A General Three-Component Alkyl Petasis Boron-Mannich Reaction

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Abstract: Aryl amines are one of the most common moieties in biologically active molecules, and approximately 37% of drug candidates contain aromatic amines. Recent advancements in medicinal chemistry, coined as "escaping from flatland", have led to a greater focus on accessing highly functionalized C(sp^3)-rich amines to improve the physiochemical and pharmacokinetic properties of compounds. This communication presents a modular and operationally straightforward three-component alkyl Petasis boron-Mannich (APBM) reaction that utilizes ubiquitous starting materials, including amines, aldehydes and alkyl boronates. Overcoming the long-standing synthetic hurdle of accomplishing the Petasis boron-Mannich reaction with alkyl boronate coupling partners was achieved via the formation of an electron donor-acceptor (EDA) complex and sequential radical-radical coupling. By adapting this transformation to high-throughput experimentation (HTE), it offers rapid access to an array of diverse C(sp^3)-rich complex amines, amenable for facile drug candidate development.

Main Text:

Introduction

Nitrogen-containing moieties, specifically aryl- and heteroaryl- amines (e.g. **1**), are omnipresent in state-of-the-art high-throughput screening (HTS) libraries and bioactive molecules[1]. The synthetic ease of forming the C–N bond with ubiquitous aromatic coupling partners[2] has greatly facilitated their prevalence. Recent advancements in medicinal chemistry have shifted focus towards compounds with high fraction of C(sp^3)-rich, as they exhibit improved physicochemical and pharmacokinetic properties (Figure 1A). This has led to an exploration of methods to access three-dimensional chemical spaces[3, 4], including novel methods to make caged hydrocarbons, such as bicyclopentanes[5] and cubanes[6]. Despite these advancements, efficient methods to access complex, C(sp^3)-rich amines (e.g. **2**-**4**) remain rare.[7] Conventional two-component methods for their synthesis include transition metal-catalyzed C–N cross-coupling reaction [7], reductive amination of aldehydes or ketones[8], *N*-alkylation of amines[9], and imine addition[10,11] (Figure 1B). While these methods offer access to simple alkyl amines, they pose challenges in rapidly synthesizing more complex aliphatic amines and constructing amine libraries for structure activity relationship (SAR) studies[12]. In recent decades, the versatility of imines has led to a significant progress in the development of multicomponent reactions as flexible routes to amine synthesis[13, 14], such as aza–Morita–Baylis–Hillman[15], Mannich[16], Petasis boron-Mannich (PBM)[17] and Strecker[18] reacion. Among these, the three-component PBM reaction, first reported in 1993 [19], has been an attractive method for medicinal chemists due to its ability to use widely available building blocks including amines, aldehydes, and aromatic boronic acids to rapidly access diverse C(sp^2)-rich chemical space[17]. However, PBM reaction remained underutilized because the substrate scope has been mainly restricted to activated aldehydes with adjacent heteroatoms as directing groups and aryl or alkenyl boronic acids. As most reactions of this class are mediated by a $2e^-$ mechanism where alkyl migration is unlikely to happen[20], extending this reactivity to unactivated alkyl boronates, to "escaping from the flatland" [3], has been a challenge. A strategy that combines the diversity of a general PBM reaction with alkyl boronic coupling partners exponentially increases the accessibility of C(sp^3)-rich alkyl amines (Figure 1C, m×n×p hypothetical products in a 3D library). Such a method would enable holistic structural diversity coverage for complex aliphatic amines that could facilitate the comprehensive SAR probing and the development of drug candidates[13]. Despite some recent advance of PBM reaction with alkyl boronates have been achieved through radical addition process, where stabilized imine intermediate is often required[11], a more general alkyl Petasis boron-Mannich (APBM) reaction is highly desirable.

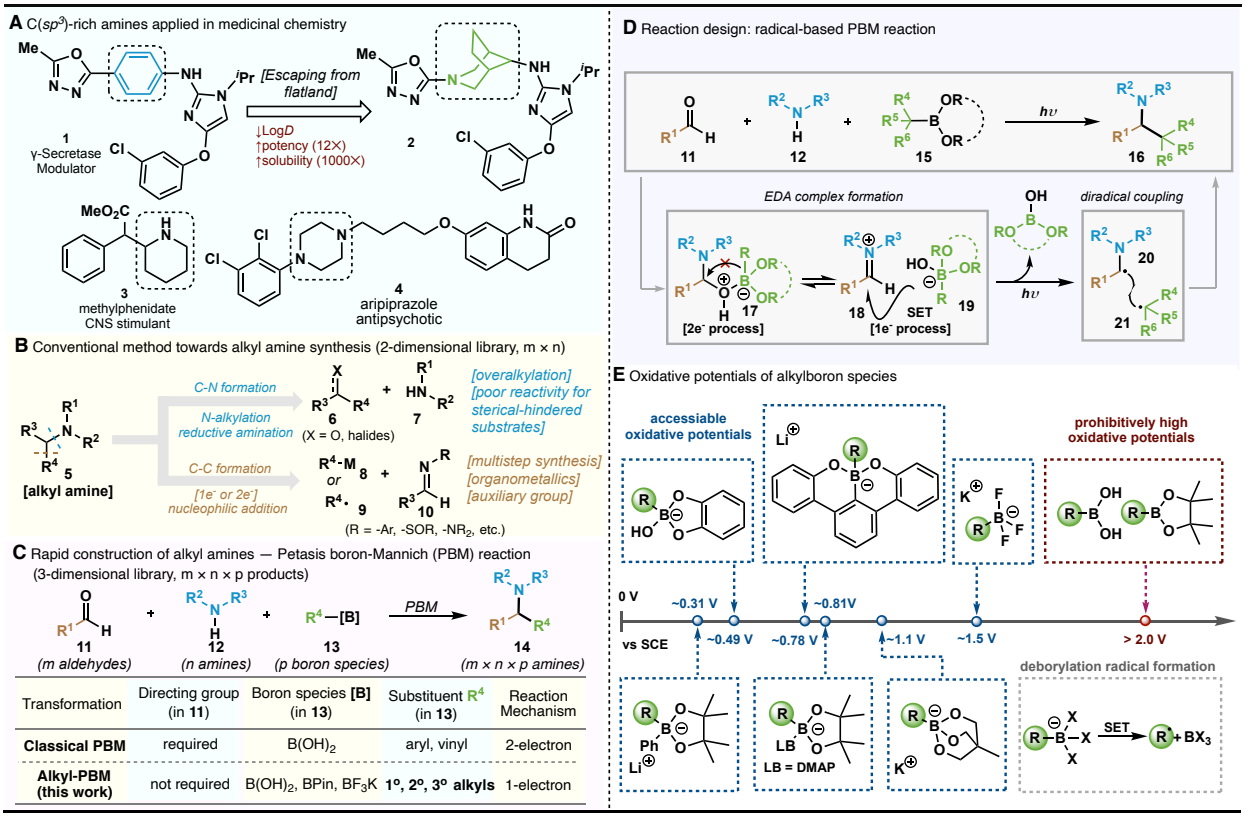


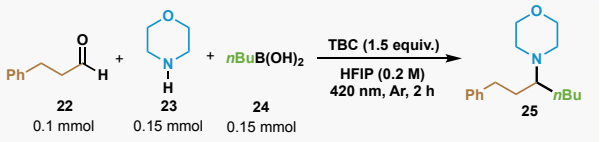
Fig. 1. Alkyl Petasis boron-Mannich reaction. A. C(sp^3)-rich amines applied in medicinal chemistry; B. Conventional method towards alkyl amine synthesis; C. Rapid construction of alkyl amines --- Petasis boron-Mannich (PBM) reaction; D. Reaction design: radical-based alkyl Petasis boron-Mannich reaction; E. Oxidative potentials of alkylboron species.

Instead of previous elegant reports using alkyl radicals addition to iminium ions to access alkyl amines[21,22], we posed an alternative hypothesis that involves an electron donor-acceptor (EDA) complex and sequential radical-radical coupling process. This tactic aims to provide a universal solution for the APBM reaction (Figure 1D). On investigating the oxidative potentials of various alkylboron ate-complex species (Figure 1E)[23], catechol installation was identified as a mild method to activate boron without the need for strong bases, inspired by Renaud and Aggarwal's seminal studies[24]. Therefore, the corresponding alkyl boronate complexes with low oxidative potentials (E_p = ~ 0.49 V, versus a saturated calomel electrode (SCE)) were anticipated to undergo facile single-electron oxidation (Figure 1E). Since the photo-excited iminium ions were found to function as strong oxidants[25], it was postulated that the *in-situ* generated catechol boron ester ate-complexes could be oxidized, resulting in the generation of alkyl radicals. These alkyl radicals would subsequently undergo radical-radical coupling with α-amino radicals to yield the desired aliphatic amines (Figure 1D).

Identification of alkyl Petasis boron-Mannich (APBM) reaction

To evaluate our hypothesis, we conducted a model reaction with 3-phenylpropanal (**22**), morpholine (**23**) and *n*-butylboronic acid (**24**). Initially, the standard PBM condition without any additive under photo irradiation was attempted, however it was unsuccessful (Table 1, entry 2).

Through extensive screening of reaction conditions, we identified an effective protocol that resulted in the formation of the desired amine (**25**) with an 85% isolated yield (NMR yield 94%) within 2 h (Table 1, entry 1). This operationally simple process involved mixing a solution of the three starting materials (**22**, **23** and **24**) with the additive *tert*-butylcatechol (TBC) in hexafluoroisopropanol (HFIP) as the solvent, irradiated with 420 nm light. In this process, *n*-butylboronic acid was hypothesized to be converted to boronic *tert*-butylcatechol ester (Bcat) *in situ*. Detailed optimization procedures can be found in the Supporting Information, with selected experiments summarized in Table 1. The utilization of less electron-rich catechols (entries 3, 4), or a reduced amount of TBC (entry 5) led to lower yields. Light irradiation was crucial, as exemplified in entries 6-11 for substrate **25**, with 420 nm being the optimal wavelength. Other polar solvents, when used instead of fluoro-substituted alcohols, afforded little product formation (entries 12, 13). The acidity of HFIP presumably facilitated the formation of the proposed EDA complex intermediate **20** from iminium ions and *n*-BuBcat intermediate. The reaction did not require an inert atmosphere, but increased yields were observed after degassing of the reaction mixture (purging with argon). (entry 14). Furthermore, we successfully extended this transformation to more commercially accessible alkyl trifluoroborate salts and boron pinacol esters, highlighting the synthetic versatility of this method. The alkyl trifluoroborate salts exhibited similar reactivity as boronic acids (entry 15). However, a longer reaction time (12 h instead of 2 h) was required for boron pinacol esters, potentially owing to a slower generation of *n*BuBcat species, as a catechol/pinacol ligand exchange was involved (entry 16).



Entry	Deviation from above	Yield (%)[a]
1	none	94 (85)[b]
2	w/o TBC	0
3	catechol instead of TBC	72
4	4-Cl-catechol instead of TBC	56
5	1.0 equiv. TBC	70
6	w/o *hν* (420 nm)	12
7	under dark condition	<5
8	300 nm instead of 420 nm	24
9	365 nm instead of 420nm	80
10	390 nm instead of 420nm	94
11	456 nm instead of 420nm	93
12	CH_2Cl_2, MeOH, DMF instead of HFIP	0
13	TFE instead of HFIP	15
14	Air instead of Ar	77
15	*n*BuBF$_3$K instead of **3a**, 12 h	94
16	*n*BuBPin instead of **3a**, 3 equiv. TBC, 12 h	62

[a] Yield determined by NMR analysis with CH_2Br_2 as an internal standard; [b] isolated yield; TBC, 4-*tert*-butylcatechol, HFIP, hexafluoro-2-propanol; TFE, trifluoroethanol.

Table 1. Optimization of the three-component alkyl Petasis boron-Mannich reaction. a) Yield determined by NMR analysis with CH_2Br_2 as an internal standard; b) isolated yield. TBC, 4-*tert*-butylcatechol, HFIP, hexafluoro-2-propanol; TFE, trifluoroethanol.

Scope of aldehydes, amines and boronic reagents.

The robust nature of this three-component APBM reaction was demonstrated by the successful synthesis of approximately 70 amines (Figure 2, Panels A–C). The applicability of this method was initially assessed with diverse boronic reagents, coupled with compounds **22** and **23** (Figure 2, Panel A). A variety of alkyl boronic reagents, such as primary (**25**), cyclic (**28, 30, 31**) branched alkyls (**38**), and tertiary (**29**), were seamlessly integrated with high yields. Interestingly,

compound **30** was obtained with identical yield under standard conditions in the absence of light, indicating irradiation is not prerequisite for every substrate (See Supporting Information for details). The reaction also demonstrated excellent functional group tolerance. Boronic species with ether (**32**), sulfide (**33**), halide (**33**), pyrazole (**34**), free alcohol (**35**), ketone (**36**), olefin (**37**), and ester (**38**) were all compatible with this transformation, giving the corresponding amines with moderate to good yields. Benzene isosters, such as bicyclo[1.1.1]pentane (**39**), adamantane (**40**) could also be efficiently installed, which can potentially providing an approach for rapid scaffold hopping of bioactive phenyl amines synthesized with classic PBM reaction using phenyl boronic acids. Sterically hindered quaternary carbons and architecturally complex structures, often incorporated in bioactive small molecules to enhance potency, selectivity, and metabolic stability through enriching three-dimensionality[4], were also addressed. Utilizing tertiary trifluoroborate salts, primarily accessed through our hydrazone coupling route[26], we were able to synthesize corresponding alkyl amines containing a quaternary center with C(sp^3)-rich chains tethered with diverse functional scaffolds. These include tetrahydropyran (**41**), linear and cyclic amines (**42**, **44**), terminal alkyne (**43**), heteroaromatics (**45**-**47**), and anisole (**48**), showcasing significant tolerance of steric hindrance around the boron center.

Moreover, this protocol facilitated the access to a wide array of functionalized secondary and tertiary saturated amines. A variety of primary amines were employed in this transformation to prepare corresponding secondary amines, demonstrating tolerance for diverse functional groups such as nitriles (**50**), protected amines (**51**), free alcohols (**52**), and heteroarenes (**54-56**). Secondary amines featuring more sterically hindered moieties, including cyclohexyl (**57**), *tert*-butyl (**58**), and 1-adamantyl (**59**) were all amenable to this transformation. It is noteworthy that no overalkylation products were detected in any of the presented cases, underscoring the excellent selectivity for secondary amine synthesis. Furthermore, a range of tertiary amines were obtained from the corresponding secondary amine precursors. Acyclic amines such as *N*-methyl benzyl amine (**60**), *N*-alkyl anilines (**61**), *N,N*-diallylamine (**62**), bis(2-chloroethyl)amine (**63**) were successfully converted into tertiary alkylamines with good yields. Cyclic amine derivatives of varying ring sizes, including azetidines (**64**), piperidines (**65**), (hetero-) piperidines (**66**, **67**), pyrrolidine (**68**), benzo-fused pyrolidines (**69**, **70**), and aza-norborane (**71**) were also effective coupling partners, resulting in good to high yields. The reaction with (*R*)-1-phenylethylamine (**72**) was highly productive, albeit with low diastereoselectivity control. Higher diastereoselectivity was observed with proline type amines featuring more rigid and bulky substituents (**73**, **74**). The structure of compound **74** was unambiguously assigned by single-crystal X-ray analysis of its debenzylated derivative (see the Supporting Information).

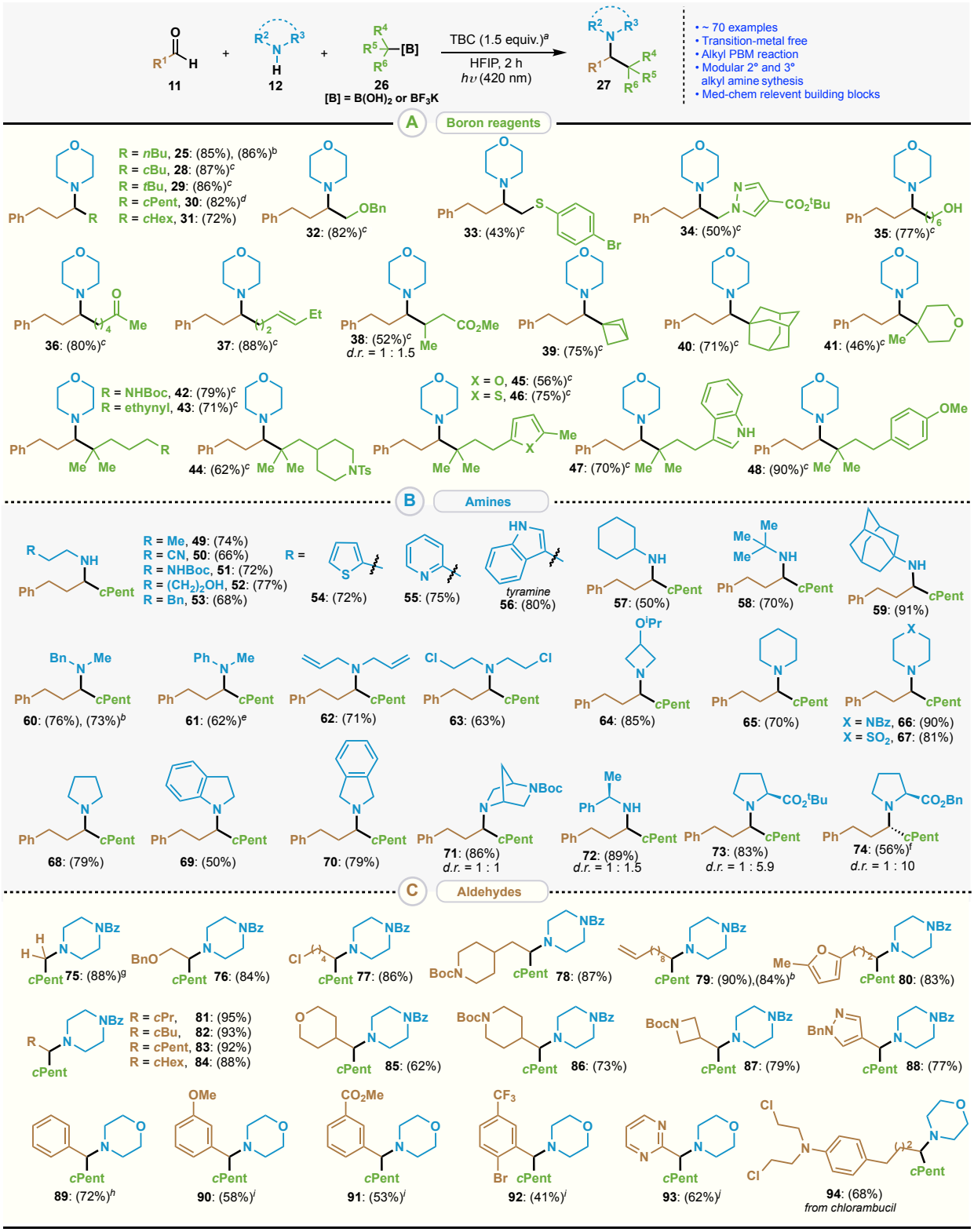


Fig. 2. Substrate scope of the three-component APBM reaction. A. Scope of boronic reagents; B. Amine scope; C. Aldehyde Scope. a) Aldehyde (0.1 mmol), amine (1.5 equiv.), $RB(OH)_2$ (1.5 equiv.), TBC (1.5 equiv.), HFIP (0.2 M), 420 nm, 2 h; b) 10 mmol scale; c) aldehyde (0.1 mmol.), amine (1.5 equiv.), RBF_3K (1.5 equiv.), TBC (1.5 equiv.), HFIP (0.2 M), 420 nm, 12 h; d) in the

absence of light; e) aldehyde (1.5 equiv.), amine (0.1 mmol); f) the structure of **74** was determined by single crystal X-ray analysis of its hydrolysis derivative hydrochloride salt; g) aldehyde (2.0 equiv.), amine (0.1 mmol); h) 390 nm, 12h; i) 16 h; j) 12 h.

The study began with the evaluation of aldehydes using formaldehyde aqueous solution, the most elementary aldehyde. As an appealing CH_2 synthon, formaldehyde successfully bridged the amine and boron species (**75**), leading to the homologation/amination of alkyl boronic acids and demonstrating the water compatibility of this process. The coupling process with a diverse set of primary aldehydes (**76-80**) was also successful, showcasing tolerance with numerous functional groups. Secondary aldehydes, particularly with saturated cyclic and heterocyclic rings, exhibited good reactivity, generating several sterically hindered tertiary amines (**81-87**). The scope of this APBM transformation was further expanded to include substituted benzaldehydes (**89-92**) and heteroaryl aldehydes (**88, 93**), both of which were compatible under these conditions, yielding (hetero)benzylic tertiary amines with moderate to good yields. This method was effectively applied to swift derivatization of chlorambucil (**94**), where an analogue was prepared with 68% yield.

Overall, the broad substrate scope, coupled with robust functional group compatibility, underscores the mildness and operational simplicity of this protocol. Additionally, scale-up syntheses with multiple substrates (**25**, **60**, **79**, on 10 mmol) showed consistent reaction outcomes without affecting the isolated yields. The transformation enables the synthesis of a wide range of C(sp^3)-rich alkyl amines, which would be challenging or inaccessible via conventional methodologies.

Construction of C(sp^3)-rich alkyl amine library

The synthetic utility of this three-component coupling is especially evident in the compound library preparation. Evaluating the potential of synthetic method to access diverse chemical space[27] is crucial for SAR exploration in medicinal chemistry.[28] Therefore, parallel library synthesis using high-throughput experimentation (HTE) represents an efficient approach. To assess the HTE compatibility of this method, a 96-well alkyl amine 3D library expansion screening was designed. Judicious selection of 4 aldehydes (**X1**–**X4**), 4 amines (**N1**–**N4**) and 6 organoboron (**B1**–**B6**) building blocks led to 96 enumerated complex amine structures (see Supplementary Information Section 'Alkylamine library syntheses' for details). These building blocks encompass an array of diverse electronically and sterically differentiated coupling partners: 1° (**B1**, **B2**), 2° (**B3**, **B4**) and 3° (**B5**, **B6**) alkylboron reagents, (hetero)anilines (**N1**, **N2**) and alkylamines (**N3**, **N4**), heteroaryl (**X1**, **X2**), 1° (**X3**) and 2° alkyl (**X4**) aldehydes (Figure 3B). Many of these motifs are prominent in medicinal chemistry, such as amino acid (**N4**) and saturated heterocycles (**N3**, **X4**). The reactions were executed in a 96-well plate with a 420 nm LED array, and LC-MS analysis confirmed formation of desired products in 66 out of the 96 entries (Figure 3A). This success rates is comparable to that of other library chemistries.[29] Representative products derived from 4 organoboron, 3 amines, and 3 aldehydes (**95-102**) were purified and characterized at milligram scale (Figure 3C). These results highlight the potential of this APBM strategy to efficiently expand the chemical space for highly complex alkylamines in a single step. Limitations were observed with the thiazole containing aldehyde (**X1**) and amine (**N2**), as little product formation was observed when they were employed as coupling partners. Overall, this APBM approach holds promise for future applications in the discovery of drug candidates in medicinal chemistry efforts and further optimization could focus on expanding the substrate scope to encompass more five-member ring heterocycles, e.g., thiazoles.

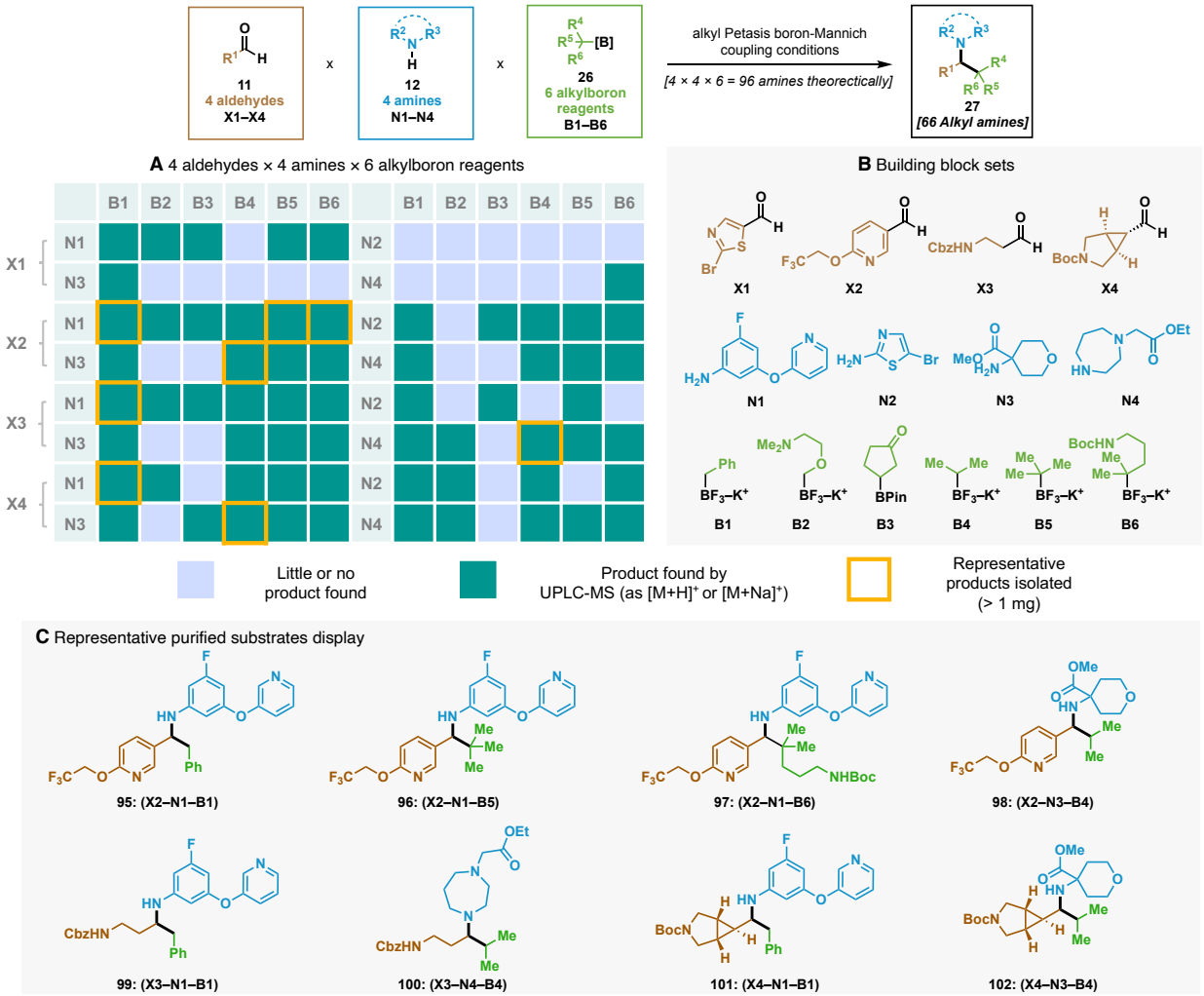


Figure 3. Alkylamine library syntheses with an APBM reaction method through HTE implementation. A. Parallel synthesis of 96 alkylamines via an APBM method, with 4 aldehydes, 4 amines and 6 alkylboron reagents as the coupling partners. B. Reaction plate design and results of a 96-well plate screening. Regarding how each building block was sorted in a 96-well plate manner, see Supplementary Information section 'Alkylamine library syntheses' for details. C. Display of representative reaction products that were purified and characterized.

Late-stage functionalization of drug derivatives & Synthetic applications

The modularity and synthetic utility of this APBM reaction in the rapid generation of complex alkyl amines was further showcased by the late-stage functionalization of drug derivatives (Figure 4, Panel A). A derivative of pentoxifylline, commonly used in the treatment of peripheral arterial disease, was successfully functionalized with amine **23** and aldehyde **22**, resulting in excellent yield (**103**). Furthermore, late-stage functionalization of various medicinally relevant and complex amine intermediates proved successful, leading to their corresponding alkylated derivatives with good yields. Some examples include tyramine (**57,** Figure 2, Panel B), guanidino-amines (**104**), desipramine (**105**), quetiapine (**106**), VHL ligand (**107**), glucosamine (**108**), spirochromane (**109**), antibacterial oxazolidinone (**110**), and paroxetine (**111**). Lastly, drug-derived aldehydes, such as chlorambucil (**94,** Figure 2, Panel C), mycophenolic acid (**112**), and

deoxycholic acid (**113**) derivatives, were effectively functionalized with alkyl and amino sidechains. This further exemplified the versatility of the APBM reaction in the late-stage modification of drug compounds.

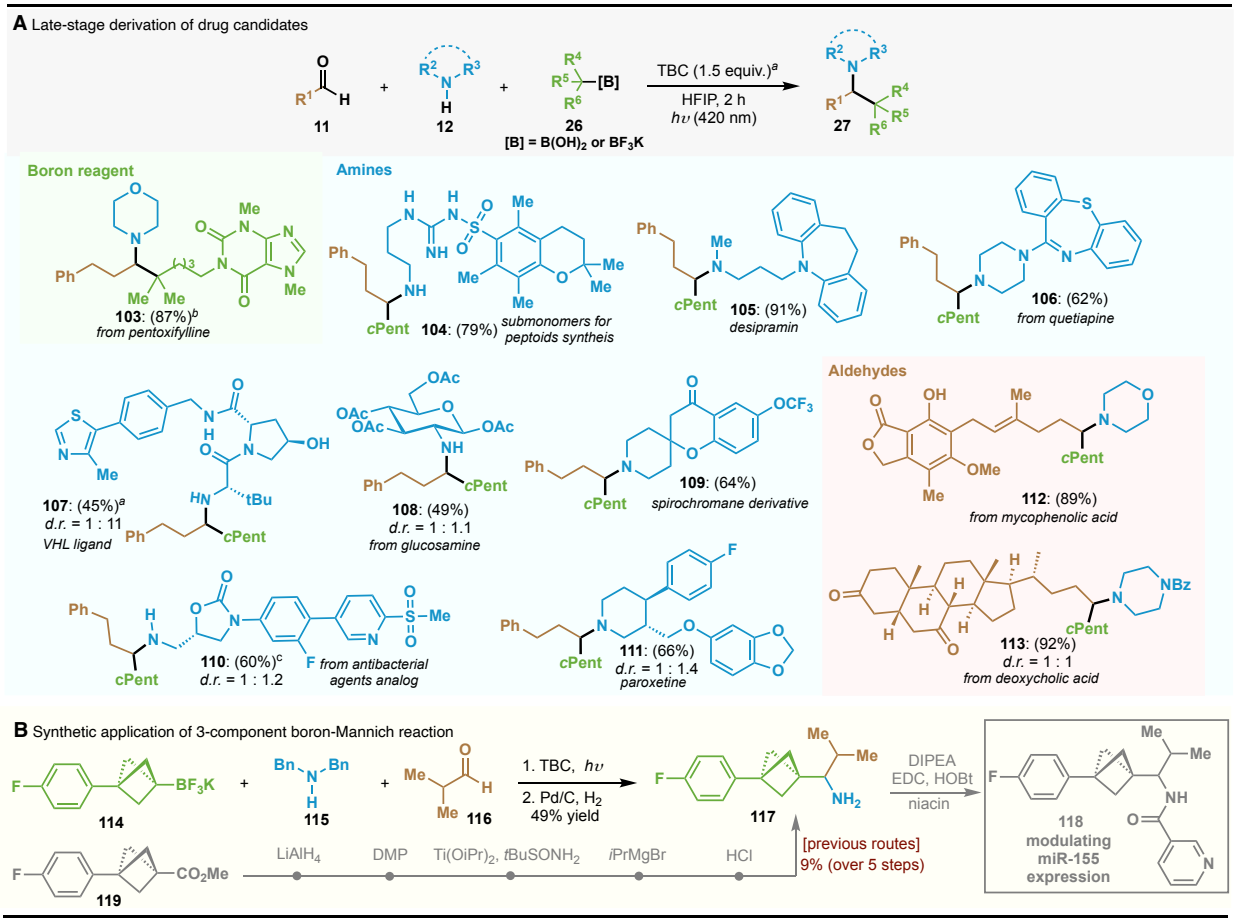


Fig. 4. Synthetic applications of the APBM reaction. A) Late-stage derivation of drug candidates; B) Synthetic approach to miR-155 expression modulator **118**. a) 6 h reaction time. **a)** Aldehyde (0.1 mmol), amine (1.5 equiv.), $RB(OH)_2$ (1.5 equiv.), TBC (1.5 equiv.), HFIP (0.2 M), 420 nm, 2 h; b) aldehyde (0.1 mmol.), amine (1.5 equiv.), RBF_3K (1.5 equiv.), TBC (1.5 equiv.), HFIP (0.2 M), 420 nm, 12 h; c) 6 h reaction time. See Supporting Information for details.

The potential of APBM strategy in improving step economy was further demonstrated (Figure 4, Panel B). In a previous synthesis of a miR-155 expression modulator (**118**), a bicyclo[1.1.1]pentyl (BCP) amine intermediate **117** was synthesized using a two-electron approach from BCP ester (**119**).[30] This prior art required 5 steps to access intermediate **117**. In contrast, we demonstrated that by employing the APBM coupling/debenzylation sequence, both the BCP and isopropyl sidechains could be efficiently installed in just 2 steps, resulting in markedly improved overall yield (49% vs. 9%). This showcases the effectiveness of the APBM strategy in streamlining the synthetic route and enhancing overall step economy.

Mechanistic investigations

To gain further insights into the reaction mechanism, a series of mechanistic experiments were carried out to illuminate various reaction pathways. Initially, UV-VIS spectroscopy was employed to analyze each building block and combinations. The emergence of a new absorption within the visible light range (~ 280-450 nm) was observed upon the mixture of aldehyde **22**, amine **23**, and boronic *n*-butylcatechol ester **119** in HFIP (Figure 5A), signaling the formation of an EDA complex.[31] Furthermore, a radical clock experiment executed with cyclopropylmethyl boronic acid **120** afforded the ring-opening product **121** in good yield, verifying the formation of the alkyl radical from alkyl organoboron species (Figure 5B). Moreover, in the presence of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO), the alkyl radical generated from the boron species under the standard reaction condition was intercepted by TEMPO, resulting in an adduct (**127**) that was isolated and characterized (Figure 5C). The reaction with cyclopropyl aldehyde **123** afforded cyclopropyl products **125** in moderate yield, accompanying a small amount of ring opening product **126** (4% yield). When $(TMS)_3SiH$ was introduced as an additive, the yield of the cyclopropyl ring opening product **126** increased to 28%. This suggests that the addition of $(TMS)_3SiH$ may facilitate a rapid quenching of the malonate carbon-centered radical via a hydrogen atom transfer (HAT) process (Figure 5B).[21, 32] These results suggested the generation of α-amino radicals from the iminium intermediate during the reaction.

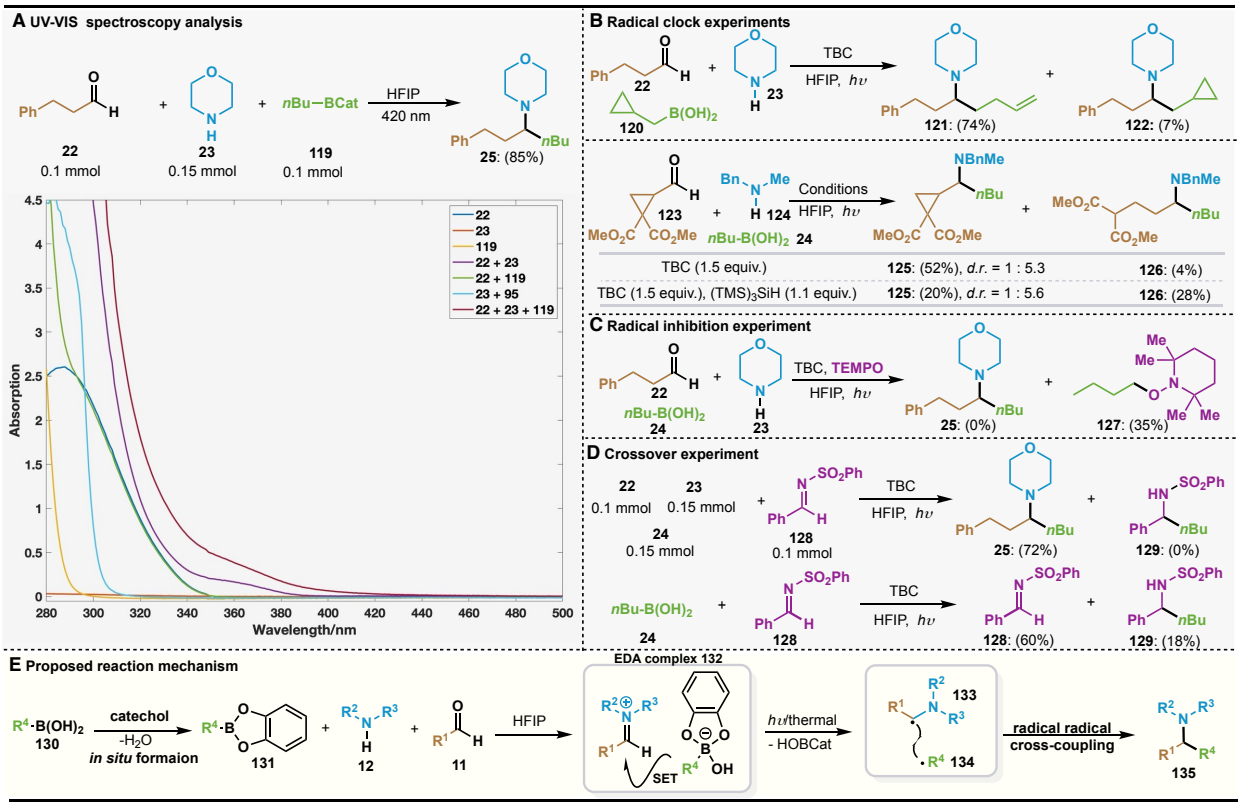


Fig. 5. Mechanism study of the APBM reaction. A. UV-Vis spectroscopy analysis; B. Radical clock experiments; C. Radical trap experiment; D. Crossover experiment; E. Proposed reaction Mechanism.

To gain further insight into the radical formation steps, a crossover experiment was conducted using aldehyde **22**, amine **23**, and *N*-benzylidene benzene sulfonamide **128**, a known excellent radical acceptor. In the absence of aldehyde **22** and amine **23**, the reaction of **128** with *n*-butyl boronic acid **24** and *tert*-butyl catechol afforded 18% of alkylated amine **129** (Figure 5D). In contrast, when aldehyde **22** and amine **23** were present, only product **25** was isolated, and **129** was not observed. This result suggests that this reaction proceeds through a confined radical pair recombination rather than a free radical addition process (Figure 5D). In this process, an α-amino radical, generated from the *in situ* formed iminium, reacts with the carbon-centered radical more rapidly than **128**. Taking into account all the results obtained from the mechanistic studies, a proposed reaction mechanism is proposed in Figure 5E. The reaction initiates with the formation of alkyl boronic *tert*-butylcatechol ester (**131**) and iminium intermediates from amine (**12**) and aldehyde (**11**). These two intermediates form an EDA complex **132** in HFIP. Under photo-irradiation or thermal SET process, the EDA complex **132** undergoes a SET process, leading to the generation of alkyl radical (**134**) and α-amino radical (**133**). Concurrently, the loss of benzo[*d*][1,3,2]dioxaborol-2-ol (HOBcat) occurs, and finally, the amine product **135** is formed through a radical-radical cross-coupling process.

Conclusion

Results obtained from this study demonstrated that alkyl Petasis boron-Mannich strategy reported herein employs readily available and bench-stable building blocks. This strategy features operational simplicity and enables the rapid and modular preparation of a variety of complex alkyl amies with a high fraction of C(sp^3). In addition to providing access to pharmaceutically relevant building blocks, this transformation also revealed a more general Petasis-type coupling of aldehyde, amine, and alkyl boronic acids via a radical process. Consequently, the construction of alkyl amines has showcased remarkable capability of this transformation to rapidly access complex amino-contained derivatives and establish C(sp^3)-N bonds that were previously challenging.

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Author contributions

H.C. and J.T. performed experiments of methodology development, synthetic applications and mechanistic studies; S-J.C. and M.K. performed high-throughput synthesis and purification of representative substrates; H.C., S-J.C., Y.K., R.M.M., and T.Q. designed and supervised the project; H.C., J.T., S-J.C., Y.K., R.M.M., and T.Q. wrote the paper.

Competing interests

Authors declare that they have no competing interests.

Data and materials availability

Experimental data as well as characterization data for all new compounds prepared in the course of these studies are provided in the Supplementary Information of this manuscript. Crystallographic data for the structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers CCDC 2335001 (derivative of **74:** hydrolyzed acid hydrochloride salt), see X-ray Crystallographic Data in Supplementary Information. Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/.

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