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Advances in Multicomponent Petasis Reaction: A 2020-2025 Review

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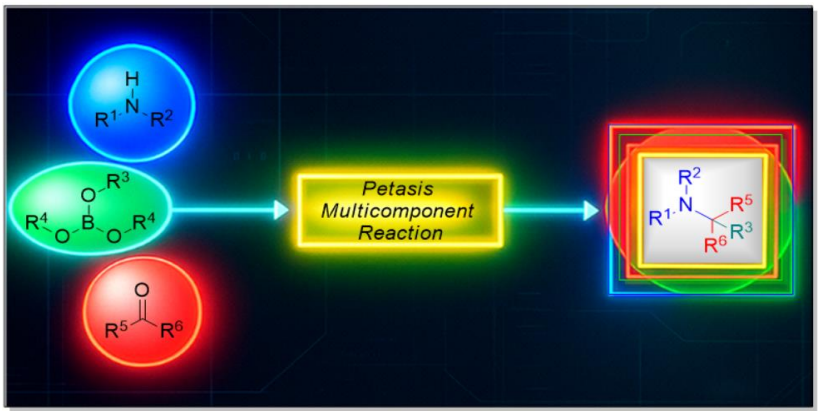
The Petasis–Boronic multicomponent reaction has emerged as a practical and versatile method for building structurally complex molecules, particularly frameworks bearing newly formed stereocenters. Known for its operational simplicity, mild conditions, and broad functional-group tolerance, it offers an attractive alternative to classical Mannich-type processes. Over time, its scope has expanded through advances that improve stereocontrol, substrate diversity, and reaction efficiency. Over the years, its scope has broadened with developments that enhance stereocontrol, functional group compatibility, and overall efficiency. Recent progress, including asymmetric variants, photoredox-mediated strategies, and continuous-flow adaptations, underscores the flexibility of this transformation. The use of novel boronic acid derivatives and unconventional substrates has further expanded its synthetic potential, enabling the rapid construction of complex molecular frameworks. Collectively, these advances establish the Petasis reaction as a dynamic platform in modern multicomponent chemistry, with wide applicability.

Graphical abstract



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1. Introduction

Multicomponent reactions (MCRs) are highly valued in modern synthesis for their efficiency and ability to generate structural complexity from simple precursors in a single operation. Among them, the Petasis–Boronic multicomponent reaction stands out due to its operational simplicity, broad functional-group tolerance, and its capacity to construct amino-substituted frameworks that incorporate newly formed stereogenic centers. Since its introduction in 1993, this transformation has enabled the coupling of aldehydes or ketones, amines, and boronic acids (or esters) in a versatile and synthetically robust fashion. Notably, several methodological advances have expanded its stereochemical control, allowing the formation of asymmetric carbon centers and chiral molecular architectures with high precision [1].

A distinctive advantage of the Petasis reaction is that many variants proceed without transition-metal catalysts,

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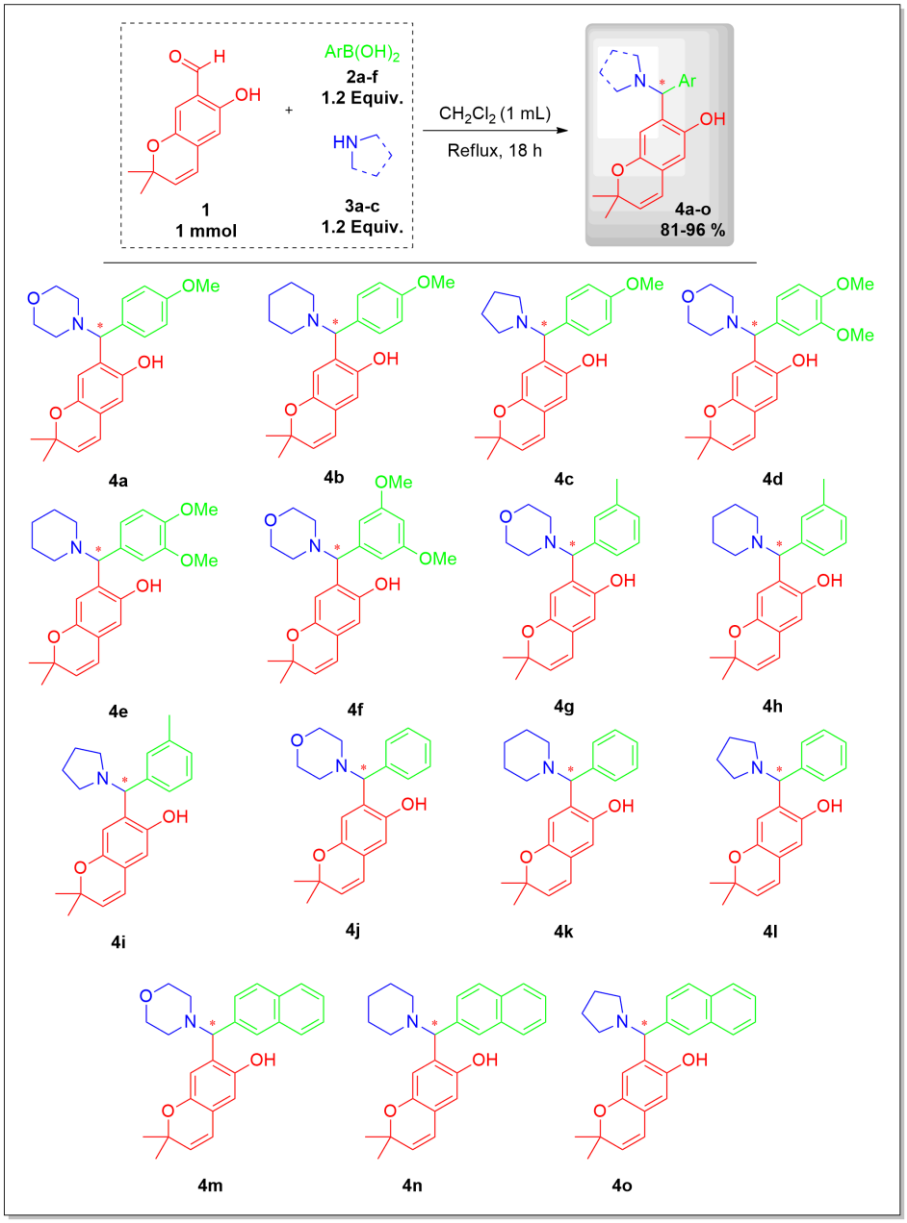
reducing costs and facilitating compatibility with sensitive functionalities. The readily available nature of its starting components further enhances its utility. Recent reviews highlight the persistence of catalyst-free protocols alongside significant progress in asymmetric and directed variants [2]. These transformations are particularly attractive for building stereocenters, and new strategies have emerged to improve enantiocontrol and broaden substrate scope [3]. Moreover, methodological advances, such as photoredox-mediated Petasis reactions, continuous-flow processing, and the use of radical pathways, have expanded the reaction's efficiency, sustainability, and applicability [4]. Taken together, these developments illustrate how the Petasis reaction has evolved into a flexible synthetic platform, with continuing opportunities for innovation across academic and industrial chemistry.

2. Advances in Petasis Reaction

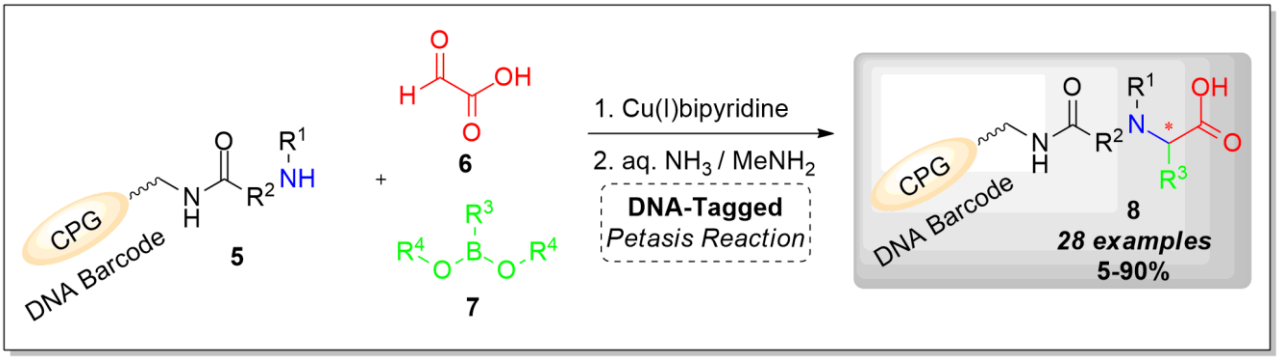
The Petasis reaction has been successfully employed in the synthesis of chromene-based scaffolds with promising biological properties (Scheme 1). Notably, biological screening of newly synthesized chromenes revealed their ability to inhibit ANO1, a calcium-activated chloride channel that plays a crucial role in numerous physiological processes across various cell types, including epithelial cells, smooth muscle cells, intestinal pacemaker cells, and sensory neurons. ANO1 is highly expressed in several carcinomas and is implicated in key stages of cancer progression, such as cell proliferation and metastasis, in head and neck squamous cell carcinoma (HNSCC), as well as gastrointestinal, breast, and prostate cancers [5].



Scheme 1

The Petasis reaction has been successfully applied to DNA-conjugated systems immobilized on solid supports, employing Cu(I)/bipyridine complexes as promoters. The transformation proceeds through the formation of a key iminium–boronate intermediate and is well tolerated in polar aprotic solvents, particularly DMF, while maintaining DNA integrity (Scheme 2). A broad range of boronic acids, including aryl, heteroaryl, and vinyl derivatives, demonstrated excellent compatibility, with electron-donating substituents generally providing higher conversions. Less sterically hindered amines exhibited good reactivity under the optimized conditions, whereas bulkier amines, such as tert-butylamine, showed low

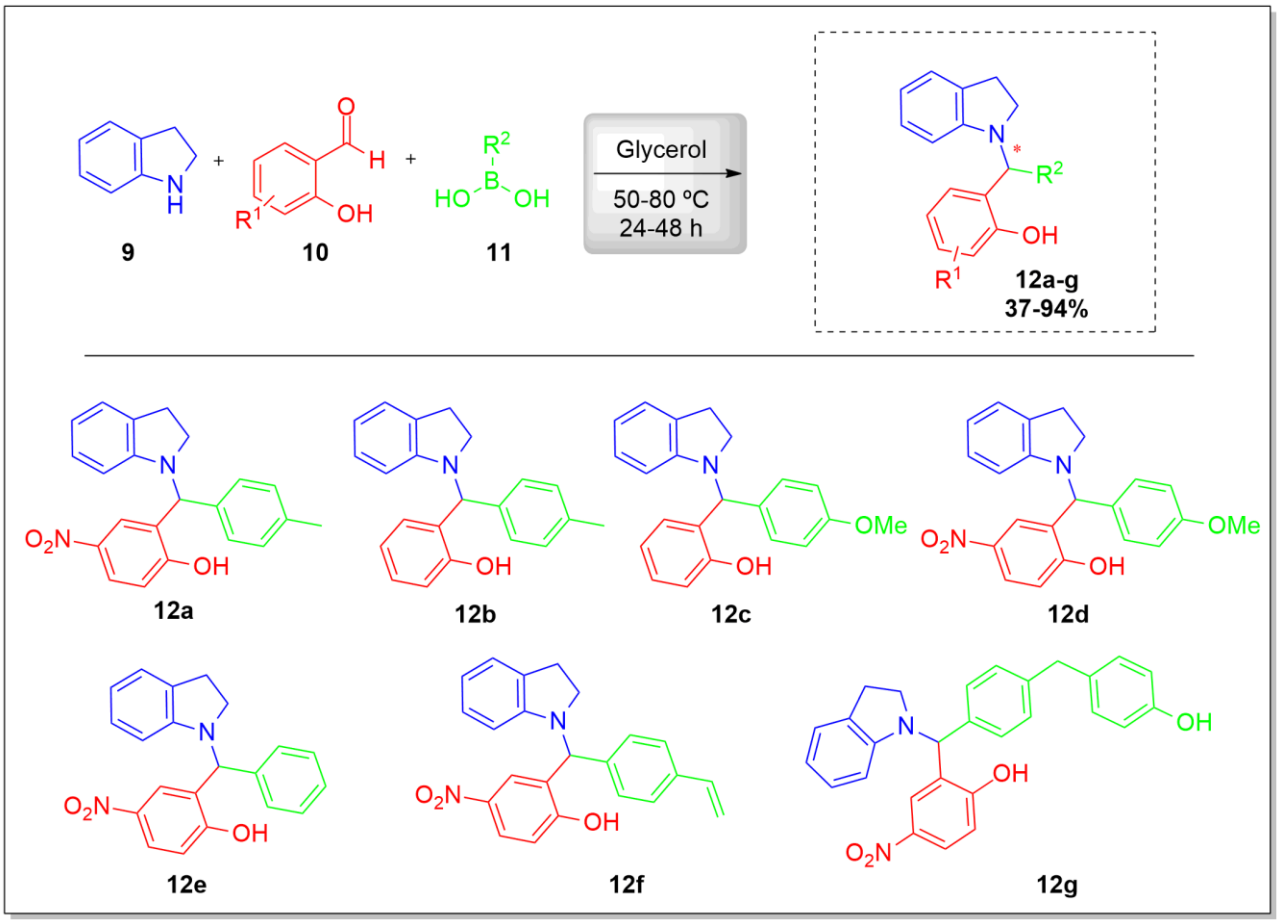
or no conversion. Secondary amines were also efficiently generated via reductive amination of DNA–aldehyde conjugates, followed by Petasis reactions that afforded high conversions for most substrates. These studies collectively highlight that the structural and steric properties of the amine component exert a significant influence on the overall efficiency of the transformation [6].



Scheme 2

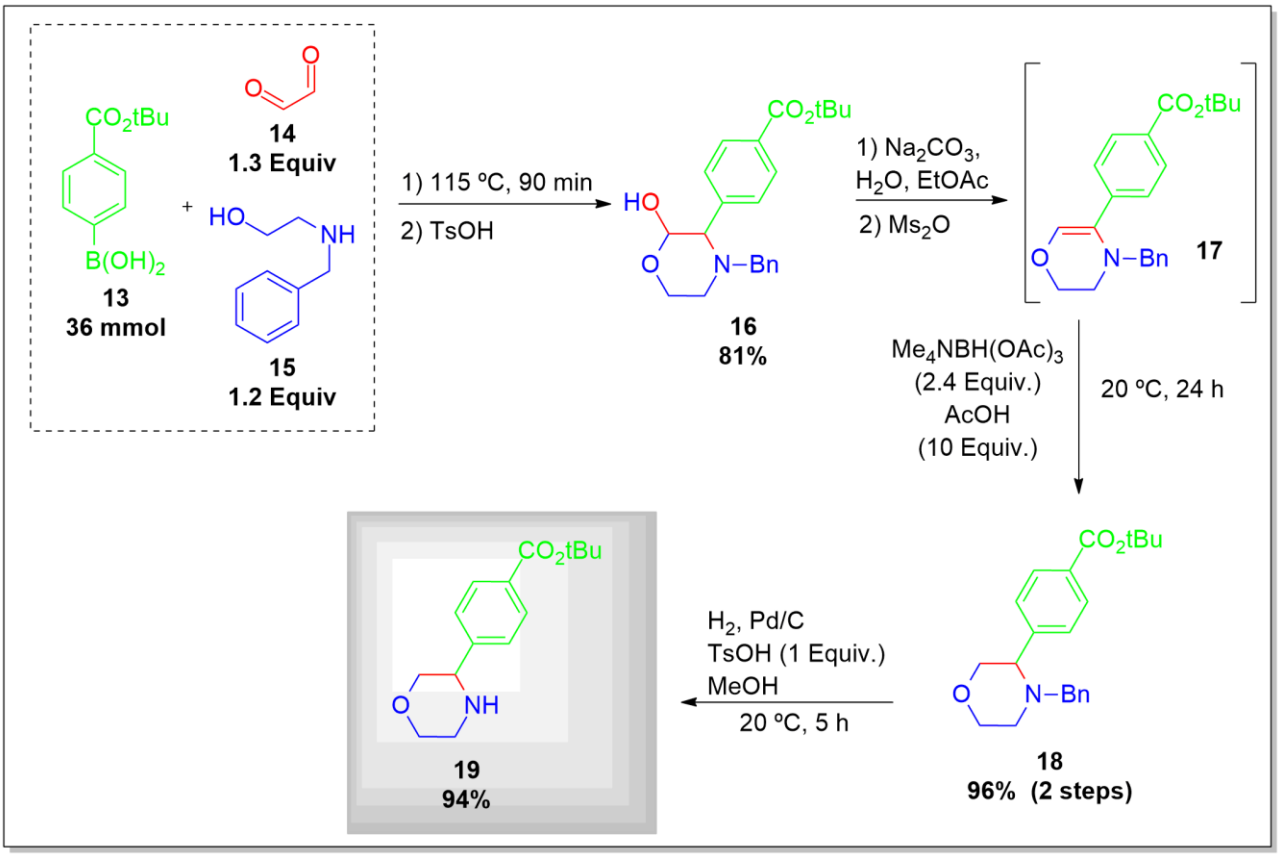
In 2020, studies demonstrated the use of glycerol as an environmentally benign solvent in PBM reactions involving salicylaldehydes or 2-pyridinecarbaldehyde with various boronic acids and secondary amines, affording alkylaminophenols, 2-substituted pyridines, and 2H-chromenes in moderate to good yields (Scheme 3). Comparative solvent analyses revealed that glycerol frequently improved product yields relative to conventional solvents, and crude glycerol—an abundant by-product of the biodiesel industry—proved to be an effective reaction medium. DFT calculations indicated that glycerol-derived boronic esters actively participated in the reaction mechanism, competing with the free boronic acid pathway and exhibiting similar Gibbs free energies for the aryl migration to the iminium intermediate [7].

Among the compounds synthesized through this approach, the indoline derivative N-(2-hydroxy-5-nitrophenyl(4'-methylphenyl)methyl)indoline (HNPMI) attracted considerable attention for its potent anticancer properties. Molecular docking identified HNPMI as a high-affinity EGFR inhibitor, displaying greater cytotoxicity than Cyclophosphamide against MCF-7 and SkBr3 breast cancer cell lines (IC_{50} = 64.10 µM and 119.99 µM, respectively) while sparing non-cancerous H9C2 cells [8, 9].



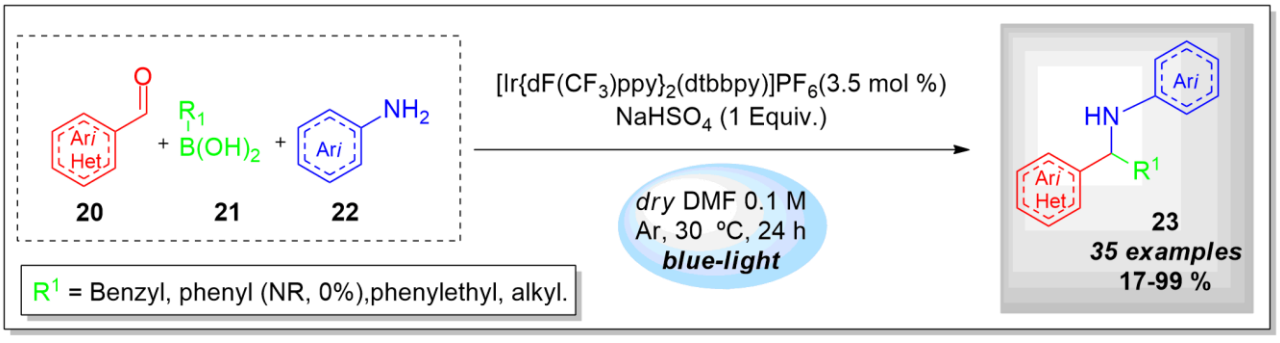
Scheme 3

Wright et al. reported the synthesis of aryl-functionalized morpholines, in which the initial step involved a Petasis borono–Mannich reaction. A series of aryl-substituted morpholine derivatives were efficiently prepared on a small scale, while compound **19** was successfully obtained on a multigram scale following a four-step synthetic sequence (Scheme 4). This study highlights the versatility of the Petasis reaction as a key transformation for the rapid construction of nitrogen-containing heterocycles with structural diversity. The morpholine products can be conveniently N-deprotected by appropriate selection of starting materials, enabling further derivatization. The synthetic route was optimized to allow the preparation of compound **19** on a multigram scale through a sequence that avoided chromatographic purification at all stages. Specifically, the Petasis borono–Mannich reaction conducted on a 36 mmol scale afforded the corresponding intermediate in 81% yield as the TsOH salt. An elimination–reduction sequence performed on a 23 mmol scale provided the subsequent intermediate in 96% yield with sufficient purity for direct use. Final hydrogenolysis of the N-benzyl protecting group on a 22 mmol scale afforded compound **19** in 94% yield, isolated as the TsOH salt [10].



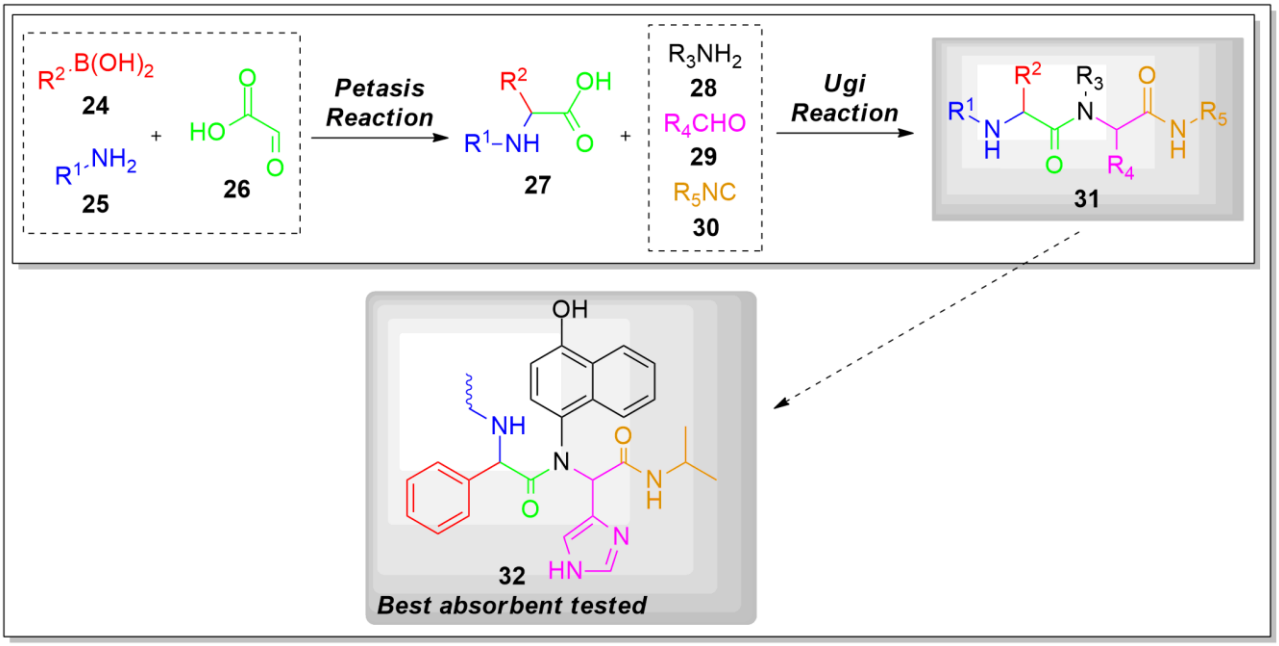
Scheme 4

Ranjan et al. (2021) developed a photocatalytic variant of the Petasis reaction utilizing free alkyl boronic acids as radical precursors through a single-electron transfer mechanism. The optimized reaction employed *p*-anisaldehyde, aniline, and cyclopentyl boronic acid as coupling partners in the presence of sodium bisulfate and 4-CzIPN as a photocatalyst under blue light irradiation. Initial experiments afforded moderate yields (45%), which were significantly improved (up to 76%) upon switching to $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ as photocatalyst and DMF as solvent (Scheme 5). Interestingly, the reaction also proceeded—though in lower yields in 1,4-dioxane, likely due to Lewis acid–base interactions between the boronic acid and the *in situ* generated imine intermediate. Control experiments confirmed that visible light, the photocatalyst, and an inert atmosphere were all essential for product formation, highlighting the radical pathway's crucial dependence on photoredox activation [11].



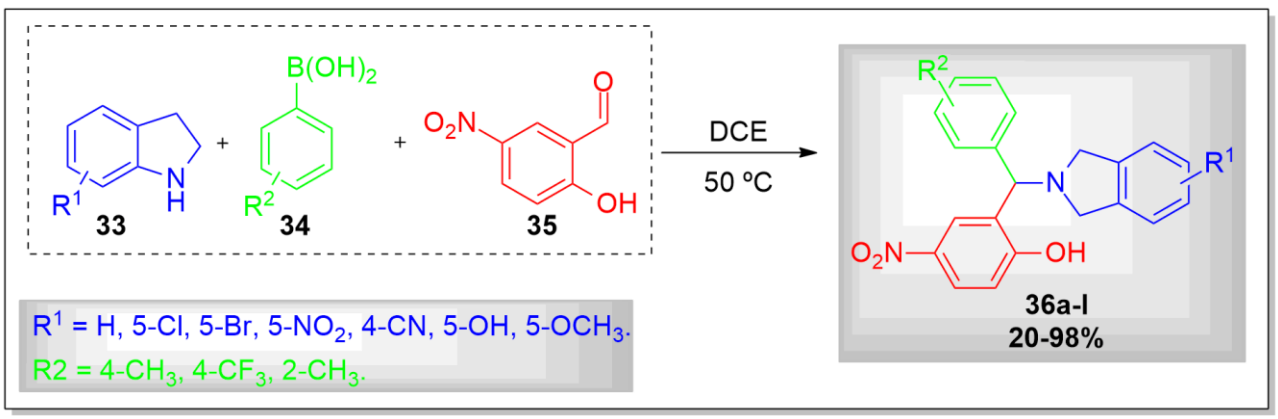
Scheme 5

Matos et al. reported the sequential use of Petasis and Ugi reactions to design and synthesize affinity adsorbents for antibody purification (Scheme 6). These combinatorial, one-pot methodologies enabled the rapid generation of a diverse library of solid-phase ligands inspired by both natural and engineered antibody-binding domains. Among the candidates, a lead adsorbent exhibited outstanding performance, allowing the single-step purification of full-length antibodies, antigen-binding fragments, and engineered single-domain antibodies from complex biological feedstocks under mild, non-denaturing conditions. The approach proved effective for antibodies from both human and non-human origins, including chicken IgY, overcoming limitations of conventional chromatographic platforms that often fail to accommodate the structural diversity of antibody subclasses. Due to its simple preparation, modular design, and broad applicability, this strategy underscores the potential of Petasis-derived scaffolds as a universal purification platform, expanding the reach of antibody-based technologies in both research and industrial bioprocessing [12].



Scheme 6

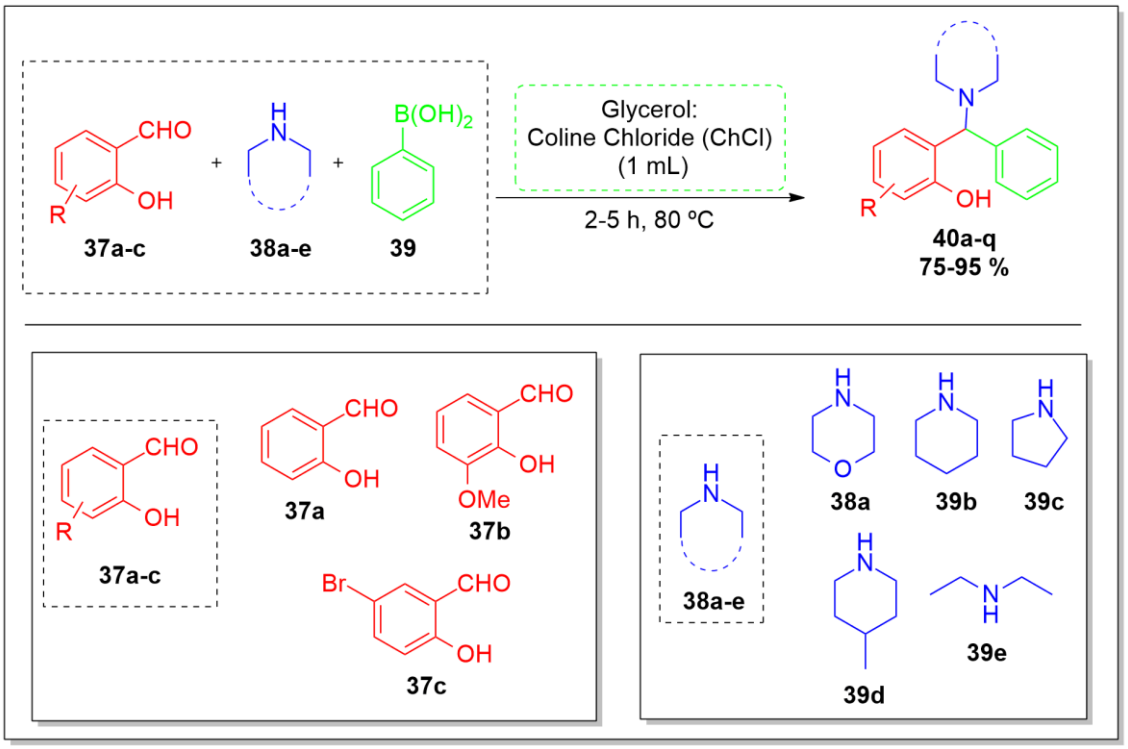
Aminoalkylphenols can be synthesized via the multicomponent Petasis reaction from 5-nitrosalicylaldehyde, substituted indolines, and boronic acids. Rimpiläinen et al. reported that some indolines can be obtained through the reduction of commercially available indoles using either sodium cyanoborohydride or triethylsilane in trifluoroacetic acid. The condensation of 5-nitrosalicylaldehyde with indolines in 1,2-dichloroethane, followed by reaction of the *in situ* formed iminium with appropriate boronic acids, affords the desired aminoalkylphenols in excellent yields (Scheme 7). This method was applied to three boronic acids (4-tolyl, 4-(trifluoromethyl)phenyl, and 2-tolyl), with products purified by column chromatography and characterized by NMR and HRMS. The antibacterial activity of the synthesized compounds was evaluated against Gram-positive strains, including *S. aureus*, *E. faecalis*, *S. epidermidis*, and *B. subtilis*. 4-Tolyl derivatives generally exhibited activity comparable or superior to previously reported compounds, with compound **33** (with 5-nitro group) and compound **34** (with 4-CF_3 group) showing the most potent effects. The presence of hydroxyl or methoxy groups at critical positions reduced activity, while the position and nature of substituents on the indolinyl ring influenced selective bacterial growth inhibition, demonstrating that small structural modifications can significantly affect antibacterial properties [13].



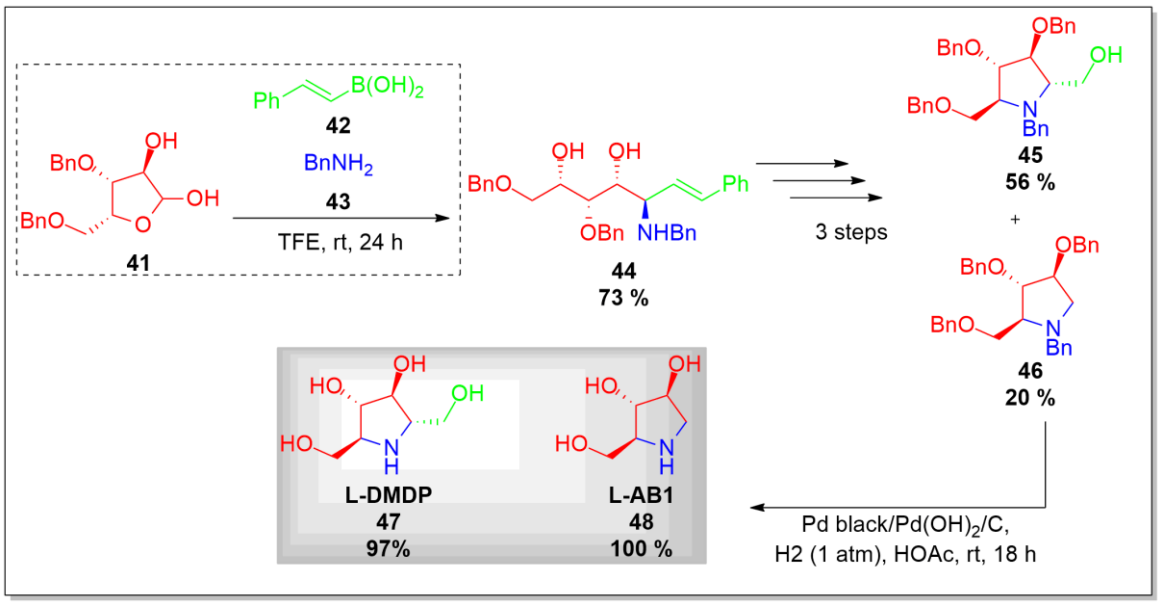
Scheme 7

Deep eutectic solvents (DESs) have gained attention as safe, inexpensive, renewable, and biodegradable alternatives to traditional organic solvents, aligning with the principles of green chemistry. In this context, efficient one-pot, three-component Petasis reactions of salicylaldehyde derivatives with various amines and boronic acids have been successfully carried out in a glycerol/choline chloride-based DES (Scheme 8). This approach affords a wide range of Mannich-type products in moderate to excellent yields under mild conditions and short reaction times. The methodology offers several advantages, including an environmentally benign and easily recyclable solvent, broad functional group tolerance, and operational simplicity. Notably, the DES system can be recycled up to four times without significant loss in yield, highlighting its potential for sustainable chemical synthesis [14].

The syntheses of L-AB1, L-DMDP, and several novel compounds, including (−)-phenethyl-L-AB1, (−)-100-deoxobroussonetine C, (−)-100-deoxobroussonetine E, (−)-10-epi-100-deoxobroussonetine E, and (−)-(*6S*)-120-hydroxydodecylmoranoline, have been reported starting from D-xylose (Scheme 9). These strategies employ the Petasis borono–Mannich reaction as a key step to stereoselectively introduce the amino group, followed by chemo- and regioselective O-mesylation to construct fully functionalized pyrrolidine moieties via intramolecular S_N2 cyclization [15].

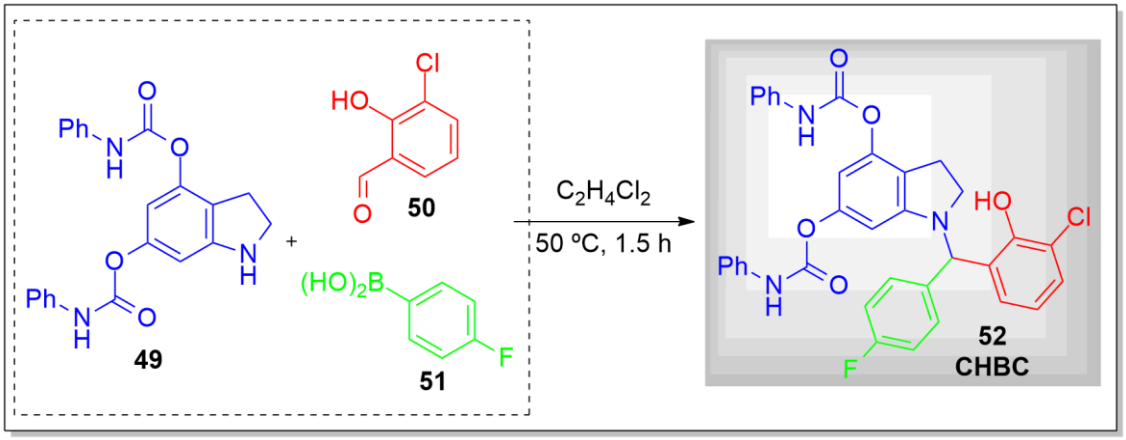


0Scheme 8



Scheme 9

The identification of novel ligands targeting G protein-coupled receptor 17 (GPR17) is a promising strategy for developing chemotherapeutic agents against glioblastoma multiforme (GBM). Nguyen et al. combined ligand- and structure-based cheminformatics with experimental validation to screen over 6000 indoline derivatives, leading to the discovery of a unique indoline-derived phenolic Mannich base as a potential GPR17 activator. Among the top hits, CHBC, which displayed a high docking score (glide score = –8.390), was synthesized *via* a multicomponent Petasis borono–Mannich reaction, showcasing the efficiency of this methodology in accessing structurally diverse aminoalkylphenols (Scheme 10). This synthetic approach allows for precise incorporation of amino and aryl substituents under mild conditions, highlighting the versatility of Petasis reactions in medicinal chemistry. Functionally, the CHBC–GPR17 interaction induces a rapid reduction of intracellular cAMP and Ca^{2+} levels, and CHBC exhibits dose-dependent cytotoxicity against GBM cells (IC_{50} = 85 μM), outperforming the known agonist MDL29,951. These results suggest that indoline-derived phenolic Mannich bases, accessible through Petasis-type multicomponent reactions, may serve as potent GPR17 agonists and represent promising leads for further pharmacological investigation in GBM therapy [16].



Scheme 10

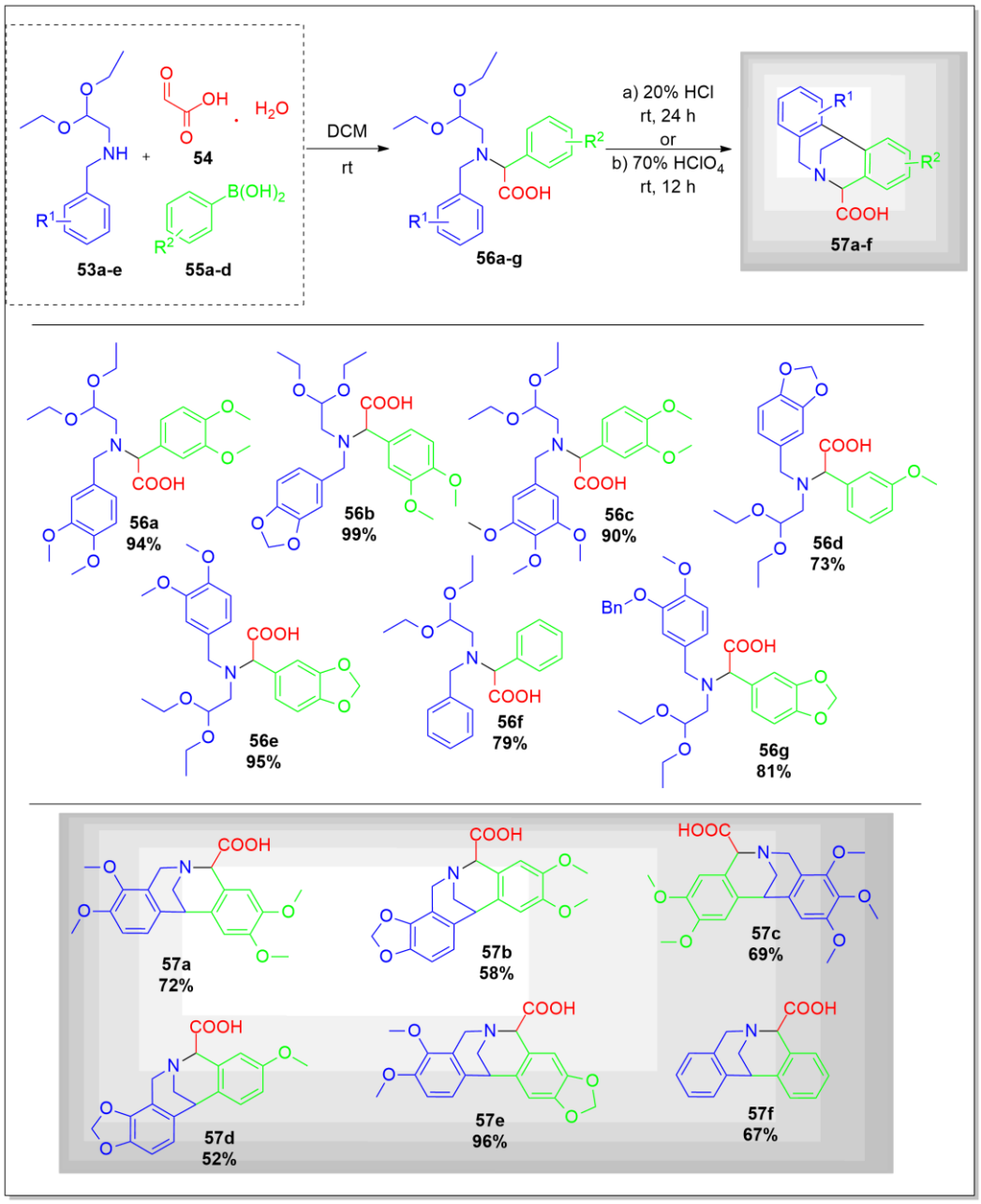
Grajewska et al. demonstrated a streamlined synthesis of tetracyclic tetrahydroisoquinoline derivatives, 7,12-dihydro-6,12-methanodibenzo[c,f]-azocine-5-carboxylic acids, *via* a three-component Petasis reaction using aminoacetaldehyde acetals with substituted benzyl groups. Subsequent Pomeranz–Fritsch double cyclization efficiently constructs the tetracyclic framework, providing a series of carboxylic acids in good yields (Scheme 11). The approach highlights the utility of multicomponent Petasis reactions as a versatile entry point for complex heterocyclic scaffolds and revealed an unusual reactivity in dilute HCl, yielding a phenylglycine derivative [17].

The development of photocatalyzed Petasis reactions has recently opened new avenues for the synthesis of functionalized amines under milder and more sustainable conditions. In this context, Oliva *et al.* (2021) reported a robust and scalable continuous-flow protocol that enables the efficient preparation of secondary amines via a light-driven Petasis coupling. The methodology employs alkyl boronic acids as radical precursors, allowing the transformation to proceed within 50 minutes under controlled flow conditions using a Vapourtec E-series reactor (Scheme 12). Compared to traditional batch Petasis reactions, this approach eliminates long reaction times and offers superior reproducibility, precise control of residence time, and enhanced safety when handling photochemical processes. The setup consists of two reagent reservoirs—one containing cyclopentyl boronic acid, *p*-anisaldehyde, and the photocatalyst $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$, and another containing aniline—both prepared under an inert atmosphere in a 3:1 DMF/acetonitrile solvent mixture (Scheme 12). The reaction coil (10 mL PFA) is irradiated by a 450 nm LED source and maintained at low temperature through a dry-ice–nitrogen cooling system. Overall, this continuous-flow design represents a significant advancement in multicomponent Petasis chemistry, demonstrating how photoredox catalysis can be effectively integrated into synthetic organic workflows for improved efficiency and scalability [18].

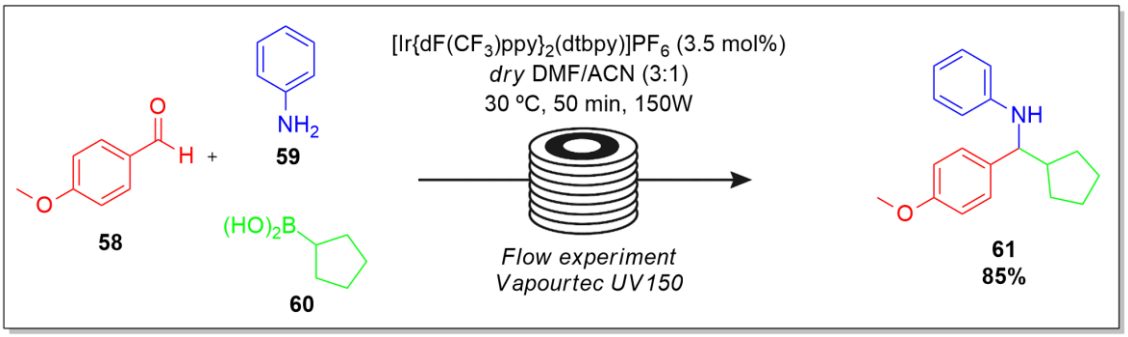
Inductive heating has emerged as a powerful and versatile indirect heating technique that has found extensive applications in chemistry and medicine. Traditionally used in industrial processes such as metal bonding, bending, and welding, this technology has recently been integrated into continuous flow chemistry, creating new opportunities for efficient and scalable organic synthesis. The combination of inductive heating and flow systems allows precise thermal control and rapid reaction rates. In this context, Kuhwald et al. employed a continuous-flow setup powered by inductive heating to perform various synthetic transformations, including a Petasis borono–Mannich reaction (Scheme 13). As reported by other studies, reactions such as Biginelli, Mannich, and Petasis have been successfully adapted to flow conditions, with steel beads acting as fixed-bed materials to achieve uniform inductive heating of glass reactors. Remarkably, the Petasis reaction under these conditions produced α-aminocarboxylic acids and phenolic derivatives in excellent yields—significantly higher than those obtained in conventional batch protocols [19].

Vytla et. al have expanded the classical scope of this reaction beyond secondary nonaromatic amines to include sulfonamides, amides, and hydrazides through photoredox catalysis. Under optimized conditions using $[Ir\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$ as photocatalyst and sodium hydrogen sulfate as additive, these substrates undergo efficient three-component coupling with benzaldehydes and alkyltrifluoroborates, affording α-substituted secondary amines in moderate to excellent yields (Scheme 14). The method proceeds under visible-light irradiation in DCE at room temperature, demonstrating broad substrate tolerance, including halogenated and electron-rich aldehydes, as well as cyclic and acyclic alkyl trifluoroborates. Mechanistic studies confirmed the radical α-alkylation pathway, while control

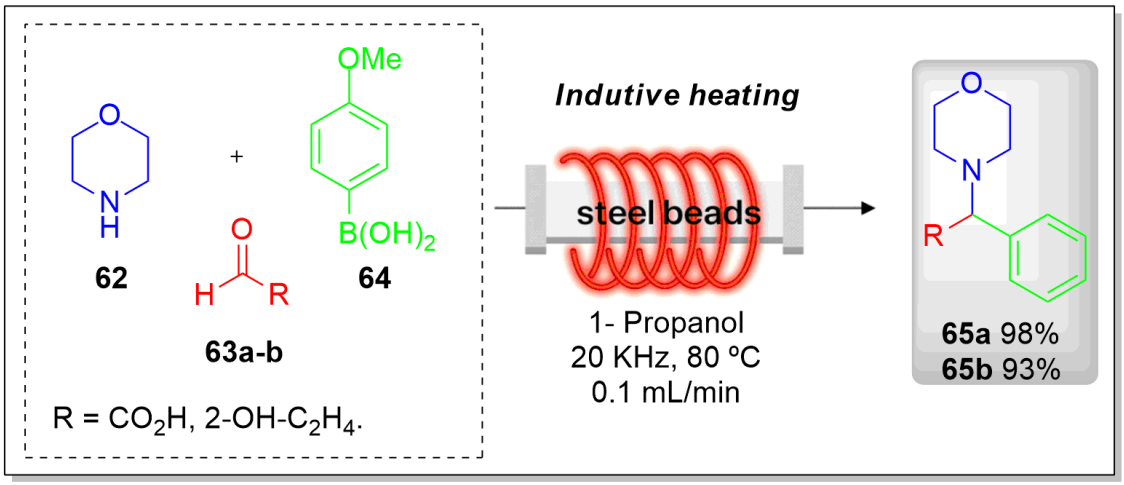
experiments validated the essential role of light, catalyst, and additive. The occurrence is successful even with the use of hydrazines, providing products with a nitrogenous portion different from traditional Petasis reactions [20].



Scheme 11



Scheme 12



Scheme 13

Scheme 14

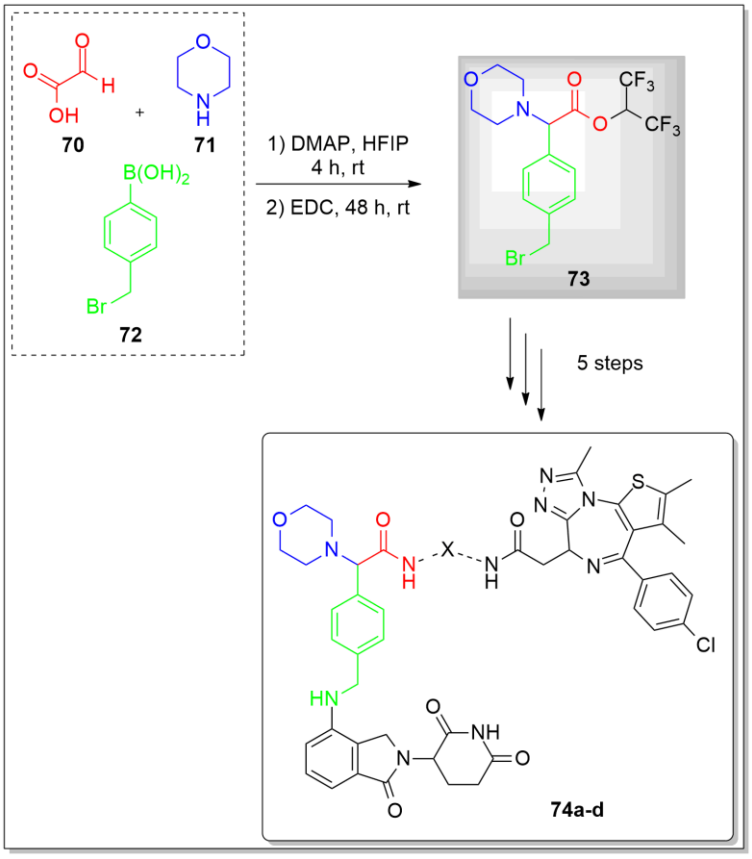
Recently, the Petasis borono–Mannich reaction was employed to access three-branched cereblon ligands capable of engaging multiple interactions on the protein surface, providing a suitable exit vector for derivatization. Using glycolic acid, morpholine, and 4-(bromomethyl)benzeneboronic acid in HFIP, the in situ generated amino acid was further esterified to afford key intermediates, which were regioselectively alkylated to yield high-affinity ligands (Scheme 15). Subsequent derivatization led to molecular glues and PROTACs targeting BRD4 and CRBN, demonstrating strong cellular activity and selective protein degradation. The approach underscores the utility of Petasis MCRs in drug discovery, enabling rapid generation of multifunctional scaffolds that are difficult to access via conventional stepwise synthesis [21].

A multistep synthetic protocol was employed to obtain a library of 4,7-dichloroquinoline and methyltriazolopyrimidine derivatives (Scheme 16). Key intermediates were generated through nucleophilic aromatic substitution and cyclization steps, followed by a one-pot multicomponent Petasis reaction to produce the final compounds, whose structures were confirmed by NMR and HRMS. These molecules were evaluated against drug-sensitive and drug-resistant *Plasmodium falciparum*, exhibiting submicromolar antimalarial activity and low cytotoxicity. In-silico studies using AutoDock Vina revealed binding free energies below −7.0 kcal/mol (PfFP2) and −8.0 kcal/mol (PfFP3), consistent with experimental inhibition of these cysteine proteases [22, 23].

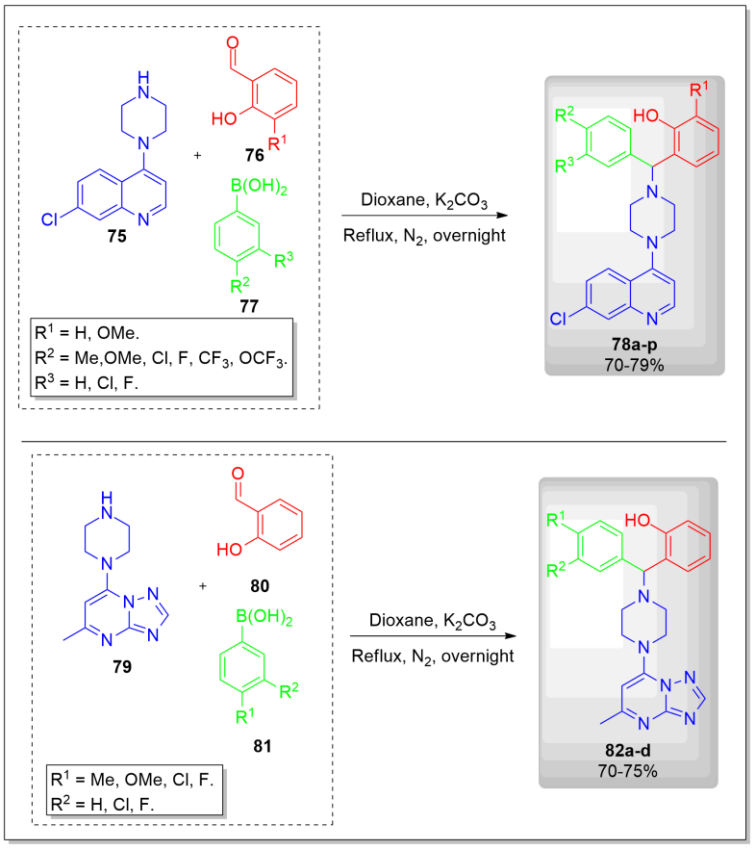
In response to increasing resistance to current antimalarials, Pal et al. designed and synthesized new tetrahydrobenzothieno[2,3-d]pyrimidine–acetamide hybrids using the multicomponent Petasis reaction as the key step, supported by a pharmacophore-combination strategy to enhance biological activity. Structural confirmation was achieved through NMR and mass spectrometry, and the synthesized hybrids (GA1–GA8 and A1–A8) showed strong *in-vitro* activity against both chloroquine-sensitive (3D7) and chloroquine-resistant (W2) *Plasmodium falciparum* strains (Scheme17). Molecular docking supported DHFR enzyme inhibition as the likely mechanism of action, while hemolysis and cytotoxicity assays revealed low toxicity toward human red blood cells and noncancerous cell lines. These results reinforce the potential of Petasis-derived hybrids as promising lead compounds for the development of new antimalarial agents [24].

In 2024, Koochakkhani *et al.* applied the Petasis multicomponent reaction as a key step to generate a small library of tetrahydroquinoline-based derivatives, aiming to explore their anticancer properties (Scheme 18). The strategy enabled the rapid assembly of eight new 2-((3,4-dihydroquinolin-1(2H)-yl)(aryl)methyl)phenol analogues, combining salicylaldehyde- and boronic acid–derived fragments in a convergent manner. Structural modifications focused on two regions of the scaffold: (i) a reduced dihydroquinoline fused to a cyclohexene ring, and (ii) variations on the attached aryl group. The nature of the substituent at the para-position of the aryl ring proved critical for biological activity. Among all synthesized molecules, the *p*-

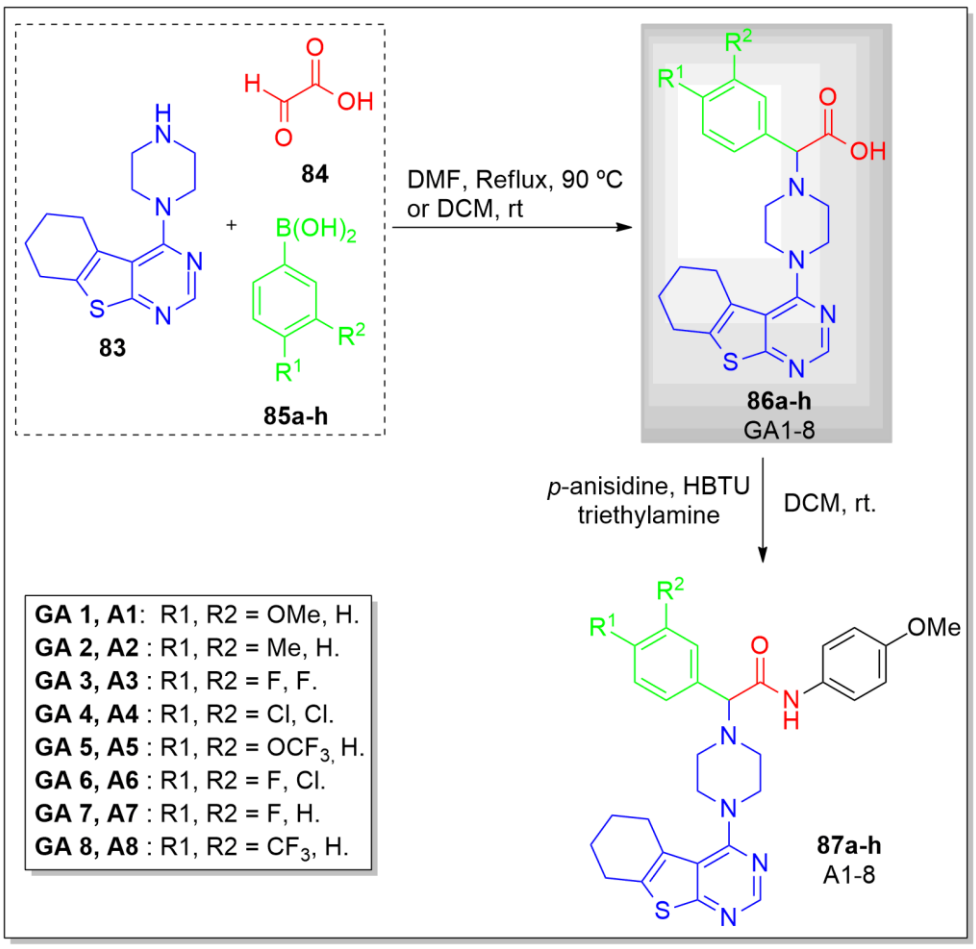
trifluoromethyl derivative displayed the highest cytotoxic effect against glioblastoma multiforme (GBM) cell lines, showing lower IC_{50} values in SNB19 and LN229 cells than the reference chemotherapeutic agent temozolomide [25].



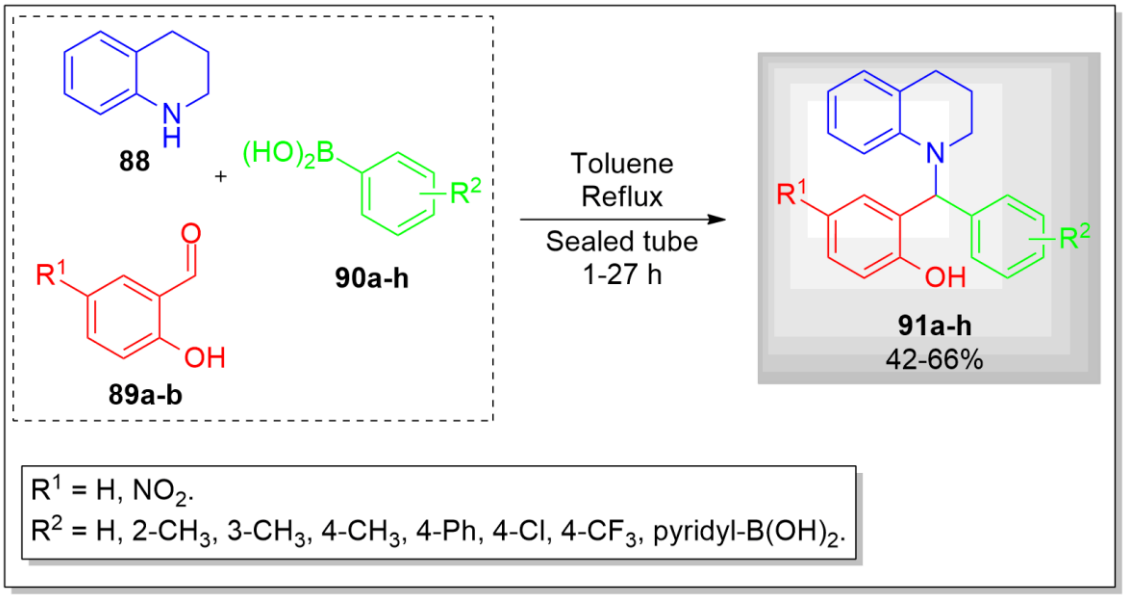
Scheme 15



Scheme 16

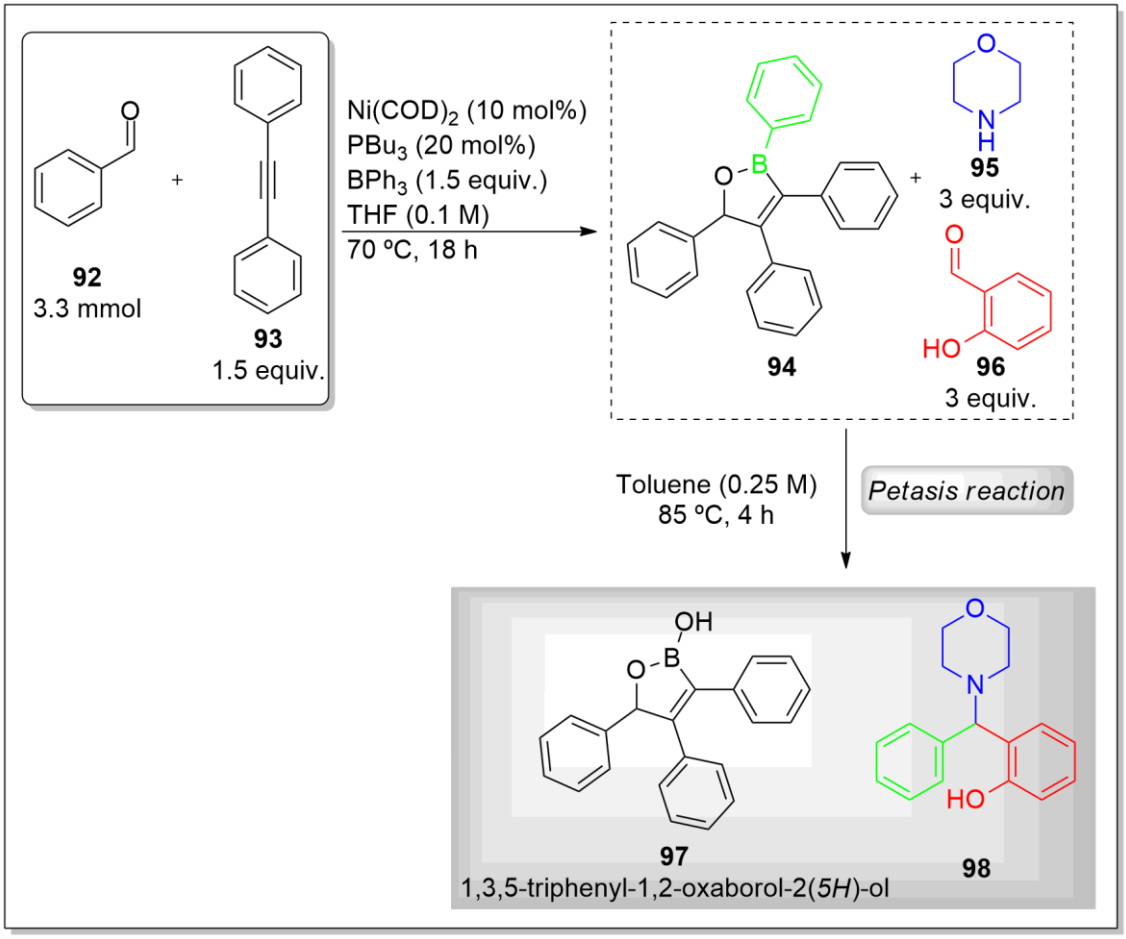


Scheme 17



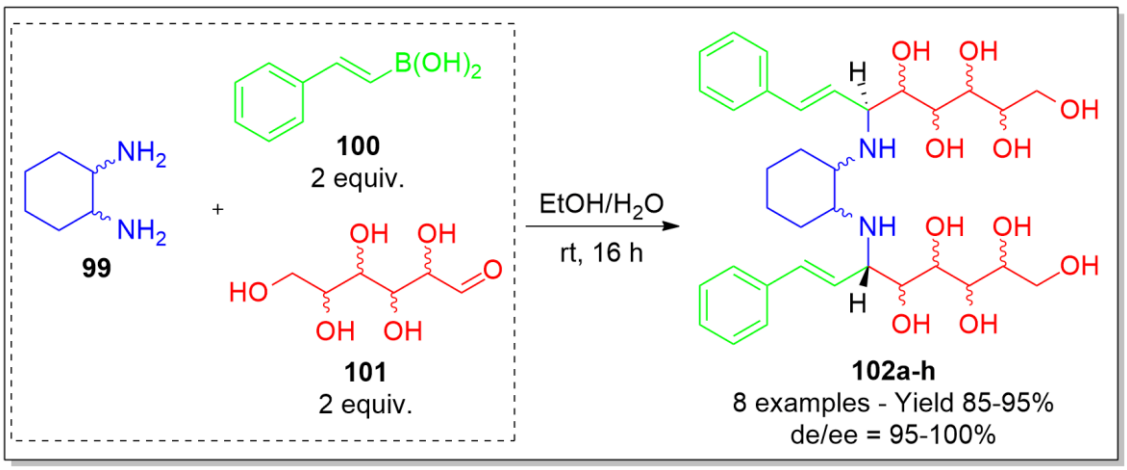
Scheme 18

Youmans and his colleagues developed a highly efficient strategy for obtaining oxaboroles from oxaboranes using a Petasis-type reaction mechanism. The approach involves selectively removing the phenyl group attached to the oxaborane, allowing this aryl fragment to actively participate in the reaction with the intermediate formed between morpholine and salicylaldehyde. Reactions carried out in toluene at 85 °C for 4 h afford densely substituted oxaboroles in yields reaching up to 93% (Scheme 19). This method demonstrates high selectivity for aryl transfer over vinyl transfer, providing exclusive migration of the phenyl group during the transformation. The strategy is compatible with a broad substrate scope, including derivatives of salicylaldehyde and boronic reagents, and enables scale-up to gram quantities without loss of efficiency [26].



Scheme 19

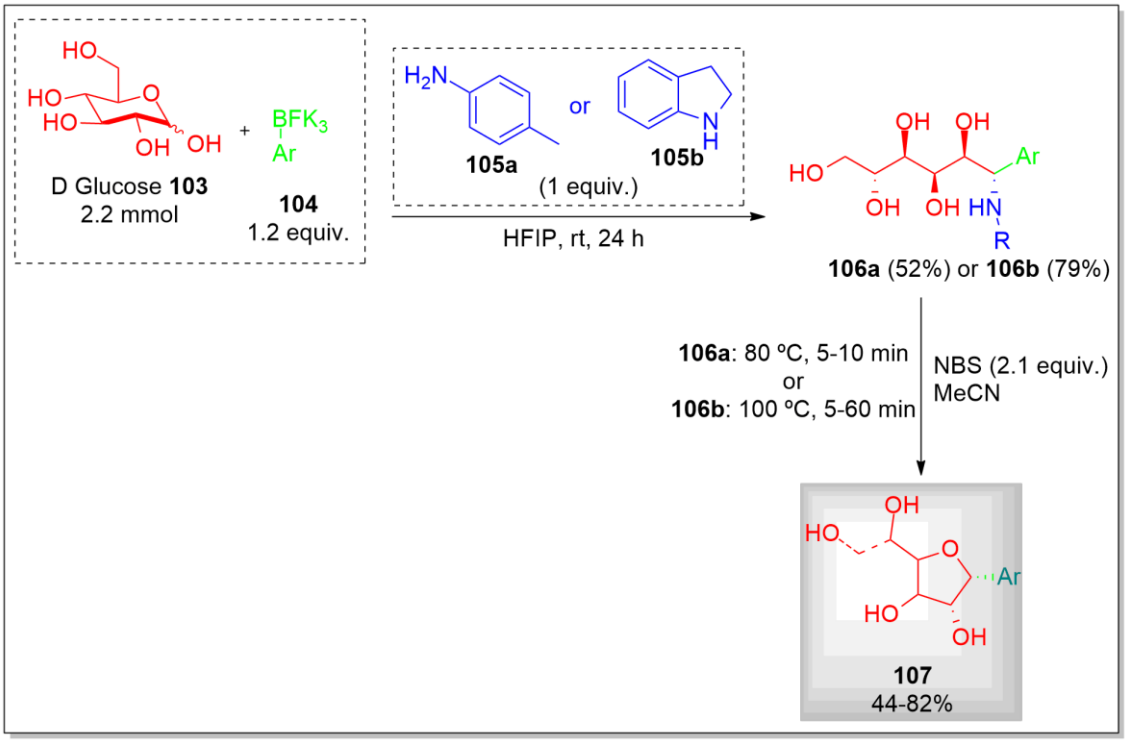
A diastereoselective one-pot dual Petasis reaction was achieved by combining sugars, styrenyl boronic acid, and *cis*/*trans*-1,2-cyclohexyldiamines, leading to the formation of bis-glyco-cyclohexylamines bearing multiple stereogenic centers. Optimal conditions were obtained using an ethanol/water (3:1) solvent mixture, providing 90% yield and 99.7% de/ee, whereas other solvents resulted in reduced solubility and diminished stereocontrol (Scheme 20). The stereochemical outcome arises from two cooperative factors: The hydroxyl-directed borylation, promoting anti-diastereoselectivity, and formation of a tetracoordinated *N,N*-chelated organoboron intermediate, favoring the syn-configuration. Structural confirmation was achieved through HMBC, HSQC, $^{1}H/^{13}C$ NMR spectroscopy, and single-crystal X-ray diffraction. Variation of both the sugar component and the diamine stereochemistry demonstrated the robustness of the method, consistently yielding highly stereodefined products. Overall, this dual Petasis strategy highlights the reaction's utility in the efficient construction of densely functionalized, stereochemically enriched cyclohexylamine architectures [27].



Scheme 20

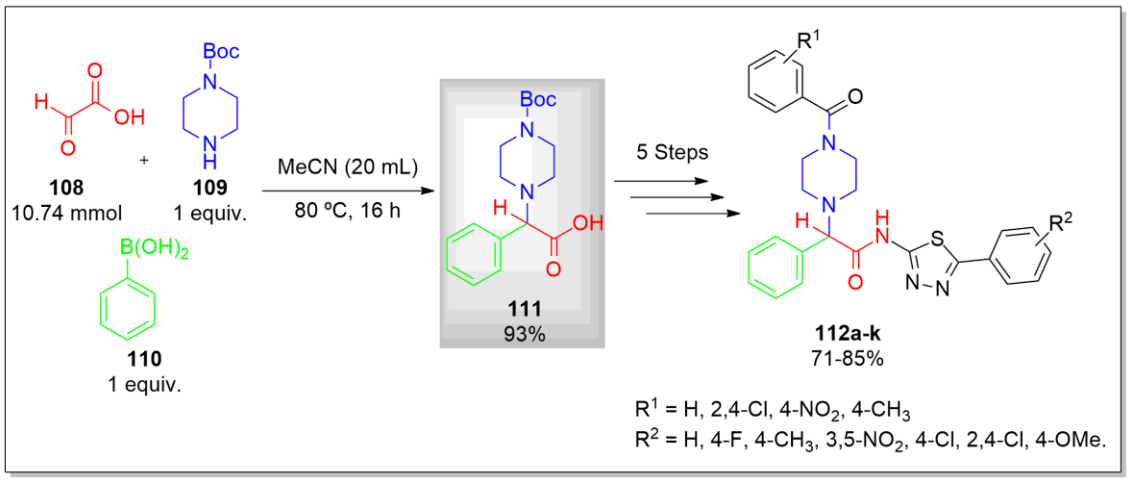
1,2-*cis* C-Aryl furanosides are well-represented in natural products and are associated with significant biological properties. However, obtaining the 1,2-*cis* configuration is synthetically demanding due to unfavorable steric and

stereoelectronic influences. Conventional approaches generally rely on multiple protection and deprotection steps, resulting in long synthetic sequences and low overall efficiency. In contrast, Wang et al. introduces a streamlined and broadly applicable strategy that generates 1,2-*cis* C-aryl furanosides starting directly from unprotected aldoses (Scheme 21). The process involves a Petasis multicomponent reaction that affords linear 1,2-*trans* 1-aryl polyhydroxyamines, followed by a deaminative cyclization. Upon halogenation, the amine moiety becomes activated, enabling an intramolecular stereoinvertive substitution of the C–N bond, ultimately producing the desired 1,2-*cis* C-aryl furanosides with outstanding chemo- and diastereoselectivity [28].



Scheme 21

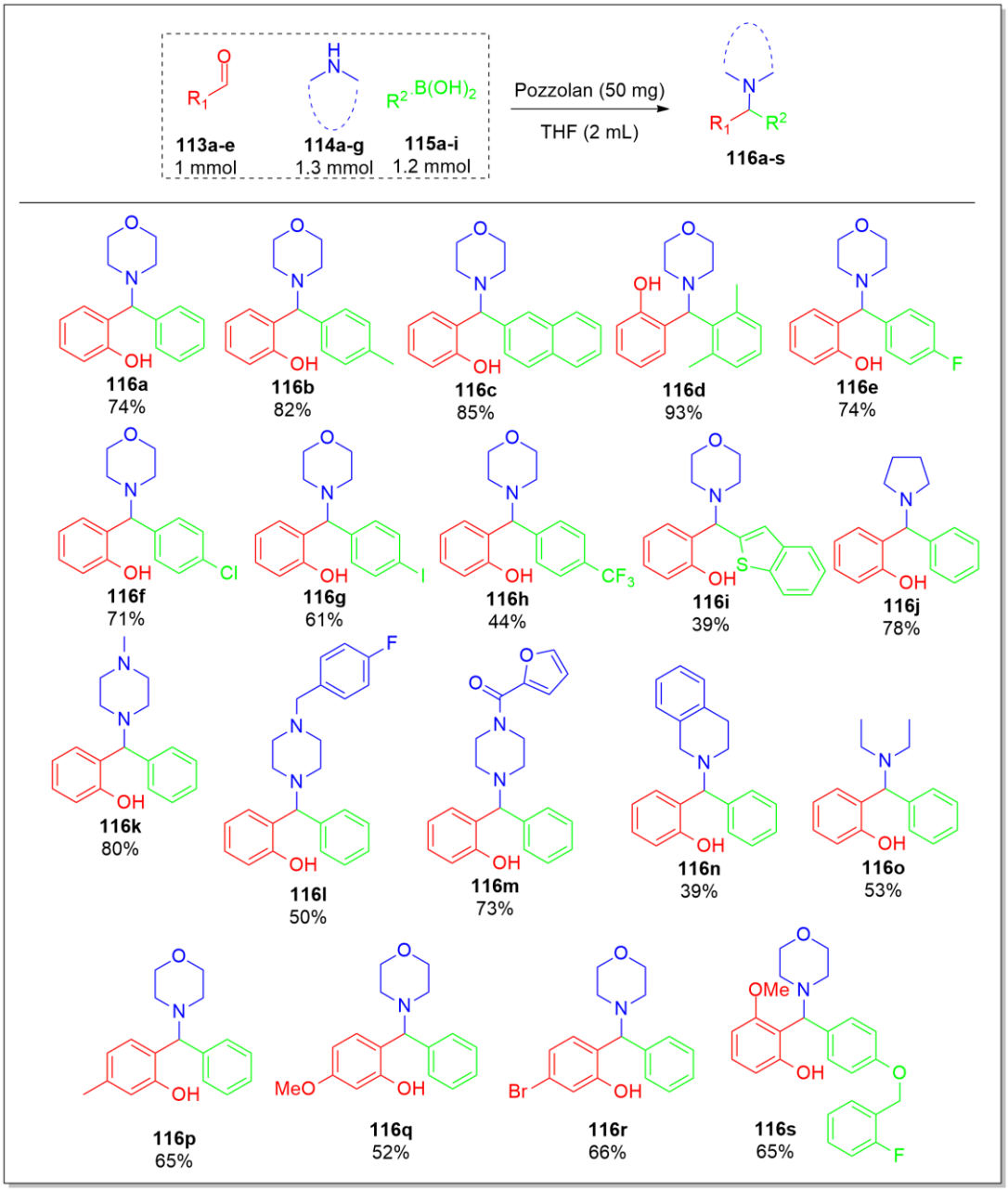
In the search for new therapeutic alternatives against drug-resistant tuberculosis (TB), Patel *et al.* designed and synthesized a series of piperazinyl-*N*-arylacetamide and 1,3,4-thiadiazole hybrid derivatives, whose precursor intermediates were obtained through a Petasis multicomponent reaction, emphasizing the strategic value of this transformation in generating structural diversity (Scheme 22). The final compounds were evaluated against *Mycobacterium tuberculosis* H37Rv using the Microplate Alamar Blue Assay (MABA), and 3 synthesized compounds displayed relevant inhibitory activity, with MIC values of 31.25 µg/mL, comparable to some standard anti-TB drugs. Molecular docking studies suggested strong interactions with DprE1, an essential enzyme for bacterial growth, while DFT calculations and molecular dynamics simulations confirmed the stability of the ligand–enzyme complexes [29].



Scheme 22

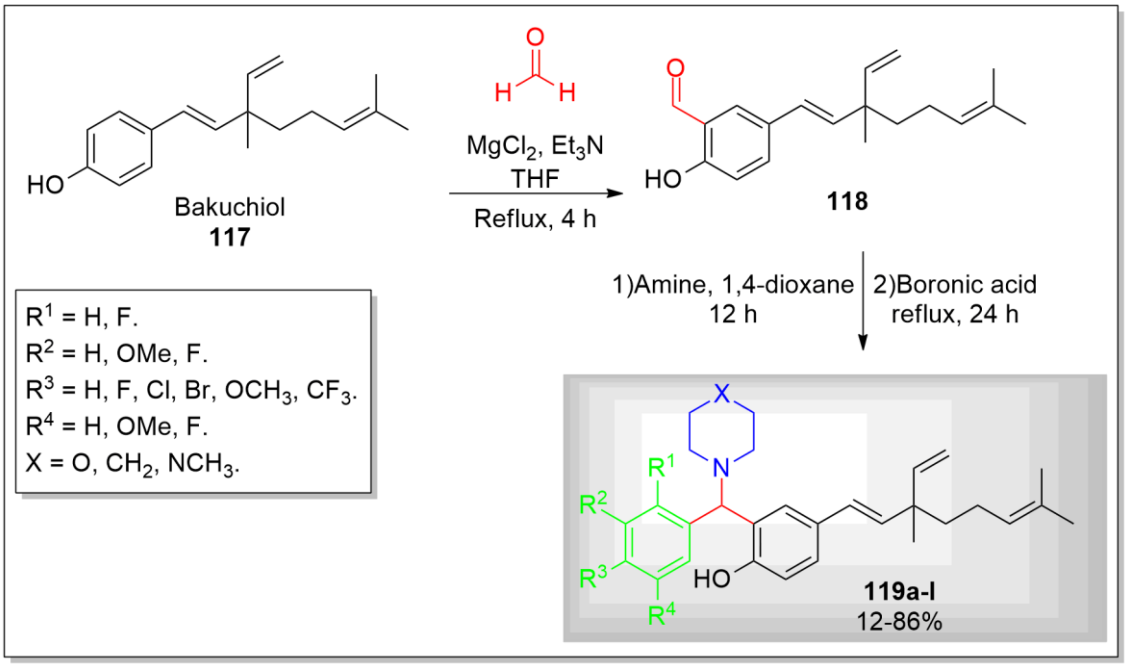
Heterogeneous catalysis is a rapidly expanding field aimed at creating more efficient, selective, and environmentally sustainable chemical processes, particularly through the use of catalysts derived from abundant and non-toxic materials. In this context, porous and natural inorganic materials have emerged as attractive candidates due to

properties such as high surface area, stability, versatility, and low cost. Boukachabia et al. demonstrated that pozzolan, a naturally occurring siliceous material, can be employed as a heterogeneous catalyst for the Petasis multicomponent reaction (Scheme 23). After structural and textural characterization (XRD, FTIR, BET, SEM), pozzolan exhibited excellent catalytic performance, enabling the synthesis of diverse alkylaminophenols with yields of up to 93%. The reaction was successfully scaled to gram-scale production, and the catalyst showed recyclability without significant loss of efficiency [30].



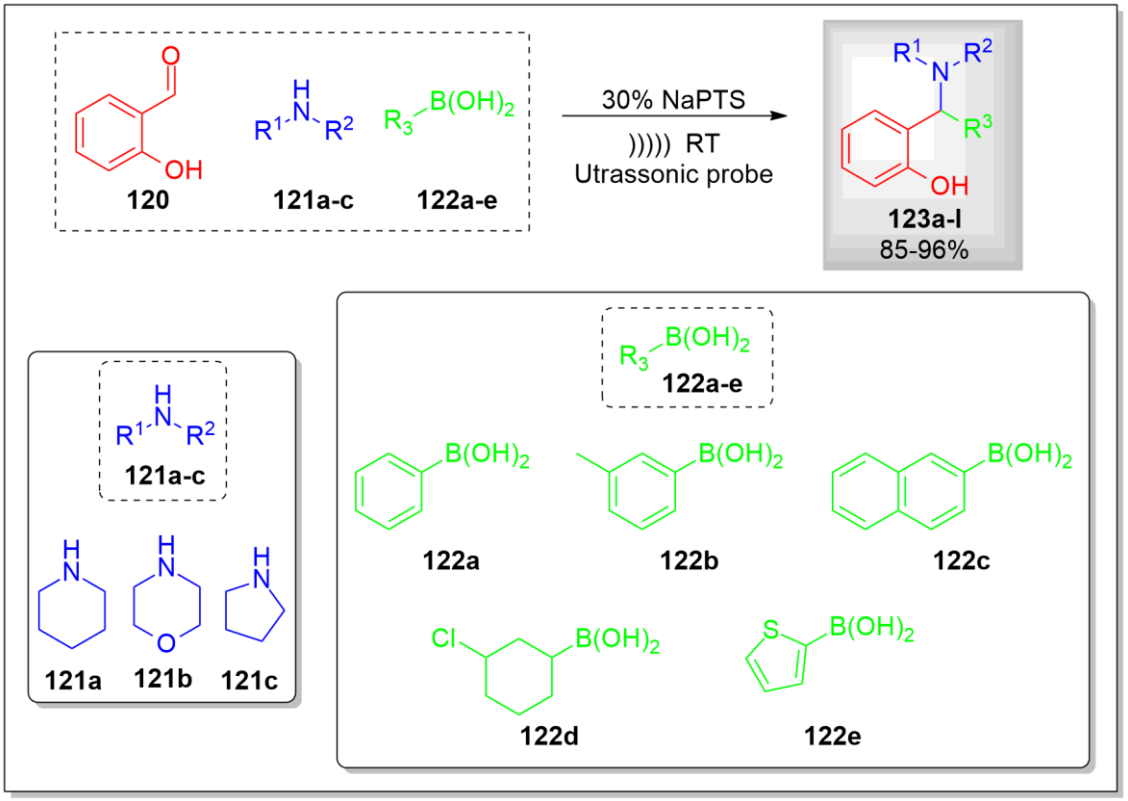
Scheme 23

Li and co-workers prepared a series of nineteen bakuchiol derivatives through a semi-synthetic route designed to improve the biological performance of this natural meroterpenoid (Scheme 24). The sequence began with the selective oxidation of bakuchiol, introducing an aldehyde at C-3 to form 3-formyl-bakuchiol, a key branching point for subsequent diversification. In the following step, the aldehyde intermediate participated in a Petasis multicomponent reaction, enabling rapid generation of compounds through the simultaneous incorporation of boronic acids and amines under mild conditions. This step proved crucial, as it allowed structural diversification in a single operational stage without the need for protecting groups. The structures of all analogues were unambiguously confirmed by ^{1}H-NMR, ^{13}C-NMR and HR-ESI-MS. Among the evaluated compounds, derivative 19 showed the highest antitumor potency against MDA-MB-231 breast cancer cells (IC_{50} = 4.13 μM), while maintaining significantly lower toxicity toward normal hepatocytes (Aml-12, IC_{50} = 31.60 μM), indicating promising selectivity [31].



Scheme 24

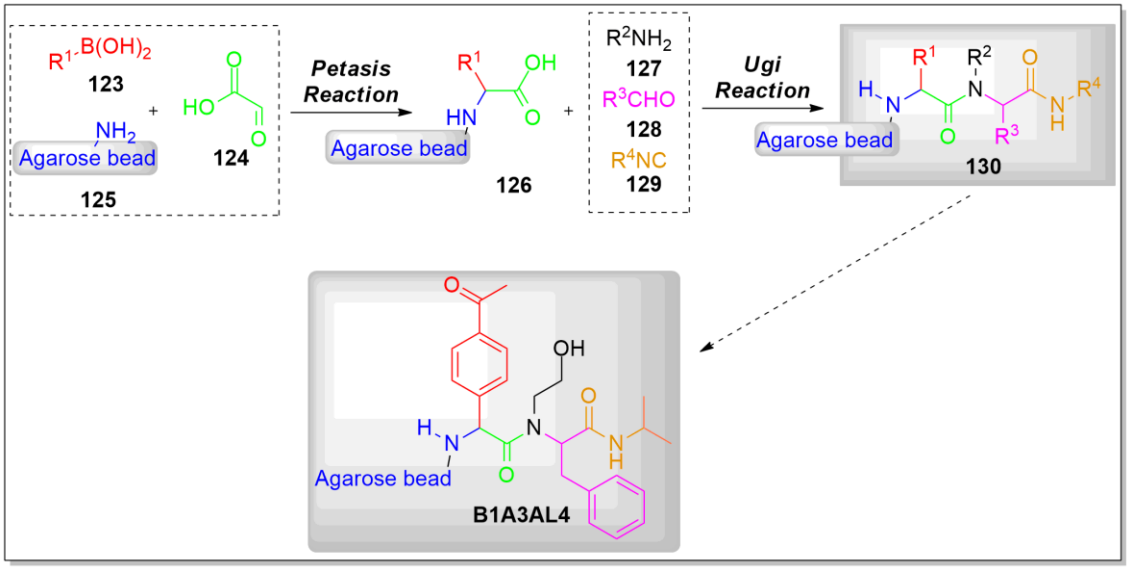
Recent studies by Pandit et al. have demonstrated a green Petasis protocol performed in an aqueous hydrotropic medium using ultrasonication, highlighting a significant advancement in eco-friendly synthesis. In particular, the use of sodium *p*-toluene sulfonate (NaPTS) as a hydrotrope markedly improved the solubility of organoboronic acids in water, leading to high yields (85–96%) within short reaction times (≈25 min) under mild conditions (Scheme 25). The reaction optimization revealed that a 30% NaPTS concentration provided the best results, balancing pH and solubilization to promote efficient coupling. Furthermore, the reaction displayed high atom economy and selectivity, with substrates bearing electron-donating groups on the boronic acid showing enhanced reactivity [32].



Scheme 25

In the work by Costa et al. (2025), the Petasis reaction was used as a key synthetic step in developing small peptidomimetic ligands designed to capture the SARS-CoV-2 spike protein. Through a smart combination of the Petasis and Ugi multicomponent reactions, the authors generated a diverse library of candidate molecules directly on a solid phase, which made the screening process both faster and more efficient. The Petasis reaction allowed the incorporation

of boronic acid units into the peptidomimetic framework, enhancing the ability of the ligands to interact selectively with the viral protein. Among the synthesized candidates, one compound (B1A3AL4) showed remarkable performance, achieving over 95% binding and around 73% recovery of the target protein (Scheme 26). This study illustrates how the Petasis reaction can go far beyond traditional organic synthesis, becoming a powerful tool in the design of biomimetic materials for biotechnological and biomedical applications [33].



Scheme 26

4. Conclusions

The studies discussed in this review clearly demonstrate the remarkable evolution of the Petasis–boronic multicomponent reaction from a convenient synthetic transformation to a broadly applicable strategy for molecular construction. Continuous advances in substrate design, catalytic systems, stereoselective methodologies, and sustainable reaction conditions have considerably expanded its scope while preserving the operational simplicity that has characterized this reaction since its introduction. These developments have enabled the efficient synthesis of structurally diverse and stereochemically defined compounds, supporting applications that extend from medicinal chemistry and carbohydrate synthesis to chemical biology and functional materials. As new reaction concepts and enabling technologies continue to emerge, further expansion of its synthetic scope and practical applications can be anticipated, ensuring that the Petasis reaction will remain an important component of the synthetic chemist's toolbox.

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