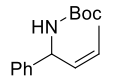
Scheme 38



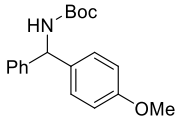
126-131



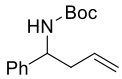
126a, R^1 = Ph, R' = Ph, yield 89%
126b, R^1 = Ph, R' = Me, yield 63%
126c, R^1 = 4-methoxyphenyl, R' = Ph, yield 78%
126d, R^1 = 4-trifluoromethylphenyl, R' = Ph, yield 83%
126e, R^1 = 3-methylphenyl, R' = Ph, yield 95%
126f, R^1 = thien-2-yl, R' = Ph, yield 99%
126h, R^1 = fur-2-yl, R' = Ph, yield 65%
126i, R^1 = pentyl, R' = Ph, yield 94%
126j, R^1 = phenethyl, R' = Ph, yield 89%
126k, R^1 = (*Z*)-hept-5-en-1-yl, R' = Ph, yield 98%
126l, R^1 = *iso*-butyl, R' = Ph, yield 90%



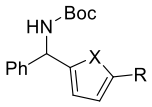
127 yield 68%



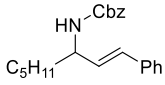
130, yield 79%



128 yield 85%



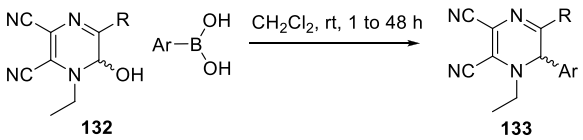
131a, X = O, R = H, yield 82%
131b, X = Boc-N, R = H, yield 73%
131c, X = S, R = Me, yield 79%



129, yield 89%*

* Synthesized from the corresponding Cbz-protected imine.

Scheme 39



132 **133**

133a, R = Ph, Ar = thien-2-yl, yield 76%
133b, R = Ph, Ar = thien-3-yl, yield 57%
133c, R = thien-2-yl, Ar = thien-2-yl, yield 68%
133d, R = thien-2-yl, Ar = thien-3-yl, yield 64%
133e, R = thien-3-yl, Ar = thien-2-yl, yield 65%
133f, R = thien-3-yl, Ar = thien-3-yl, yield 79%
133g, R = Ph, Ar = benzo[*b*]thien-2-yl, yield 55%
133h, R = thien-2-yl, Ar = benzo[*b*]thien-2-yl, yield 58%
133i, R = thien-3-yl, Ar = benzo[*b*]thien-2-yl, yield 98%
133j, R = Ph, Ar = benzo[*b*]thien-3-yl, yield 59%
133k, R = thien-2-yl, Ar = benzo[*b*]thien-3-yl, yield 76%
133l, R = thien-3-yl, Ar = benzo[*b*]thien-3-yl, yield 80%
133m, R = Ph, Ar = fur-2-yl, yield 75%
133n, R = thien-2-yl, Ar = fur-2-yl, yield 86%
133o, R = thien-3-yl, Ar = fur-2-yl, yield 71%
133p, R = Ph, Ar = (*E*)-styryl, yield 86%
133q, R = thien-2-yl, Ar = (*E*)-styry, yield 80%
133r, R = thien-3-yl, Ar = (*E*)-styry, yield 78%
133s, R = Ph, Ar = (*E*)-2-([1,1'-biphenyl]-4-yl)vinyl, yield 84%
133t, R = thien-2-yl, Ar = (*E*)-2-([1,1'-biphenyl]-4-yl)vinyl, yield 92%
133u, R = thien-3-yl, Ar = (*E*)-2-([1,1'-biphenyl]-4-yl)vinyl, yield 77%

crotylboronates for nucleophilic addition to imines derived formed by aldehyde and amine building blocks of diverse structural and electrophilic properties.[154] Chiral homoallylic amines **149**−**155** were obtained in good to excellent yield and with good to excellent enantioselectivity (Scheme 43). Both syn- and anti-diastereomers of allylic amines **156** and **157** with two vicinal stereogenic centers were accessible with (*Z*)- and (*E*)-crotylboronates, respectively (Scheme 44).[154] A catalyst-free Petasis-allylboration of 1,2-amino alcohol, aldehyde, and pinacolallylboronate was recently reported for the synthesis both racemic and chiral homoallyl amines at room temperature.[155]

A copper-catalyzed Petasis-type reaction was developed for the synthesis of functionalized α-substituted amides **159** 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 **158**, which reacted with the in situ formed organocopper complex derived from copper catalyst CuCl and $NaBPh_4$ to give amides **159** (Scheme 45). One claimed advantage of this method is the compatibility with imines that are not activated by electron-withdrawing groups on the nitrogen, although the *N*-acyliminium species is presumably involved in the formation of the stabilized pyridinium salts. This study stands out as an example of applying acyliminium salts for the Petasis-type addition with tetraarylboranes.[156]

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.[157] 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 **160**, from which the loss of sulfinic acid yielded diazine **161**. A subsequent nitrogen extrusion step gave the desired allenes **162**. 2-Nitrobenzenesulfonylhydrazide was successfully applied in this reaction, whereas 4-tosylhydrazide led only to the corresponding propargyl hydrazide intermediate.[158] A series of alkylnyl trifluoroborates were tolerated in this reaction, leading to the corresponding hydroxyallenes **162a**−**m** 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 **163**−**169**, respectively (Scheme 46). It is noteworthy how benzyloxyacetaldehyde, which lacks an α-hydroxy group, led to the allene product in 23% yield.[157] 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.[159] The most effective condition, using $BF_3{\cdot}OEt_2$ 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 $BF_3{\cdot}OEt_2$ was then successfully performed under solution-phase conditions to give substituted allenes **170**−**175** using aldehyde substrates without a hydroxyl activating group (Scheme 47).[159]

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.[160] In the first approach,

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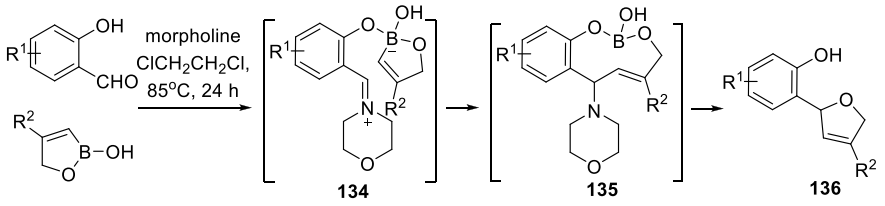
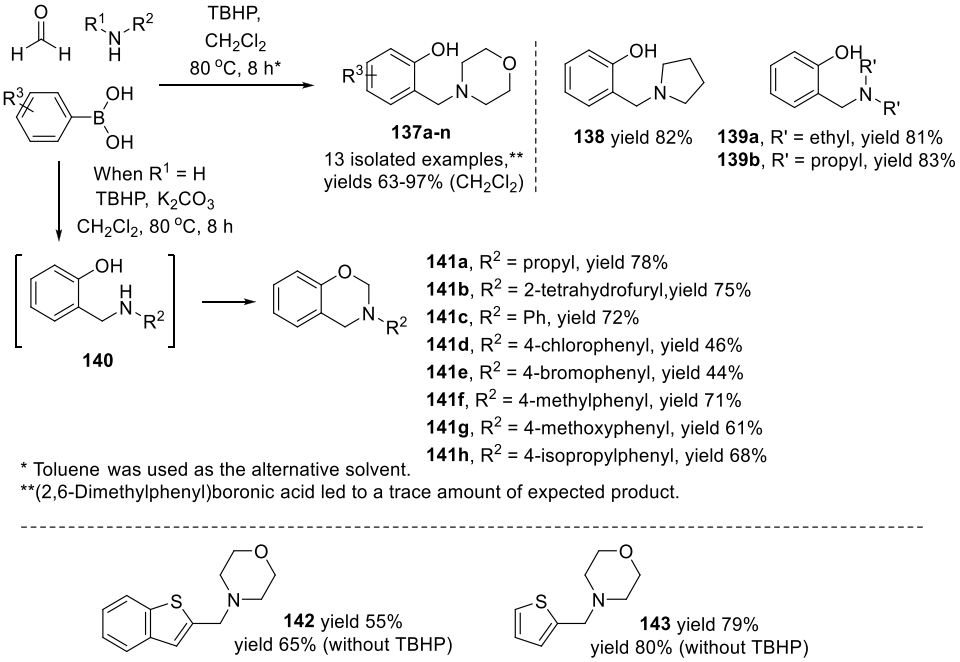
Scheme 40



136a, R^1 = H, R^2 = phenyl, yield 85%
136b, R^1 = 5-iodo, R^2 = phenyl, yield 74%
136c, R^1 = 5-*tert*-butyl, R^2 = phenyl, yield 82%
136d, R^1 = 5-nitro, R^2 = phenyl, yield 83%
136e, R^1 = 5-bromo, R^2 = phenyl, yield 89%
136f, R^1 = 3-methyl, R^2 = phenyl, yield 85%
136g, R^1 = 3-methoxy, R^2 = phenyl, yield 79%
136h, R^1 = H, R^2 = phenethyl, yield 68%
136i, R^1 = H, R^2 = 4-methylphenyl, yield 90%
136j, R^1 = H, R^2 = 3-methylphenyl, yield 92%
136k, R^1 = H, R^2 = ethyl, yield 71%
136l, R^1 = H, R^2 = butyl, yield 76%

Scheme 41



alkynyl boronates were added to glycolaldehyde-derived imines to generate allylic hydroxyl allenes. A 2D evaluation of the sulfonyl hydrazide to make the hydrazone **176** and the chiral biphenol to catalyze the traceless PRs revealed optimal reaction conditions with 2,5-dibromophenylsulfonyl hydrazide and 3,3′,6,6′-$(CF_3)_4$-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 **179**. Additionally, α-hydroxyacetone was used as the electrophile to give trisubstituted allene **180**. Chiral bicyclic alkynyl boronates were used for the diastereoselective synthesis of allenes **181** and **182** 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).[160]

In the second approach, allyl boronates were added to alkynyl hydrazones **183** to afford 1,3-alkenyl allenes **184**−**187**. A similar 2D evaluation of the sulfonyl hydrazide to make the alkynyl hydrazone **183** and the chiral biphenol to catalyze the traceless PRs revealed an optimal condition using 2-nitro-4-trifluoromethylphenylsulfonyl hydrazide and 3,3′-Ph_2-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 **184**−**186** with excellent enantioselectivity. When a protected chiral 1,2-diol-containing propionaldehyde was used, allene **187** was obtained with excellent diastereoselectivity (Scheme 49).[160]

Very recently, the Schaus group reported an asymmetric traceless PR of enals, sulfonylhydrazines, and allylboronoates for the synthesis of acyclic 1,4-dienes **189**−**193** via a reductive transposition pathway of the in situ generated allylic diazene intermediates **188**.[161] The scope of the reaction was initially evaluated by using β-methyl enals to afford the rearranged allylated products **189** and **190** containing benzylic stereocenters in high yield and with excellent enantioselectivity. As

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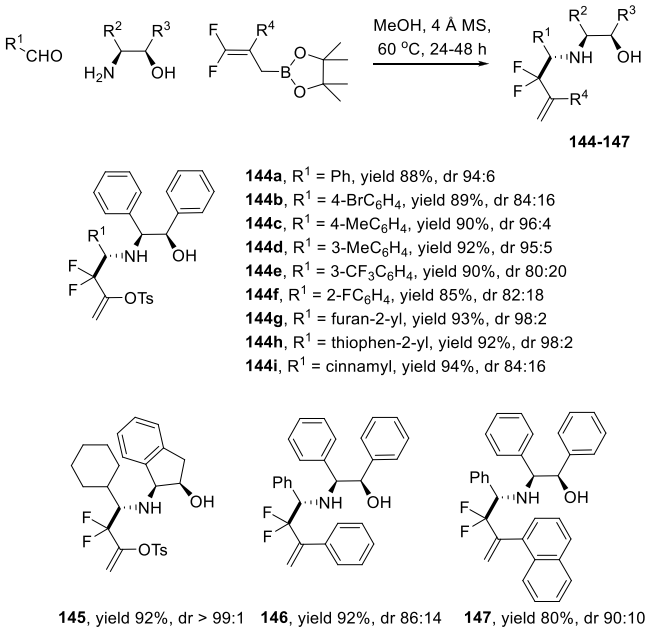
Chem. Rev. 2019, 119, 11245−11290

Scheme 42



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-dienes **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*)-crotylboronates, 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-dienes 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 sp^3-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, glycoaldehyde dimer, and furan-2-boronic acids.[162] 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/IMPDA cascade led to the desired hexahydroepoxyisoindoles **196** diastereoselectively in comparable yields.[102] A cascade using α-hydroxylated aldehydes, Bn-protected allyl amine, and 5-Boc-amine-substituted fur-2-ylboronic 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 K_2OsO_4 and NMO as the oxidants with the subsequent treatment of $NaIO_4$ yielded key dialdehyde intermediates **199**, which were reduced to give the diols **200** in the presence of $NaBH_4$. An additional Mitsunobu reaction mediated by di-*tert*-butyl azodicarboxylate (DBAD) and PPh_3 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 glyoxylic 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 tricyclic pyrrolidinones **205** and **206** with a diversified handle at the 2-position of the octahydro-6*H*-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/IMPDA 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 hydroxyfuroindole **208**, which featured five stereogenic centers and multiple appended substituents suitable for further structural diversification.[162] 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).[163]

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.[163−165]

A PR–acryloylation/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

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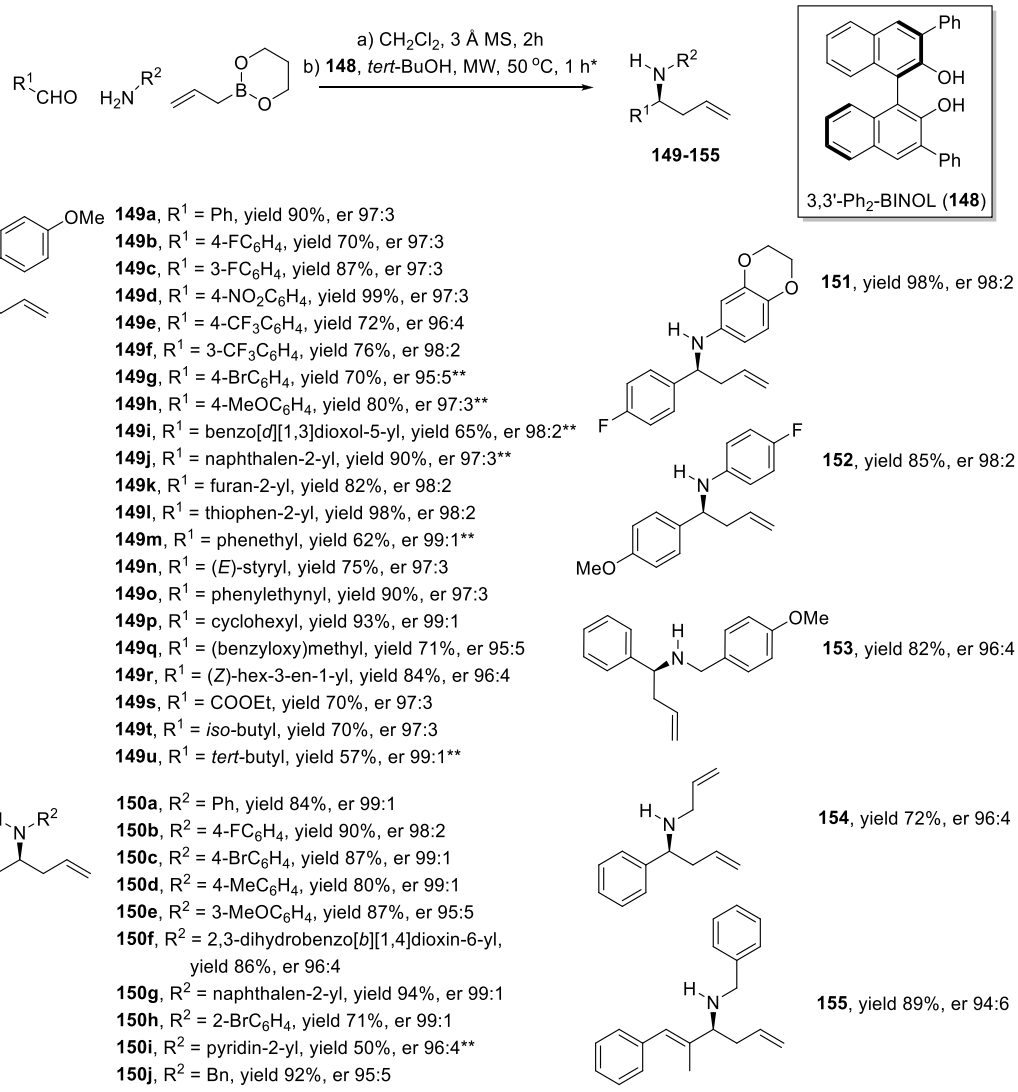
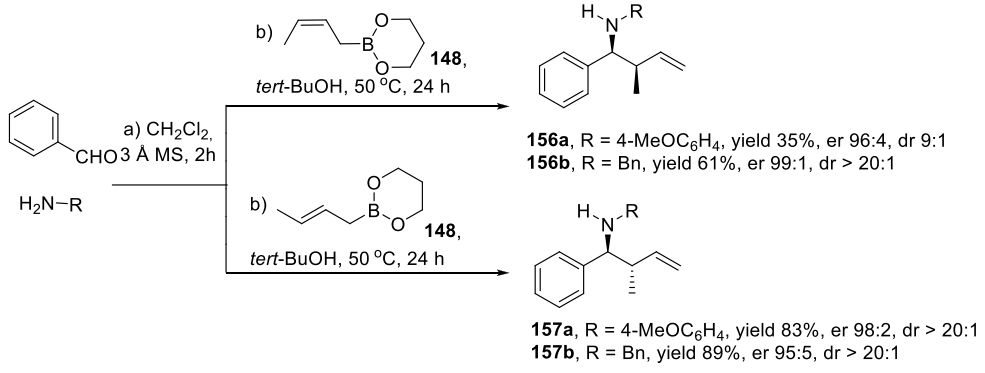
Chem. Rev. 2019, 119, 11245–11290

Scheme 43



* Allyldioxaborolane and 2-8 mol% of 3,3'-Ph_2-BINOL was addition in step (b); **Conventional heating at 50 °C for 24 h

Scheme 44



219 via the formation of the allyl dioxadiazaborocine **218** (Scheme 56).[128]

Beau and coworkers reported a PR/IMDA cascade in combination with an RCM/Michael addition cascade to access hexahydroisoindoles **223** with up to five newly formed stereogenic centers.[33,34] The PR/IMDA cascade was initially tested in the reaction of (*E*)-(3-methylbutal-1,3-dien-1-yl)-boronic acid, diallylamine, and (*S*)-2-hydroxyheptanal, which was obtained by regioselective oxidation of the corresponding (*S*)-1,2-diol to give hexahydroisoindole **221a** as a single isomer with complete stereocontrol at all three newly formed stereogenic centers. The stereochemical configuration of **221a** was indirectly confirmed by the X-ray crystal structure of a *p*-nitrobenzoylated analog. The aldehyde scope of the PR/

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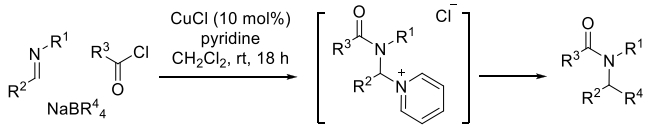
Chem. Rev. 2019, 119, 11245−11290

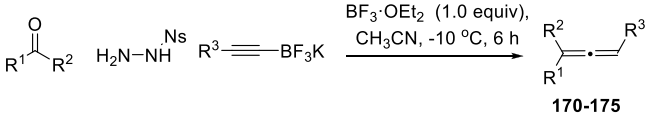
Scheme 45

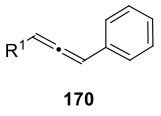


159a, R^1 = ethyl, R^2 = thien-2-yl, R^3 = phenyl, R^4 = *p*-tolyl, yield 74%
159b, R^1 = Bn, R^2 = *p*-tolyl, R^3 = Ph, R^4 = 4-fluorophenyl, yield 90%
159c, R^1 = Bn, R^2 = *p*-tolyl, R^3 = thien-2-yl, R^4 = thien-2-yl, yield 80%
159d, R^1 = methyl, R^2 = naphthalen-2-yl, R^3 = Ph, R^4 = *p*-tolyl, yield 71%
159e, R^1 = Bn, R^2 = *p*-tolyl, R^3 = phenyl, R^4 = Bn, yield 71%
159f, R^1 = Bn, R^2 = *p*-tolyl, R^3 = *p*-tolyl, R^4 = ethyl, yield 74%
159g, R^1 = Bn, R^2 = 4-fluorophenyl, R^3 = furan-2-yl, R^4 = Ph, yield 70%
159h, R^1 = Bn, R^2 = *p*-tolyl, R^3 = *iso*-propyl, R^4 = Ph, yield 57%
159i, R^1 = 4-methoxyphenyl, R^2 = *p*-tolyl, R^3 = 4-nitrophenyl, R^4 = Ph, yield 83%
159j, R^1 = allyl, R^2 = (*E*)-styryl, R^3 = *p*-tolyl, R^4 = Ph, yield 62%

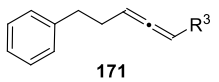
IMDA cascade was later expanded to include different optically pure α-hydroxyaldehydes and carbohydrates under the optimal condition of microwave irradiation at 120 °C for 30 min. The allyl appendage of the PR/IMPDA product **221** then underwent a ruthenium-catalyzed cross metathesis with methyl vinyl ketone to form enone intermediate **222**, which yielded the tricyclic or tetracyclic octahydrooxazinoisoindole **223** as an enantiopure isomer (Scheme 57).[33] A follow-up study from the same group expanded the scope for the three substrates in this PR/IMPDA−metathesis/Michael addiction sequence.[34] 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.[33,34]

Scheme 47

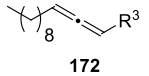



170

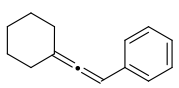
170a, R^1 = phenethyl,yield 69%
170b, R^1 = nonyl, yield 91%
170c, R^1 = *iso*-butyl, yield 80%
170d, R^1 = *iso*-propyl, yield 78%
170e, R^1 = cyclopentyl, yield 80%
170f, R^1 = cyclohexyl, yield 91%
170g, R^1 = benzyloxy, yield 70%
170h, R^1 = pent-4-yn-1-yl, yield 50%
170i, R^1 = cyclohex-3-en-1-yl, yield 66%, dr 1:1
170j, R^1 = 1-phenylethyl,yield 53%, dr 2:1

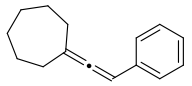

171

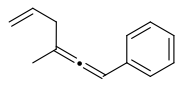
171a, R^3 = octyl,yield 70%
171b, R^3 = butyl, yield 69%
171c, R^3 = *tert*-butyl, yield 84%
171d, R^3 = cyclohex-1-en-yl, yield 80%
171e, R^3 = cyclopropyl, yield 87%
171f, R^3 = cyclopentyl, yield 63%
171g, R^3 = cyclohexyl, yield 65%
171h, R^3 = 3-FC_6H_4, yield 59%
171i, R^3 = 2-MeC_6H_4, yield 72%


172

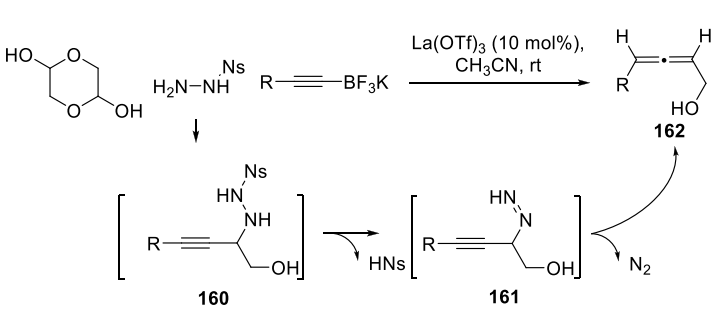
172a, R^3 = 4-$MeOC_6H_4$,yield 53%
172b, R^3 = 3,4,5-$(MeO)_3C_6H_4$, yield 63%


173
yield 66%

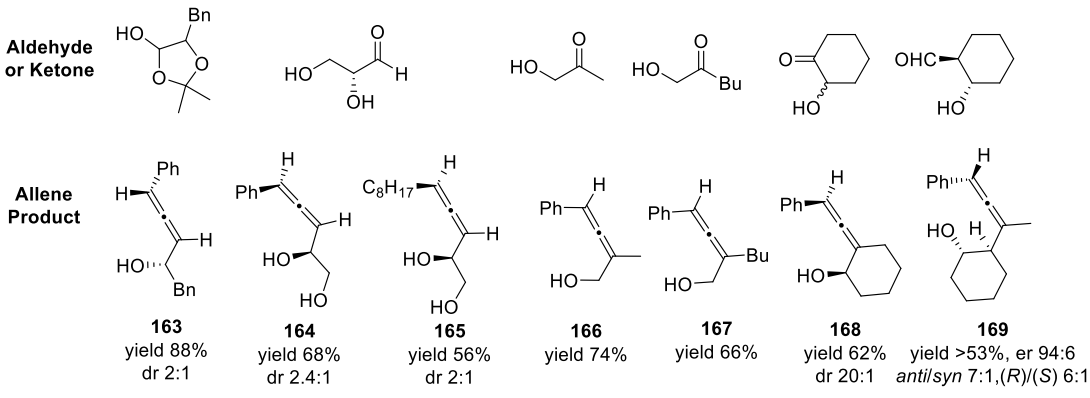

174
yield 45%


175
yield 89%

Scheme 46

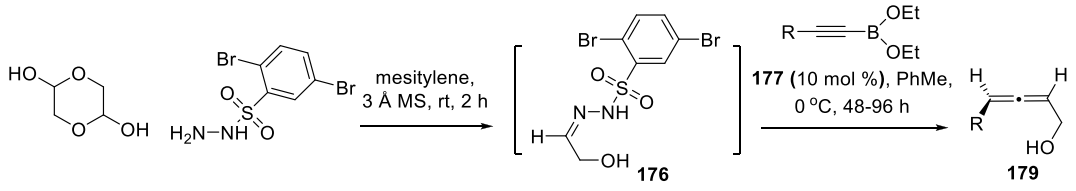


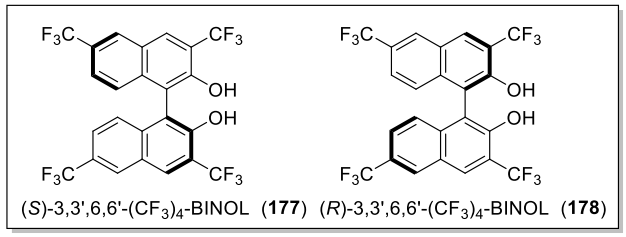
162a, R = Ph, yield 86%
162b, R = 4-MeC_6H_4, yield 75%
162c, R = 4-$MeOC_6H_4$, yield 76%
162d, R = 4-FC_6H_4, yield 83%
162e, R = 3-$MeOC_6H_4$, yield 83%
162f, R = 2-MeC_6H_4, yield 81%
162g, R = 2-naphthalen-2-yl, yield 84%
162h, R = cyclohexyl, yield 64%
162i, R = phenethyl, yield 90%
162j, R = (benzyloxy)methyl, yield 61%
162k, R = (benzyloxy)ethyl, yield 66%
162l, R = $TBDPSOC_3H_6$, yield 86%
162m, R = octyl, yield 82%



DOI: 10.1021/acs.chemrev.9b00214
Chem. Rev. 2019, 119, 11245−11290

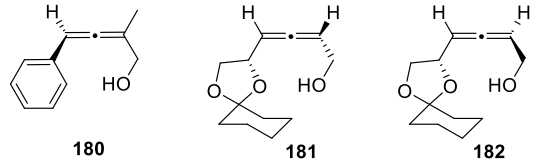
Scheme 48





179a, R = Ph, yield 85%, er 93:7
179b, R = 4-MeOC$_6$H$_4$, yield 80%, er 91:9*
179c, R = 4-FC$_6$H$_4$, yield 78%, er 93:7
179d, R = 2-CF$_3$C$_6$H$_4$, yield 71%, er 93:7
179e, R = thien-3-yl, yield 70%, er 92:8
179f, R = naphthalen-2-yl, yield 85%, er 90:10
179g, R = phenethyl, yield 72%, er 92:8
179h, R = (*E*)-4-styryl, yield 71%, er 90:10
179i, R = cyclohexyl, yield 63%, er 90:10
179j, R = hexyl, yield 73%, er 90:10
179k, R = (benzyloxy)methyl, yield 60%, er 90:10
179l, R = (5,5-dimethyl-1,3-dioxan-2-yl)methyl, yield 70%, er 85:15
179m, R = TBDMS, yield 62%, er 95:5

*20 mol% of **177**, at -10 °C
10 mol% of **178

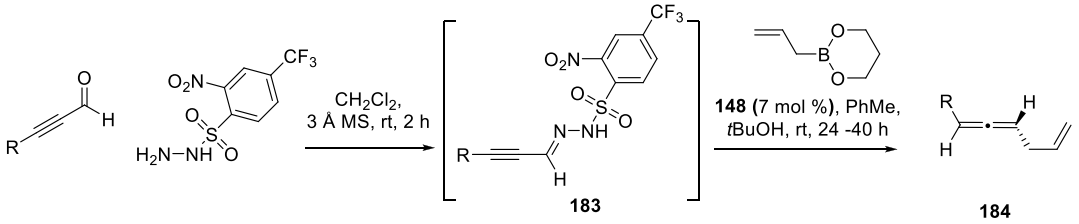


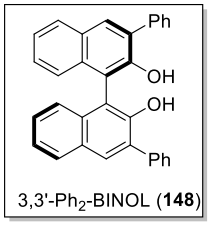
180
yield 91%, er 90:10

181
yield 71%, dr 93:7

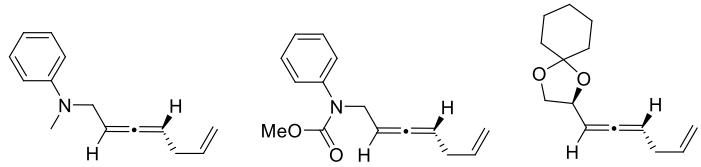
182
yield 68%, dr 91:9**

Scheme 49





184a, R = Ph, yield 83%, er 99:1
184b, R = 4-MeOC$_6$H$_4$, yield 88%, er 98:2
184c, R = 4-FC$_6$H$_4$, yield 87%, er 99:1
184d, R = 4-NO$_2$C$_6$H$_4$, yield 87%, er 98:2
184e, R = 2-BrC$_6$H$_4$, yield 60%, er 99:1
184f, R = naphthalen-2-yl, yield 89%, er 98:2
184g, R = thien-3-yl, yield 87%, er 99:1
184h, R = pyridin-3-yl, yield 27%, er 98:2
184i, R = DMPS, yield 73%, er 98:2
184j, R = (benzyloxy)methyl, yield 90%, er 98:2
184k, R = dodecyl, yield 98%, er 98:2
184l, R = cyclohexyl,yield 62%, er 99:1



185
yield 50%, er 99:1

186
yield 85%, er 99:1

187
yield 79%, dr 99:1

5.2. Petasis Reaction–Ring-Closing Metathesis Sequences

Schreiber and coworkers reported early examples of applying the PR for the synthesis of skeletally and stereochemically diverse small molecules.[103] More recently, Nielsen and coworkers reported the synthesis of diverse scaffolds using a PR–RCM sequence.[104] The functionalized α-hydroxy-hydrazides **224**–**228** with pairwise reactive diene substituents, obtained from the three-component hydrazido–PR,[101,102] were subjected to RCM using Grubbs II catalyst. Different scaffolds **229**–**233** ranging from five-membered to seven-membered ring systems were obtained in moderate to good yield ranging from 58 to 80% (Scheme 58).

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.[128] The allyl substrate **234**, which was obtained through a three-component hydrazido–PR,[101] 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 59).

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*-butyldiphenylsilyl-protected α-hydroxyl aldehydes, substituted allylamines, and

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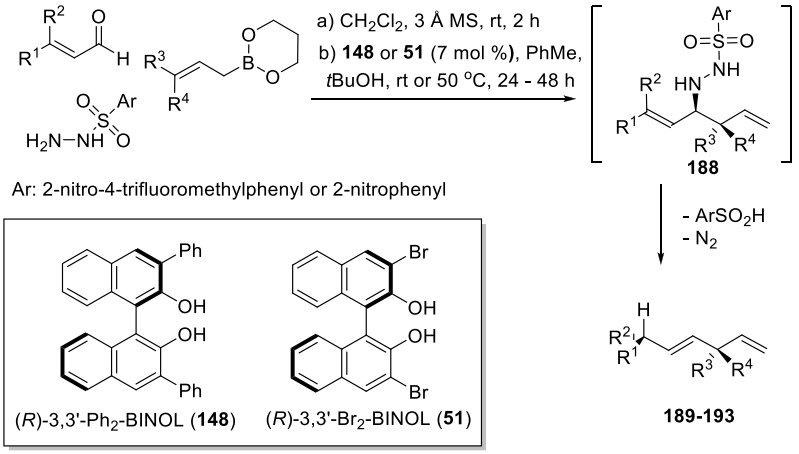
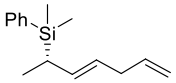
Chem. Rev. 2019, 119, 11245–11290

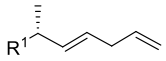
Scheme 50



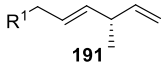
Catalyst **148**:



189 yield 88%, er 97:3



190

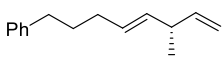


191

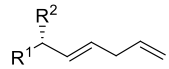
190a, R^1 = Ph, yield 83%, er 98:2
190b, R^1 = 4-FC_6H_4, yield 75%, er 97:3
190c, R^1 = 3-$MeOC_6H_4$, yield 89%, er 97:3
190d, R^1 = 2-BrC_6H_4, yield 60%, er 96:4
190e, R^1 = naphthalen-1-yl, yield 85%, er 95:5
190f, R^1 = thien-2-yl, yield 73%, er 99:1
190g, R^1 = 4-methylpent-3-en-1-yl, yield 80%, er 85:15

191a, R^1 = Ph, yield 83%, er 97:3
191b, R^1 = 4-FC_6H_4, yield 65%, er 97:3
191c, R^1 = 4-$MeOC_6H_4$, yield 81%, er 98:2
191d, R^1 = 2-$NO_2C_6H_4$, yield 79%, er 98:2
191e, R^1 = 2-$MeOC_6H$, yield 81%, er 99:1
191f, R^1 = thien-2-yl, yield 73%, er 99:1
191g, R^1 = (*E*)-styryl, yield 54%, er 98:2*

Catalyst **51**:



192 yield 53%, er 99:1*



193

193a, R^1 = $C_{11}H_{23}$, R^2 = Ph, yield 97%, er 96:4
193b, R^1 = *iso*-propyl, R^2 = Ph, yield 82%, er 98:2
193c, R^1 = CF_3, R^2 = Ph, yield 85%, er 97:3
193d, R^1 = 4-$MeOC_6H_4$, R^2 = Ph, yield 86%, er 98:2
193e, R^1 = 4-BrC_6H_4, R^2 = Ph, yield 87%, er 98:2
193f, R^1 = 3,5-$(CF_3)_2C_6H_4$, R^2 = Ph, yield 87%, er 98:2
193g, R^1 = 2-$MeOC_6H_4$, R^2 = Ph, yield 99%, er 98:2
193h, R^1 = naphthalen-2-yl, R^2 = Ph, yield 87%, er 95:5
193i, R^1 = Ph, R^2 = ethyl, yield 75%, er 96:4
193j, R^1 = Ph, R^2 = fluoromethyl, yield 77%, er 93:7
193k, R^1 = 4-$MeOC_6H_4$, R^2 = 4-FC_6H_4, yield 85%, er 98:2

*14% of catalyst was used.

(*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).[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 diastereoisomer could be isolated after esterification and then allylated, albeit with partial epimerization occurring to give inseparatable 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 $Ti(OEt)_4$ as the Lewis acid to suppress "poisoning effect" toward the Grubbs catalyst by the nucleophilic nitrogen of **244** gave the chromatographically separatable cyclic amino esters **245** (Scheme 61).[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-ylmethanol was reported for the synthesis of bicyclic pyrrolo[2,1-*c*][1,4]oxazin-3-ols **246** with good yields

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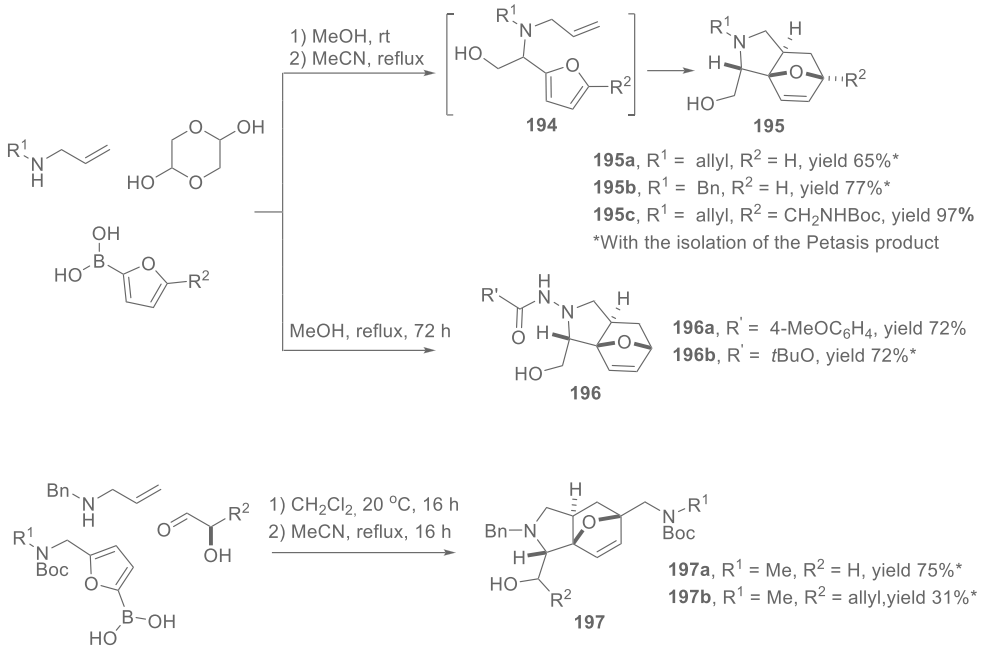
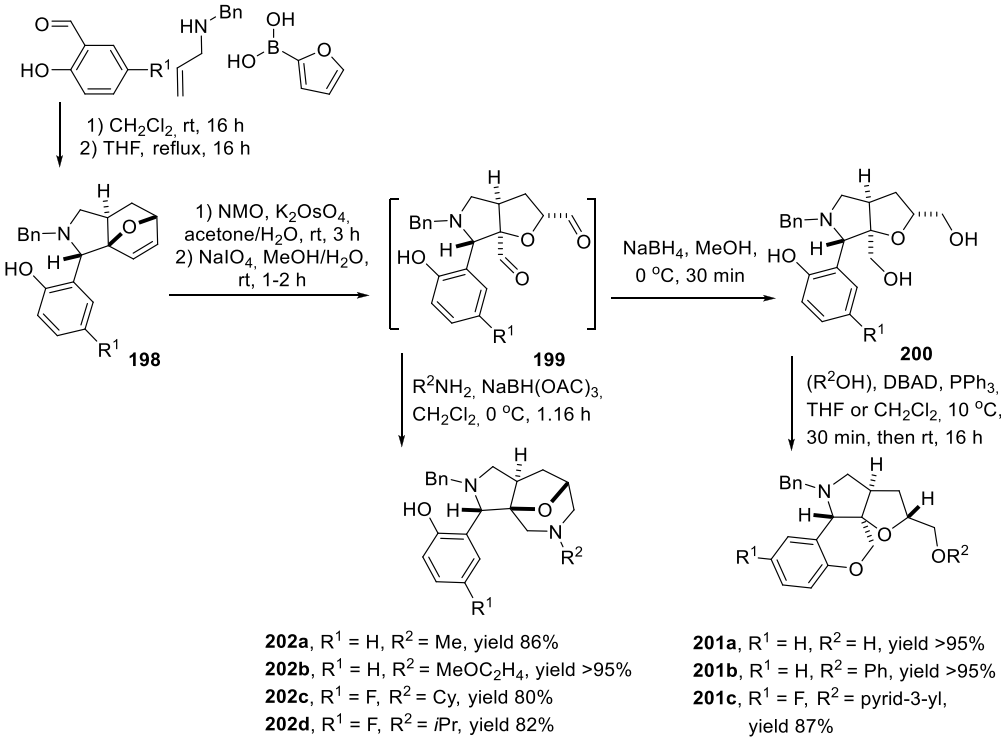
Chem. Rev. 2019, 119, 11245–11290

Scheme 51



* Yield over four steps including two steps to synthesize (5-Boc-aminomethyl)furan-2-boronic acid from (5-formylfur-2-yl)boronic acid

Scheme 52

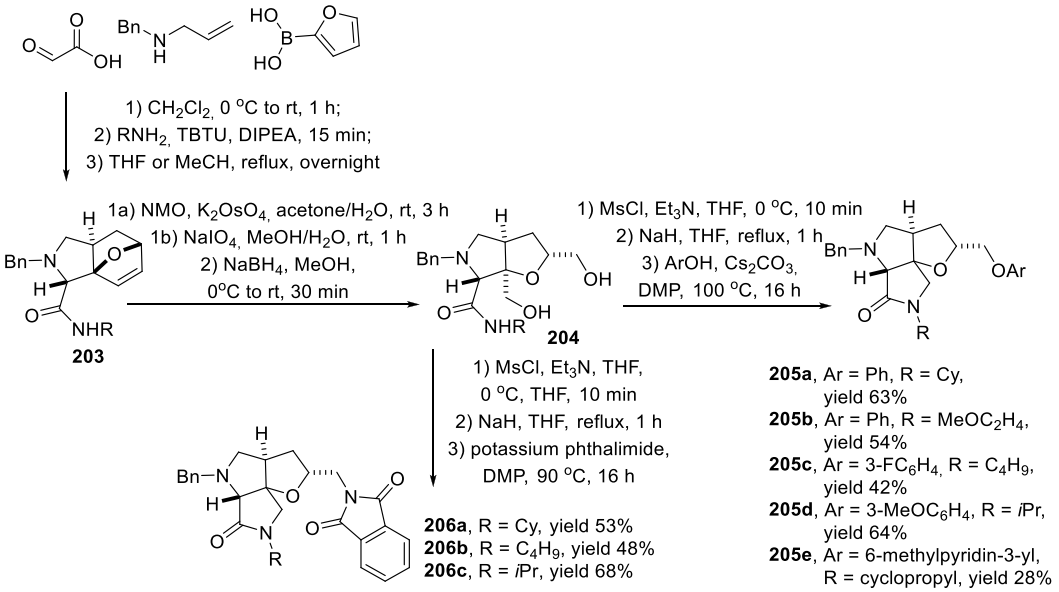


but low *dr* values. When thien-2-ylboronic acid and 3-pyridylboronic acid were applied, none of the expected products were isolated, but electron-poor 3,5-difluorophenylboronic acid did lead to a 37% yield of the desired material **246h** (Scheme 62). The synthesized compounds were tested for their insecticidal activity against armyworm and their nematicidal activity.[168]

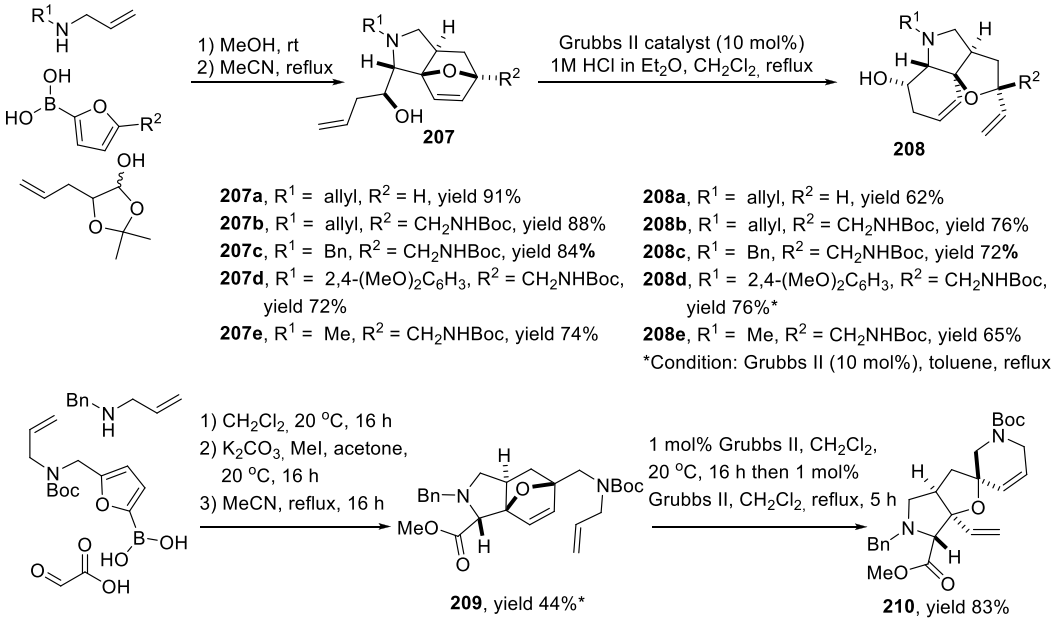
A series of secondary amines, 2-(benzylamino)phenols **247**, obtained via the condensation of 2-aminophenols and benzaldehydes were used as the amine component in a PR involving glyoxal and phenylboronic acids. Bicyclic compounds **248**, with the *trans*-2-hydroxy-1,4-benzoxazine products being the 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

DOI: 10.1021/acs.chemrev.9b00214
Chem. Rev. 2019, 119, 11245−11290

Scheme 53



Scheme 54



* Yield over four steps including two steps to synthesize (5-Boc-aminomethyl)furan-2-boronic acid from (5-formylfuran-2-yl)boronic acid

p-toluene-sulfonate-catalyzed PR with a reduced reaction time of 3 h in refluxing methanol.[170]

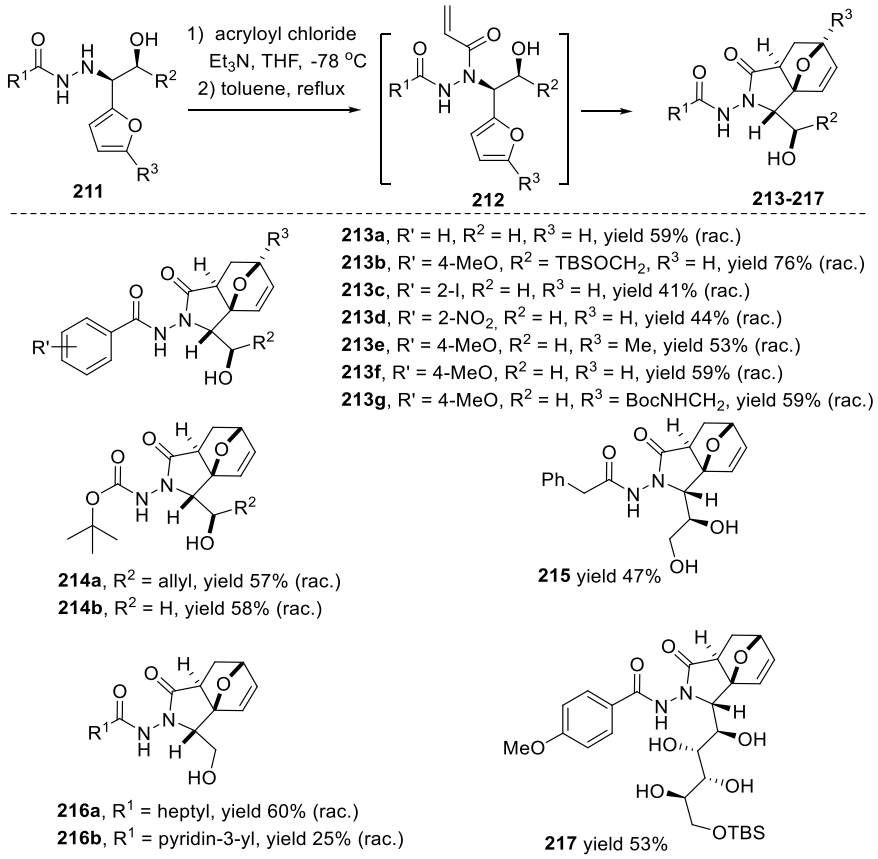
A three-component PR was used for the synthesis of imidazo[1,2-α]pyridine-3-ols **250** using 2-aminopyridine, glyoxylic acid, and arylboronic acid with microwave irradiation at 160 °C. This transformation involved the formation of the Petasis product **249** as an intermediate undergoing intramolecular 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 **249** 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.[172,173] 2-Amiobenzamides, formed from isatoic anhydride and amines, were reacted with glyoxalic 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 **251**, which underwent intramolecular amidation to give cyclized compound **252** 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]

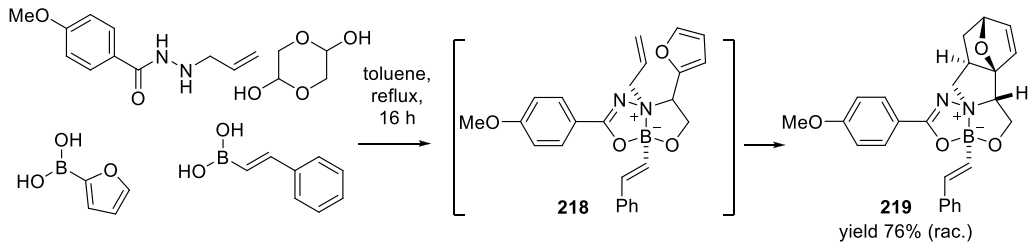
Rozwadowska and coworkers reported the synthesis of tetrahydroisoquinolines through a PR−Pomeranz−Fritsch−Bobbitt cyclization sequence.[174,175] Petasis products **253** were synthesized from glyoxylic acid, aminoacetaldehyde acetal, and

DOI: 10.1021/acs.chemrev.9b00214
Chem. Rev. 2019, 119, 11245−11290

Scheme 55



Scheme 56



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 **254** in generally excellent yield. The use of chiral amino-acetaldehyde acetals led to enantiomerically pure isoquinoline acids **254** (Scheme 66).[176]

Hulme and coworkers reported a PR–nucleophilic cyclization sequence to synthesize quinoxalines **256** 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 **255** were subject to acid-mediated Boc deprotection and intramolecular nucleophilic cyclization to give quinoxalines **256** in mostly good to excellent yield (Scheme 67).[177]

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 **258** and **259**, whereas the treatment of **257b** with TBAF led to lactone **260**, which could be further acetalized to give a bicyclic morpholine (Scheme 68).[178]

Norsikian and Beau reported a PR for the synthesis of amino alcohol **263** from diallylamine, α-hydroxy aldehyde **261**, and boronic acid **262**. Amino alcohol **263** was deallylated and acetyl-protected to give amide **264**, which was cyclized to give oxazoline **265** catalyzed by $FeCl_3$. The ring opening of oxazoline **265** in the presence of trimethylsilyl azide, followed by saponification and amino-iminomethanesulfonic acid

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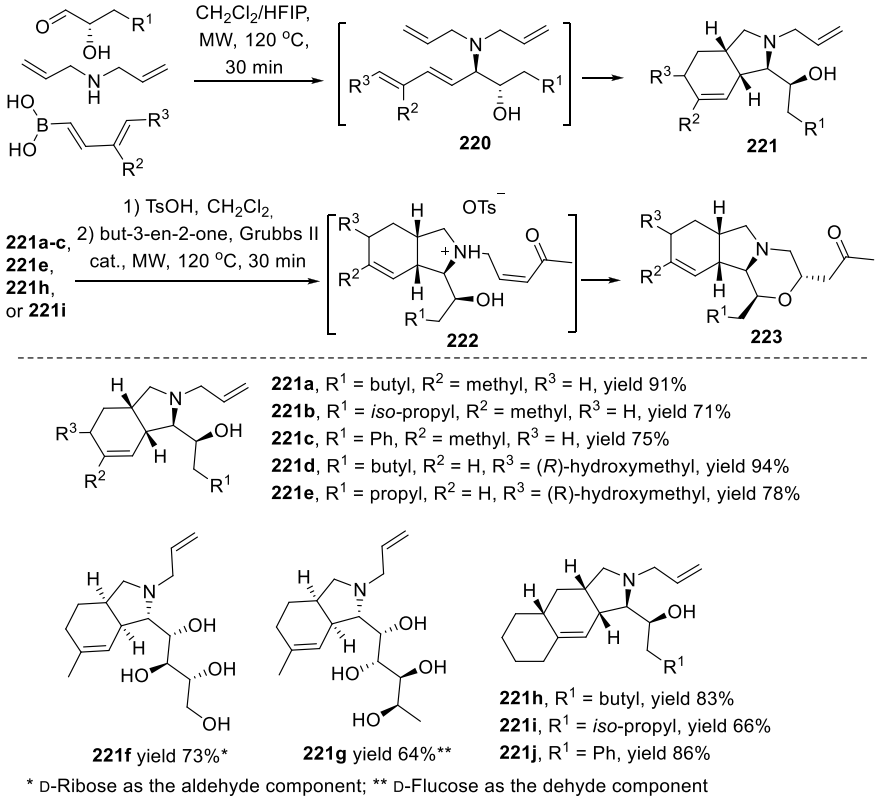
Scheme 57



substitution gave the guanidine **266** as a zanamivir analog (Scheme 69).[179]

5.4. PR−Suzuki Sequence and Suzuki−PR Sequence

Carboni and coworkers reported several studies using alkenyl boronic esters or 1,2-diboronic esters for the synthesis of functionalized heterocycles.[180−183] 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).[184] The same group recently reported a Suzuki coupling−intermolecular 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-1*H*-indenes **271** in good yield ranging from 66 to 92% (Scheme 71).[182] 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,[185−187] 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.[185,188] 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).[188]

A PR−Ugi sequence reactions was performed on an automated continuous-flow microreactor system.[189] 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

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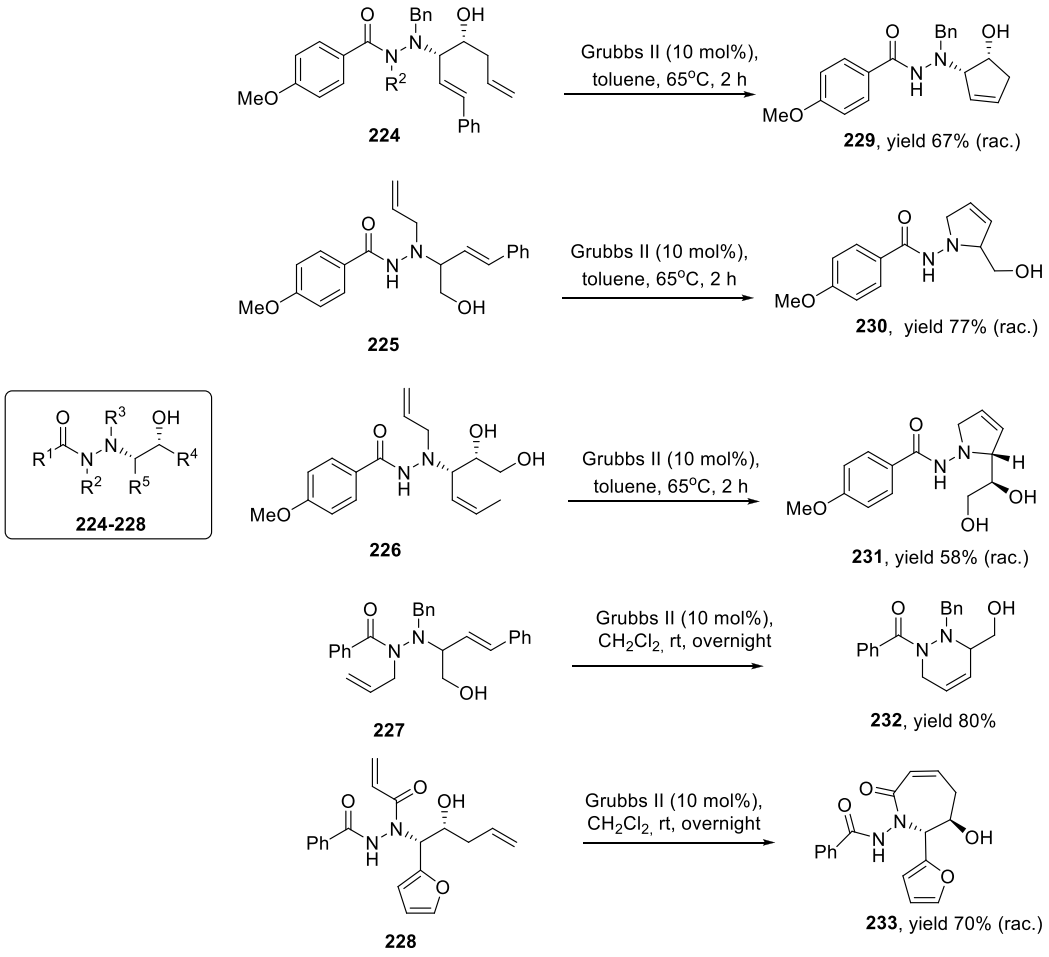
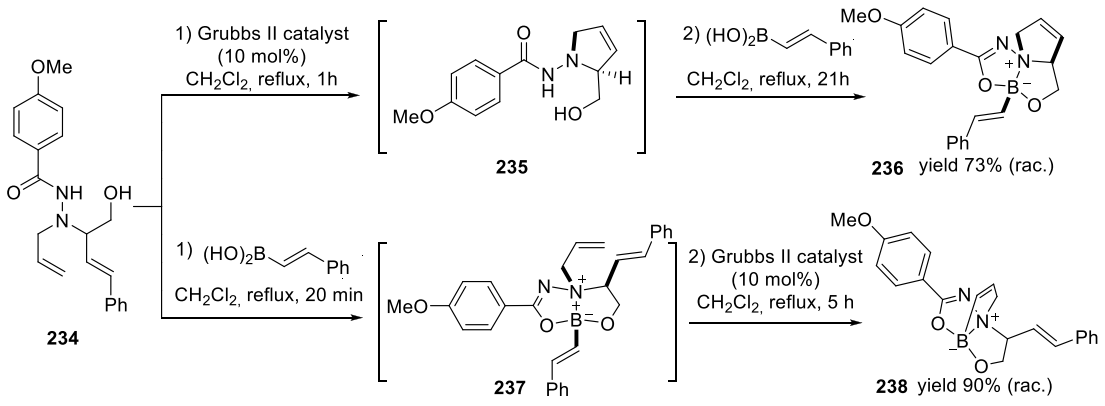
Scheme 58



Scheme 59



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 α-amino acids or β-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

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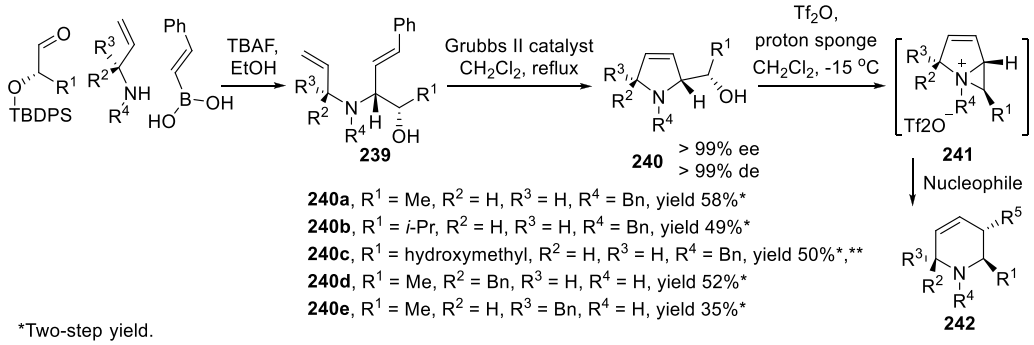
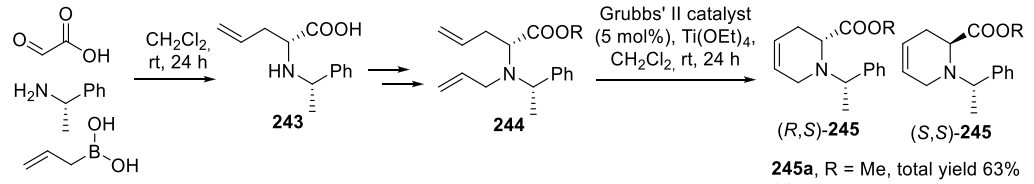
Chem. Rev. 2019, 119, 11245−11290

Scheme 60

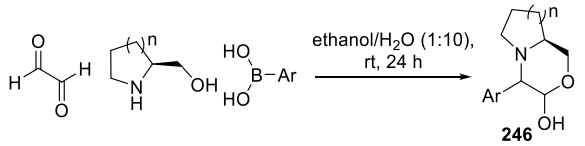


*Two-step yield.
**Unprotected hydroxyaldehyde was used, no TBAF treatment.

Scheme 61



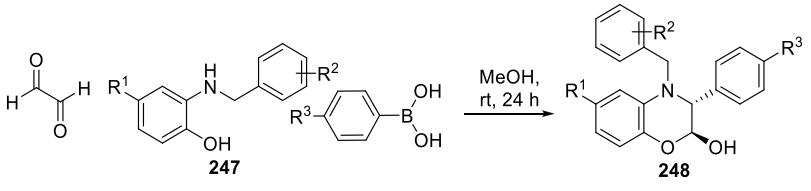
Scheme 62



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.[198]

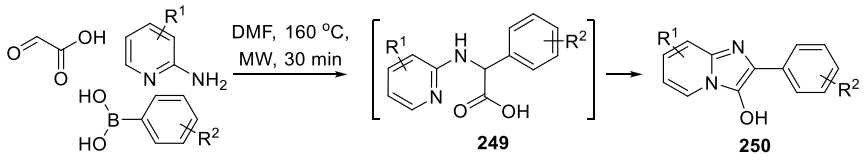
Conduramine oligomers, aminocyclohexenetriols in which an amino group is present, are common fragments included in several natural products. The synthesis of conduramines has been achieved via different approaches.[200] Norsikian, Beau, and coworkers reported the synthesis of conduramine A1 **292** and 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 63



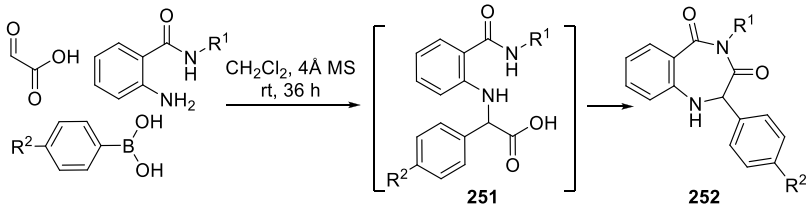
DOI: 10.1021/acs.chemrev.9b00214
Chem. Rev. 2019, 119, 11245−11290

Scheme 64



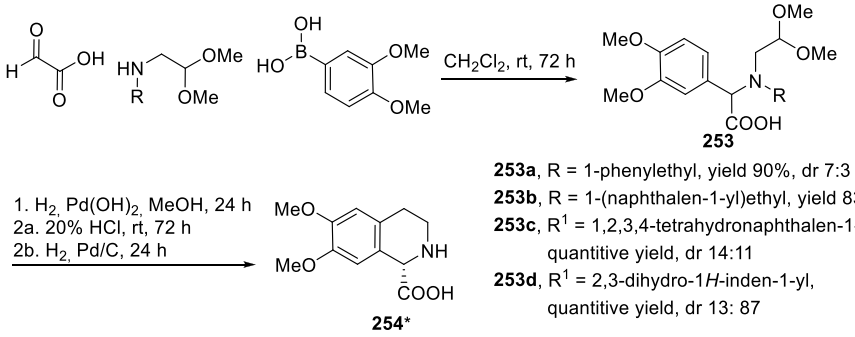
250a, R^1 = 6-methyl, R^2 = 4-methoxy, yield 80%
250b, R^1 = 8-methyl, R^2 = 4-methoxy, yield 85%
250c, R^1 = 5-methyl, R^2 = 4-methoxy, yield 66%
250d, R^1 = H, R^2 = 4-methoxy, yield 48%
250e, R^1 = 8-bromo, R^2 = 4-methoxy, yield 40%
250f, R^1 = 6-bromo, R^2 = 4-methoxy, yield 48%
250g, R^1 = 7-chloro, R^2 = 4-methoxy, yield 53%
250h, R^1 = 6-methyl, R^2 = 3-methoxy, yield 78%
250i, R^1 = 6-methyl, R^2 = 2,5-dimethoxy, yield 67%
250j, R^1 = 6-methyl, R^2 = 3,4-dimethyl, yield 65%
250k, R^1 = 6-methyl, R^2 = 4-trifluoromethoxy, yield 61%
250l, R^1 = 6-methyl, R^2 = H, yield 60%
250m, R^1 = 6-methyl, R^2 = 3,4-ethylenedioxy, yield 69%
250n, R^1 = 6-methyl, R^2 = 4-chloro, yield 51%*
250o, R^1 = 6-methyl, R^2 = 4-bromo, yield 55%*
250p, R^1 = 6-methyl, R^2 = 4-fluoro, yield 54%*
250q, R^1 = 6-methyl, R^2 = 3-fluoro, yield 45%*
* MW condition: HFIP, 120 °C, 30 min

Scheme 65



252a, R^1 = phenyl, R^2 = H, yield 72%
252b, R^1 = phenyl, R^2 = methoxy, yield 78%
252c, R^1 = 4-methylbenzyl, R^2 = H, yield 62%
252d, R^1 = 4-chlorobenzyl, R^2 = H, yield 65%
252e, R^1 = 4-fluorobenzyl, R^2 = H, yield 60%
252f, R^1 = 4-fluorobenzyl, R^2 = methoxy, yield 68%
252g, R^1 = 3,4-dimethoxyphenethyl, R^2 = H, yield 69%
252h, R^1 = butyl, R^2 = fluoro, yield 62%

Scheme 66



253a, R = 1-phenylethyl, yield 90%, dr 7:3
253b, R = 1-(naphthalen-1-yl)ethyl, yield 83%, dr 79:21
253c, R^1 = 1,2,3,4-tetrahydronaphthalen-1-yl, quantitive yield, dr 14:11
253d, R^1 = 2,3-dihydro-1*H*-inden-1-yl, quantitive yield, dr 13: 87

* When chiral aminoacetaldehyde acetals were used as the amine component, and the products were enantiomerically enriched by crystallization.

component for the PR with diallylamine to yield allyl-protected conduramine **295** as a single diasteroisomer in 60%. Conduramine C4 **296** 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.[201] A separate PR−RCM sequence was applied for the synthesis of both enantiomers of conduramine E **300** 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*)-styrylboronic 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 E **300** and **304**, respectively (Scheme 76).[202]

Pyne and coworkers reported various synthetic studies for the synthesis of polyhydroxylated monocyclic alkaloids as well as their application as starting materials to access more complex alkaloids.[195,196,198,203−205] Polyhydroxylated pyrrolidine alkaloids dihydroxymethyl−dihydroxypyrrolidine

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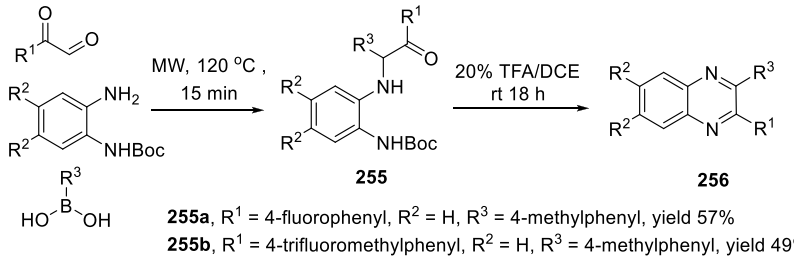
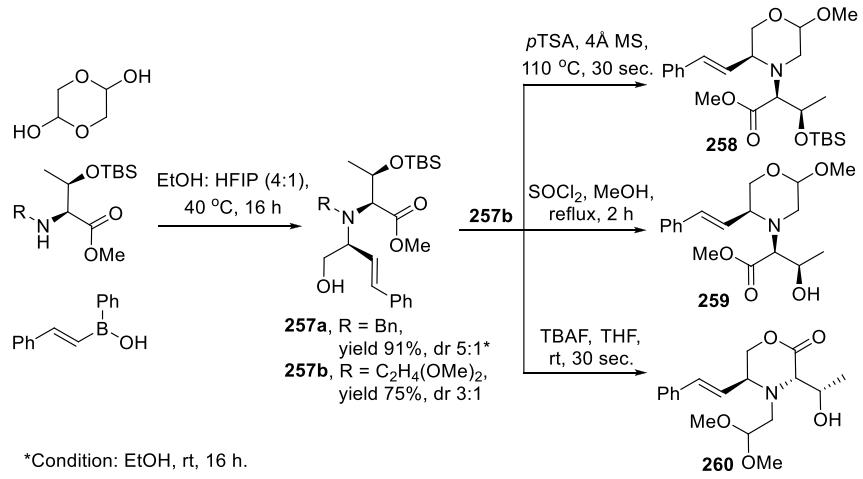
Scheme 67



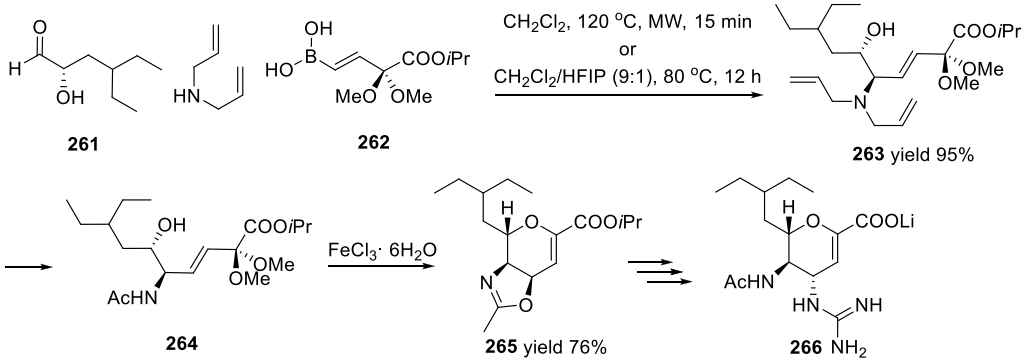
255a, R^1 = 4-fluorophenyl, R^2 = H, R^3 = 4-methylphenyl, yield 57%
255b, R^1 = 4-trifluoromethylphenyl, R^2 = H, R^3 = 4-methylphenyl, yield 49%
255c, R^1 = Ph, R^2 = H, R^3 = 3-fluorophenyl, yield 48%
255d, R^1 = 4-trifluoromethylphenyl, R^2 = H, R^3 = naphth-2-yl, yield 71%
255e, R^1 = Ph, R^2 = H, R^3 = (*E*)-styryl, yield 39%
255f, R^1 = Ph, R^2 = H, R^3 = 2-methoxyphenyl, yield 63%
255g, R^1 = Ph, R^2 = H, R^3 = 2,4,6-trifluorophenyl, yield 83%
255h, R^1 = 4-triflurometh ylphenyl, R^2 = H, R^3 = 3-trifluoromethylphenyl, yield 87%
255i, R^1 = 4-trifluoropemthylphenyl, R^2 = methyl, R^3 = naphth-2-yl, yield 45%
255j, R^1 = Ph, R^2 = methyl, R^3 = 2,4,6-trifluorophenyl, yield 24%
255k, R^1 = 2,4,6-trimethylphenyl, R^2 = H, R^3 = 2-methoxyphenyl, yield 0%
255l, R^1 = 2,4,6-trimethylphenyl, R^2 = H, R^3 = 4-methylphenyl, yield 0%

Scheme 68



*Condition: EtOH, rt, 16 h.

Scheme 69



(DMDP) **307** and 1,4-dideoxy-1,4-imino-D-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_N2 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).[206]

Pyne and coworkers reported several synthetic studies using the PR as a key step to obtain α-amino alcohols for the

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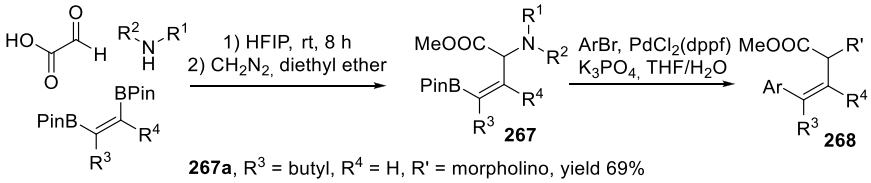
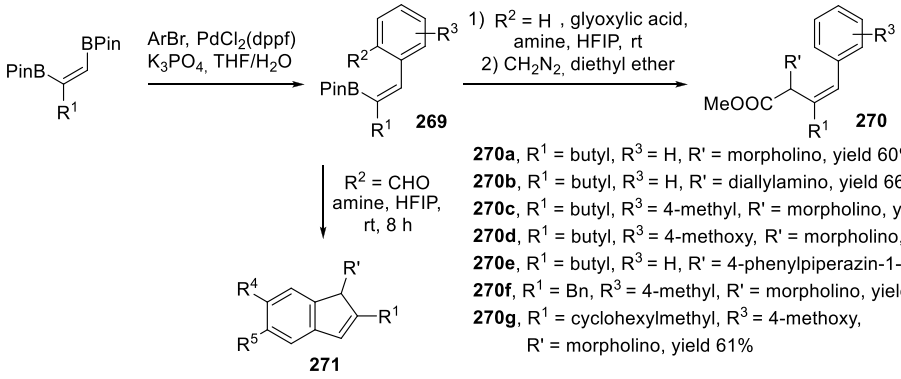
Scheme 70



267a, R^3 = butyl, R^4 = H, R' = morpholino, yield 69%
267b, R^3 = butyl, R^4 = H, R' = dibenzylamino, yield 50%
267c, R^3 = butyl, R^4 = H, R' = 4-(pyrid-4-yl)piperazin-1-yl, yield 57%
267d, R^3 = butyl, R^4 = H, R' = 4-Boc-piperazin-1-yl, yield 63%
267e, R^3 = butyl, R^4 = H, R' = (*S*)-benzyl(1-phenylethyl)amino, yield 69%, dr 58:42
267f, R^3 = butyl, R^4 = H, R' = benzylamine, yield 0%
267g, R^3 = $TMSCH_2$, R^4 = H, R' = morpholino, yield 60%
267h, R^3 = $TMSCH_2$, R^4 = H, R' = benzylmethylamino, yield 53%
267i, R^3 = Ph, R^4 = H, R' = morpholino, yield 53%
267j, R^3 = Ph, R^4 = H, R' = dibenzylamino, yield 54%
267k, R^3 = Et, R^4 = Et, R' = morpholino, yield 0%

Scheme 71

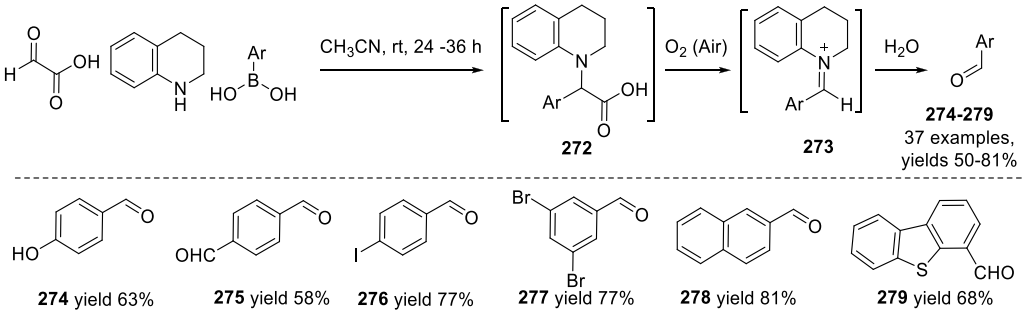


270a, R^1 = butyl, R^3 = H, R' = morpholino, yield 60%
270b, R^1 = butyl, R^3 = H, R' = diallylamino, yield 66%
270c, R^1 = butyl, R^3 = 4-methyl, R' = morpholino, yield 48%
270d, R^1 = butyl, R^3 = 4-methoxy, R' = morpholino, yield 51%
270e, R^1 = butyl, R^3 = H, R' = 4-phenylpiperazin-1-yl, yield 62%
270f, R^1 = Bn, R^3 = 4-methyl, R' = morpholino, yield 62%
270g, R^1 = cyclohexylmethyl, R^3 = 4-methoxy, R' = morpholino, yield 61%

22 examples, yields 66-92% selected examples:

271a, R^1 = morpholino, R^1 = butyl, R^4 = H, R^5 = H, yield 92%
271b, R^1 = morpholino, R^1 = butyl, R^4 = methoxy, R^5 = H, yield 73%
271c, R^1 = morpholino, R^1 = butyl, R^4 = methoxy, R^5 = methoxy, yield 71%
271d, R^1 = 4-phenylpiperazin-1-yl, R^1 = butyl, R^4 = methoxy, R^5 = methoxy, yield 82%
271e, R^1 = diallylamino, R^1 = butyl, R^4 = methoxy, R^5 = methoxy, yield 78%
271f, R^1 = benzylmethylamino, R^1 = butyl, R^4 = methoxy, R^5 = methoxy, yield 82%
271g, R^1 = propargylamino, R^1 = cyclohexyl, R^4 = methoxy, R^5 = methoxy, yield 80%
271h, R^1 = morpholino, R^1 = Bn, R^4 = methoxy, R^5 = H, yield 76%
271i, R^1 = propargylamino, R^1 = TMS, R^4 = H, R^5 = H, yield 75%

Scheme 72



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** or **312**, which was used as the precursor to synthesize hyacinthacine-B-type compound **313** or **314** (Scheme 78).[196] A very recent PR of protected L-xylose derivative **315**, α-methylallyl amine, and (*E*)-styrylboronic acid to obtain the amino diol **316** was used as a key step for the total synthesis of a series of polyhydroxyated alkaloids, including hyacinthacine C_5 **317** and **318** with a bicyclic hexahydro-1*H*-pyrrolizine core (Scheme 79).[207,208] 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

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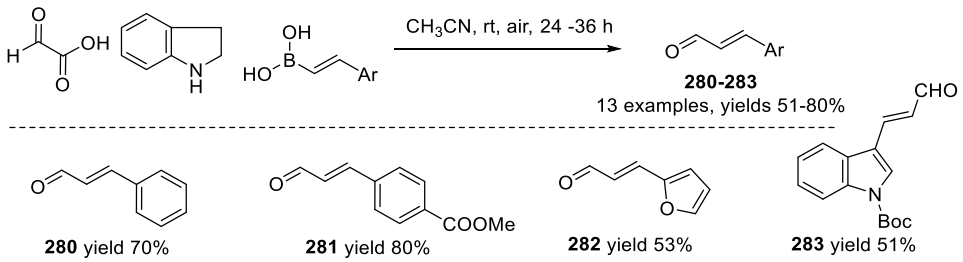
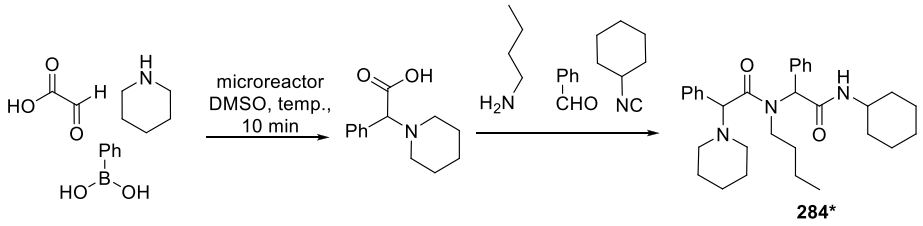
Scheme 73

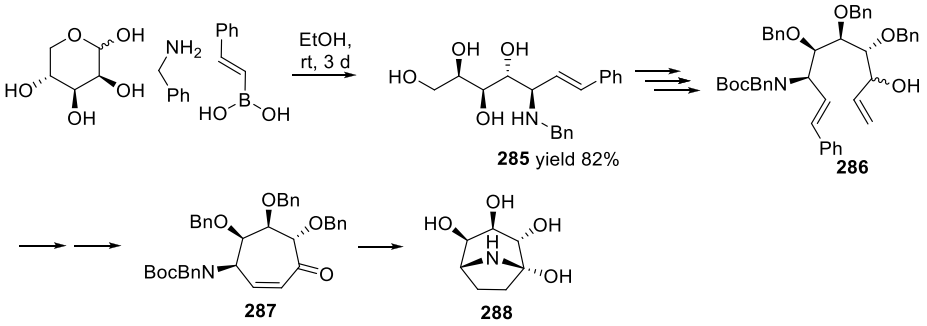


Scheme 74



* Yield range: approx. 10 - 50 %, depending on different temperatures ranging from 60 -150 °C

Scheme 75



key precursors. Seven obtained hyacinthacine C_5 compounds were then evaluated as weak to moderate α-glycosidase inhibitors (9.9 to 130 μM).[207]

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),[209] have been the subject of many synthetic works.[210] A two-component Petasis-like step was used to synthesize the loline alkaloid scaffold **322**. The diastereoselective addition of tetramethylpentanediol boronates to the *N*-acyliminium ion species, which was derived from dihydroxypyrrolidine **319**, gave vinylpyrrolidinol **320**. Six following steps, including a tethered aminohydroxylation, led to the formation of pyrrolooxazinone **321**, from which the *N*-Boc norlodine **322** was obtained as the loline alkaloid scaffold in another five steps (Scheme 80).[211]

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.[212] 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 **323**. The PR of α-hydroxyl aldehyde **323**, (*E*)-styrylboronic acid, and monoallylamine gave aminol **324** 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 **325**, which was used for the further synthesis of a linker-equipped legionaminic acid **326** (Scheme 81).[213] A recent study reported the total biosynthesis of the same type of legionaminic acid acetylated at the 5- and 7-positions.[214]

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

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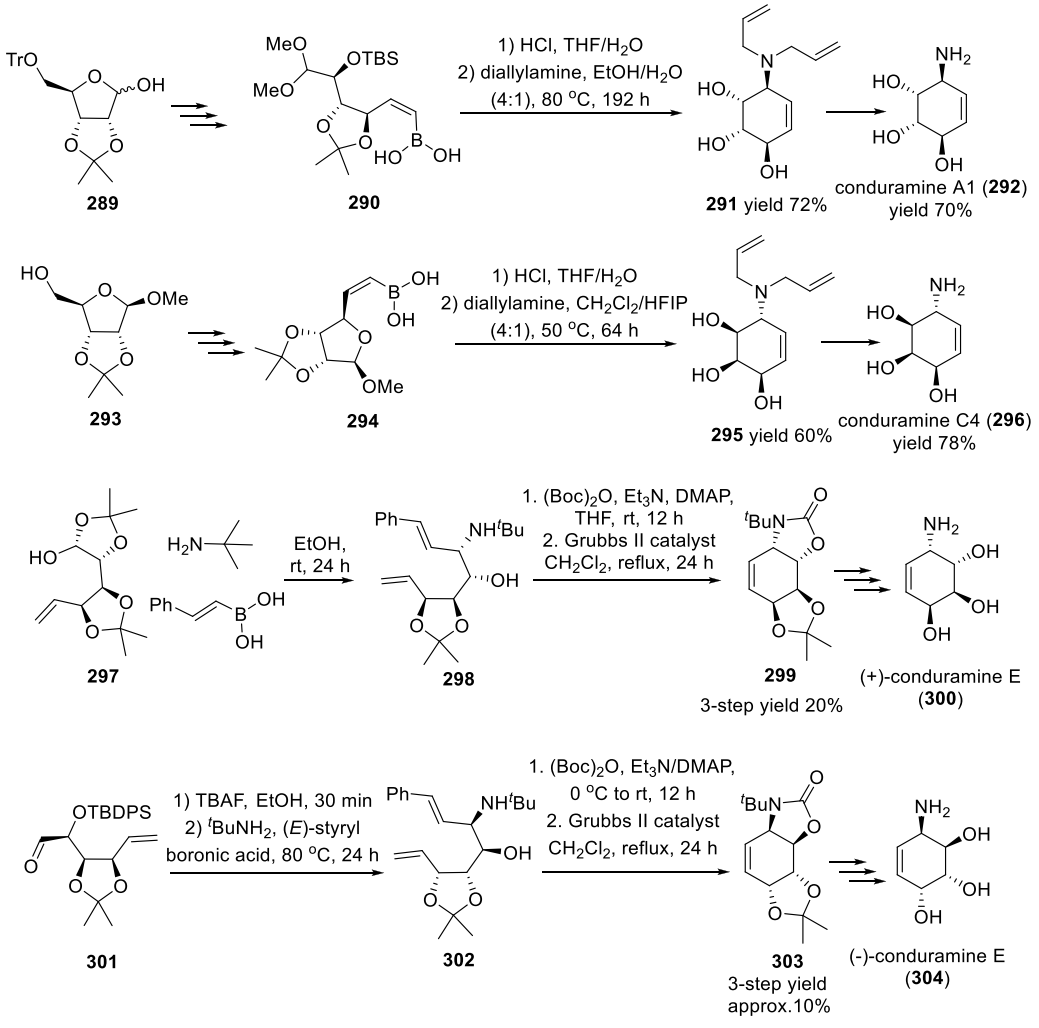
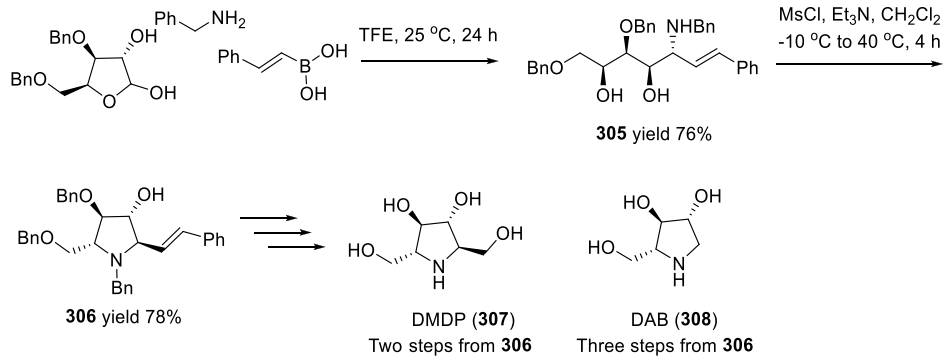
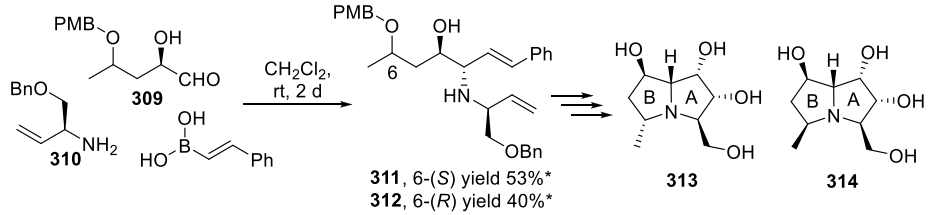
Scheme 76



Scheme 77



Scheme 78



* 2-Step yield including a metathesis reaction to obtain a vinyl sulfone as the precursor of **309**.

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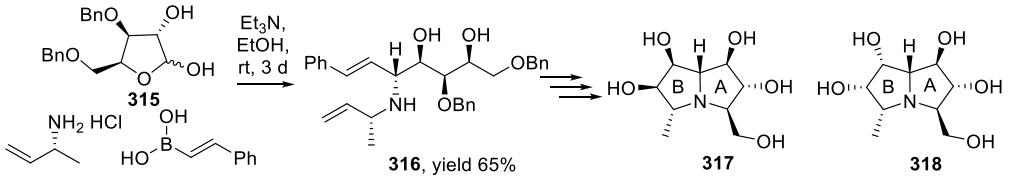
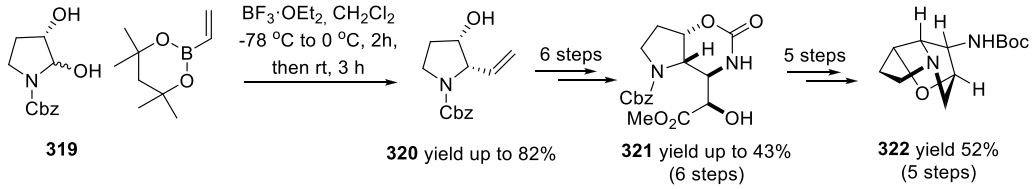
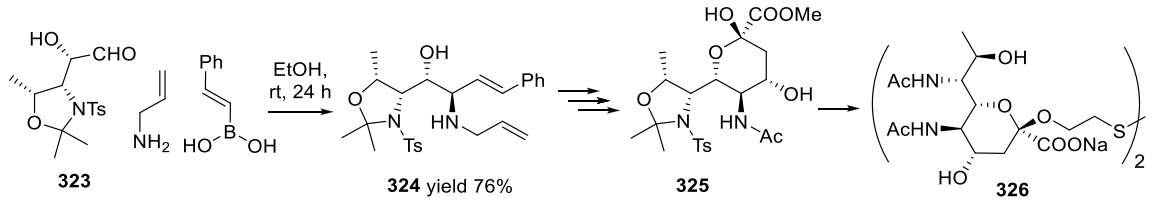
Scheme 79



Scheme 80



Scheme 81



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 sp^3-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 show varied biological activities.

Given the many inherent merits of the PR such as but not limited to the easy access of reaction substrates, the minimal protection of functional moieties, the mild and robust reaction condition, the easy and friendly operation, and the rapid access to structural diversity, we expect that the interest around the exploration of PR-based transformations and the application of Petasis products will remain and will probably intensify in the coming years from both a chemical and a biochemical perspective. The substrate scope will be further expanded to include noncanonical or previously nonreactive carbonyls, amines, and boronic acids. Asymmetric PRs using a pool of newly tested chiral catalysts will follow. Additional components are likely to be incorporated in the polycomponent PR as well as the Petasis-type reaction of new substrate variants. A secondary transformation based on Petasis products and combination strategies involving the PR is expected to be an appealing area because most these natural-product-leading cascade and sequence reactions have mainly been reported in the past 5 years. Thus advances in PRs will attract sustaining interest from not only synthetic chemists but also researchers in developing biologically active structural diverse molecules as biological probes or potential therapeutics.

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Notes

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

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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 thr Singapore Center for Environmental Life Sciences Engineering (SCELSE) and was appointed Research Director and Professor in 2011. In 2013, he founded the Costerton Biofilm Center (CBC) at UCPH, where he was appointed Managing Director and Professor. He still upholds his 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	benzotriazole
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
Ns	*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-FVIIa	tissue factor/factor VIIa

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