Published in final edited form as:
Org Lett. 2019 June 21; 21(12): 4853–4858. doi:10.1021/acs.orglett.9b01747.

Photoredox-Catalyzed Multicomponent Petasis Reaction with Alkyltrifluoroborates

Jun Yi[†,‡,§], **Shorouk O. Badir**[†,§], **Rauful Alam**[†], **Gary A. Molander**[*,†]

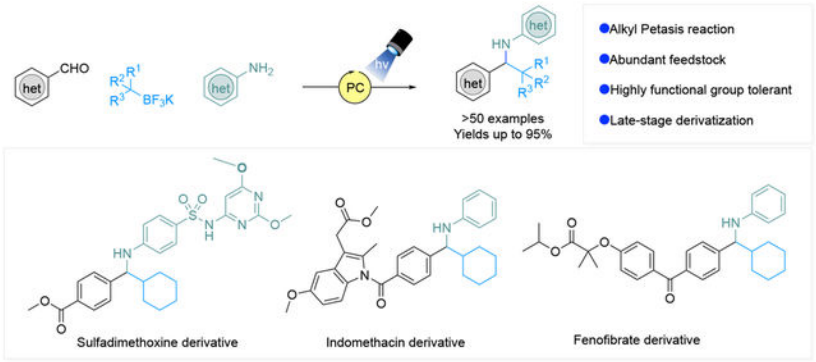
[†]Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, 231 South 34th Street, Philadelphia, Pennsylvania 19104-6323, United States

[‡]Jiangsu Laboratory of Advanced Functional Materials, School of Chemistry and Materials Engineering, Changshu Institute of Technology, Changshu 215500, China

Abstract

A redox-neutral alkyl Petasis reaction has been developed that proceeds via photoredox catalysis. A diverse set of primary, secondary, and tertiary alkyltrifluoroborates participate effectively in this reaction through a single-electron transfer mechanism, in contrast to the traditional two-electron Petasis reaction, which accommodates only unsaturated boronic acids. This protocol is ideal to diversify benzyl-type and glyoxalate-derived aldehydes, anilines, and alkyltrifluoroborates toward the rapid assembly of libraries of higher molecular complexity important in pharmaceutical and agrochemical settings.

Graphical Abstract



Multicomponent reactions (MCRs) have emerged as powerful transformations to condense three or more partners to deliver novel scaffolds with inherent molecular complexity.[1] The

[*]**Corresponding Author:** gmolandr@sas.upenn.edu.
[§]These authors contributed equally to this work.

Supporting Information
The Supporting Information contains a description of the reaction optimization, the general procedure for alkylation as well as a larger scale reaction, outline of mechanistic studies, starting material preparation, and full spectral data and characterization for all compounds prepared. The Supporting Information is available free of charge on the ACS Publications website.

Notes
The authors declare no competing financial interest.

advantages of MCRs include the preservation of atom- and step economies, shorter reaction times, and the ability to access highly diverse chemical space rapidly and efficiently. These integral benefits make MCRs highly attractive for diversity-oriented synthesis of small molecule libraries in drug discovery,[2] as well as in a variety of other useful endeavors.[3]

Presently, the tool box of a synthetic chemist is composed of many MCRs, including Mannich,[4] Biginelli,[5] Passerini,[6] and Ugi transformations.[7] The Petasis reaction[8] is another such reaction, and is perhaps unique by virtue of its generation of amines and amino acid derivatives with pivotal activity in biology. The majority of traditional Petasis applications require adjacent heteroatoms as directing groups to form the key boron “ate” complex intermediate (Scheme 1a).[9] This initial complexation is followed by an irreversible, two-electron nucleophilic addition to an imine or iminium ion intermediate, stemming from a condensation reaction of the aldehyde and amine. The propensity of the boron “ate” complex to migrate depends on its ability to stabilize negative charge: alkynyl > aryl ≈ alkenyl > alkyl.[10] Thus, the traditional Petasis reaction is restricted to alkenyl, aryl, alkynyl, allyl, benzyl, and allylic boronic acid derivatives.[8, 9] As far as we are aware, there are no reports of multicomponent Petasis reactions using alkylboron derivatives. A widely utilized alternative approach to amines stemming from two-electron nucleophilic addition to imines or iminium ions uses strongly nucleophilic organometallic reagents.[11] These transformations, however, rely on harsh reaction conditions that compromise functional group tolerability, restricting their widespread use in late-stage functionalization of complex molecules. It is also important to note that the formation of water as a byproduct under a multicomponent platform would hinder the efficacy of these pyrophoric reagents. In the context of single-electron transfer (SET) in the multicomponent Petasis reaction, the only examples reported require preformed imines[12] or the use of stoichiometric indium as a reductant with limited scope, being restricted to secondary alkyl iodides.[13]

Other SET approaches to C═N bond alkylation, including Minisci reactions, are well documented.[14] Our group, as well as others, recently demonstrated that photoredox catalysis enables the generation of alkyl radicals from organotrifluoroborates, while maintaining broad functional group tolerance.[15] Given the robust stability of alkyl radicals to aqueous conditions, a photoredox approach to a multicomponent Petasis-type reaction would appear feasible. We envisioned that a suitable photocatalyst in its excited state ([PC]*, **II**) would initiate the process by oxidizing an alkyltrifluoroborate **IV** to the desired alkyl radical **V** (Scheme 1b), generating BF_3 as a byproduct. The radical **V** could then add to the *in situ* condensed imine **VIII** to form the amine radical cation **IX**. A subsequent reduction of **IX** by the reduced state of the photocatalyst **III** terminates the photocatalytic cycle. The use of trifluoroborates as radical precursors was viewed as critical for the success of the proposed protocol, because the BF_3 Lewis acid generated in the SET process was anticipated to facilitate the condensation between the aldehyde and the amine, and could also activate the resultant imine toward radical addition.

Relevant to the present investigation, the Doyle[16] and Gaunt[17] groups recently reported elegant multicomponent reactions to access benzhydryl amines as well as tertiary amines, respectively. In a unique transformation, Li reported a Ru-catalyzed addition of aldehydes to preformed aryl imines, accessing phenylalkyl amines. The scope of this process was

restricted predominantly to benzaldehydes.[18] The multicomponent synthesis of analogous phenylalkyl amines is thus underexplored.

After a systematic survey of reaction parameters (see Supporting Information), we were able to identify suitable reaction conditions. Thus, in exploratory studies a mixture of methyl 4-formylbenzoate (**1**), aniline (**2**, 1.5 equiv), and potassium cyclohexyltrifluoroborate (**3**, 1.5 equiv), was catalyzed by $[Ir\{dF(CF_3)ppy\}_2(bpy)]PF_6$ (2 mol %, $E_{1/2}^{red}[*Ir^{III}/Ir^{II}]$ = +1.32 V vs. SCE)[19] in the presence of sodium bisulfate (1.0 equiv) in 1,4-dioxane (0.1 M) (Scheme 2). The desired product (**4**) was afforded in 84% isolated yield under irradiation with blue LEDs for 24 hours at rt.[20, 21] In expanding the method, diverse secondary alkyltrifluoroborates, including heteroaromatic-based systems, were found to be amenable substrates in this transformation. In the heteroaromatic substructures (e.g., **10**), no Minisci byproduct was detected. Sterically disfavored tertiary alkyltrifluoroborates gave excellent yields (**12**, **13**). Surprisingly, primary aliphatic alkyltrifluoroborates, with a markedly higher oxidation potential ($E_{1/2}^{red}$ = +1.90 V vs. SCE)[22] reacted well under the reaction conditions (**14**-**16**).

Assessing the aldehyde scope, halo-substituted benzaldehyde derivatives whose products are suitable for further processing provided the targets in good yield (**25**-**27**). The reaction is highly chemoselective. In a dicarbonyl substrate, only the aldehyde derivative reacted, while the ketone remained untouched (**24**). Electron-donating groups are amenable structural motifs (**32**-**37**). Given that heteroarenes represent prevalent substructures in pharmaceutically relevant molecules,[23] a variety of such systems were evaluated and proved to be effective partners (**38**–**43**). Additionally, an unnatural α-amino acid derivative is accessible using glyoxyl aldehyde instead of a benzaldehyde derivative (**44**).

Next, we turned our attention to the aniline partner, where a wide array of functional groups was tolerated, such as chloro (**45**, **46**, **49**, **50**), trifluoromethyl (**47**), ester (**48**), and methoxy (**54**). The electronic effect on the aniline component was inconspicuous. Meanwhile, the reactions were not sensitive to steric hindrance at the ortho position of the aniline (**52**, **53**).

To demonstrate the utility of this protocol for late-stage modification of intricate molecules, we prepared benzaldehyde derivatives from commercially available drug cores.[24] Both Indomethacin and Fenofibrate were successfully converted to the corresponding products in excellent yields (**55**, **56**). Sulfadimethoxine was also elaborated with acceptable yield, especially considering its high functional group density (**57**). To highlight the application of this photoredox alkyl Petasis reaction further, we utilized this method to expedite the synthesis of a key intermediate toward a Pfizer glucagon receptor modulator (Scheme 3b).[25] The key intermediate (**60**) was assembled with good yield in one step using this newly developed, convergent MCR reaction.

To highlight the amplification of this method, a transformation was successfully performed on a larger scale, whereby the desired product **54** was obtained in 51% yield, in agreement with the small-scale reaction. It is worth indicating that the *para*-methoxyphenyl (PMP) group of **54** could be readily removed by ceric ammonium nitrate (CAN) oxidation to release the primary amine (**61**).[26]

To probe the reaction pathway, we conducted preliminary mechanistic studies. The ring-opening product was exclusively observed when potassium (cyclopropylmethyl)trifluoroborate was used as the starting material (Scheme 4a). In the presence of the radical scavenger TEMPO [(2,2,6,6-tetramethylpiperidin-1-yl)oxyl], the reaction was completely inhibited, and a TEMPO-alkyl adduct was isolated, as well as the imine (Scheme 4b). This is suggestive of the involvement of alkyl radical generation under this reaction manifold. When the preformed imine was used instead of the aldehyde/aniline partners, a yield similar to that obtained in the multicomponent reaction was observed (Scheme 4c). Furthermore, during the course of the reaction, the reductive dimerization byproduct of the imine was not observed.[27] Although Stern-Volmer studies indicate no significant quenching of the excited state of the photocatalyst ($E_{1/2}^{red}$ [Ir^{IV}/*Ir^{III}] = −1.00 V vs. SCE)[19] by the imine intermediate, we cannot rule out the possibility of direct reduction of the imine ($E_{1/2}^{red}$= −1.91 V vs. SCE)[14e, 28] by the reduced state of the photocatalyst ($E_{1/2}$ [Ir^{III}/Ir^{II}] = −1.37 V vs. SCE).[19] In particular, variabilities in reaction concentration and pH levels could exert an impact on redox potential values.[29]

In conclusion, a multicomponent alkyl Petasis reaction under photoredox conditions has been developed. This procedure employs bench stable, commercially available alkyltrifluoroborates, easily accessible benzaldehydes, and anilines as feedstock. Taking advantage of the stability of alkyl radicals in water, preformed imines are no longer required, providing a highly step-efficient process that should be amenable to the industrial setting. Other favorable factors include the elimination of harsh reaction conditions (elevated temperatures and strong organometallic reagents), and the toleration of an exceptional array of functional groups as well as complex structural scaffolds. The facile diversification inherent in this MCR positions this technology as being extremely suitable for diversity-oriented synthesis in drug discovery scenarios.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

The authors are grateful for the generous financial support provided by the NSF (CHE-1664818) and NIGMS (R01 GM 113878) to GM. J. Y. acknowledges funding from the National Natural Science Foundation of China (Grant No. 21602017), the Natural Science Foundation of Jiangsu Province (Grant No. BK20160405), the University Science Research Project of Jiangsu Province (16KJB150001), and China Scholarship Council (201708320115). R.A. thanks the Swedish Chemical Society for a *Bengt Lundqvist* postdoctoral fellowship. We thank Dr. Charles W. Ross III (UPenn) for his assistance in obtaining HRMS data. Frontier Scientific is kindly acknowledged for donating alkyltrifluoroborates in support of this research. Kessil is acknowledged for providing the lights used in this study.

REFERENCES

(1). (a)Zhu J; Wang Q; Wang M-X Multicomponent Reactions in Organic Synthesis, Wiley-VCH, Weinheim, 2015;(b)Rotstein BH; Zaretsky S; Rai V; Yudin AK Small Heterocycles in Multicomponent Reactions. Chem. Rev 2014, 114, 8323–8359; [PubMed: 25032909] (c)Dömling A; Wang W; Wang K Chemistry and Biology of Multicomponent Reactions. Chem. Rev 2012, 112, 3083–3135. [PubMed: 22435608]

(2). (a)Schreiber SL Target-Oriented and Diversity-Oriented Organic Synthesis in Drug Discovery. Science 2000, 287, 1964–1969; [PubMed: 10720315] (b)Galloway WRJD; Isidro-Llobet A; Spring DR Diversity-oriented synthesis as a tool for the discovery of novel biologically active small molecules. Nat. Commun 2010, 1, 80; [PubMed: 20865796] (c)O' Connor CJ; Beckmannw HSG; Spring DR Diversity-oriented synthesis: producing chemical tools for dissecting biology. Chem. Soc. Rev 2012, 41, 4444–4456. [PubMed: 22491328]

(3). Boukis AC; Reiter K; Frölich M; Hofheinz D; Meier MAR Multicomponent reactions provide key molecules for secret communication. Nat. Commun 2018, 9, 1439. [PubMed: 29651145]

(4). Verkade JMM; van Hemert LJC; Quaedflieg PJLM; Rutjes FPJT Organocatalysed asymmetric Mannich reactions. Chem. Soc. Rev 2008, 37, 29–41. [PubMed: 18197331]

(5). Suresh, Sandhu JS Past, present and future of the Biginelli reaction: a critical perspective. ARKIVOC, 2012, 66–133.

(6). Wang Q; Wang D-X; Wang M-X; Zhu J Still Unconquered: Enantioselective Passerini and Ugi Multicomponent Reactions. Acc. Chem. Res 2018, 51, 1290–1300. [PubMed: 29708723]

(7). Dömling A; Ugi I Multicomponent Reactions with Isocyanides. Angew. Chem. Int. Ed 2000, 39, 3168–3210.

(8). (a)Petasis NA; Akritopoulou I The boronic acid mannich reaction: A new method for the synthesis of geometrically pure allylamines. Tetrahedron Lett. 1993, 34, 583–586;(b)Kumagai N; Muncipinto G; Schreiber SL Short Synthesis of Skeletally and StereochemicallyDiverse Small Molecules by Coupling PetasisCondensation Reactions to CyclizationReactions. Angew. Chem. Int. Ed 2006, 45, 3635–3638;(c)Ricardo MG; Llanes D; Wessjohann LA; Rivera DG Introducing the Petasis Reaction for Late-Stage Multicomponent Diversification, Labeling, and Stapling of Peptides. Angew. Chem. Int. Ed 2019, 58, 2700–2704.

(9). (a)Candeias NR; Montalbano F; Cal PMSD; Gois PMP Boronic Acids and Esters in the Petasis-Borono Mannich Multicomponent Reaction. Chem. Rev 2010, 110, 6169–6193; [PubMed: 20677749] (b)Batey RA Nucleophilic Addition Reactions of Aryl and Alkenylboronic Acids and Their Derivatives to Imines and Iminium Ions In Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine; Hall DG, Ed.; Wiley-VCH: Weinheim, Germany, 2005; pp 279–304. Some traceless examples:(c)Jiang Y; Diagne AB; Thomson RJ; Schaus SE Enantioselective Synthesis of Allenes by Catalytic Traceless Petasis Reactions. J. Am. Chem. Soc 2017, 139, 1998–2005; [PubMed: 28121128] (d)Jiang Y; Thomson RJ; Schaus SE Asymmetric Traceless Petasis Borono-Mannich Reactions of Enals: Reductive Transposition of Allylic Diazenes. Angew. Chem. Int. Ed 2017, 56, 16631–16635.

(10). (a)Miyaura N; Sasaki N; Itoh M; Suzuki A The coupling reaction of copper(I) methyltrialkylborates with aroyl chlorides. A convenient synthesis of alkyl aryl ketones from organoboranes. Tetrahedron Lett. 1977, 18, 173–174;(b)Aggarwal VK; Fang GY; Ginesta X; Howells DM; Zaja M Toward an understanding of the factors responsible for the 1,2-migration of alkyl groups in borate complexes. Pure Appl. Chem 2006, 78, 215–229.

(11). (a)Hatano M; Suzuki S; Ishihara K Highly Efficient Alkylation to Ketones and Aldimines with Grignard Reagents Catalyzed by Zinc(II) Chloride. J. Am. Chem. Soc 2006, 128, 9998–9999; [PubMed: 16881613] b)Hatano M; Yamashita K; Mizuno M; Ito O; Ishihara K C-Selective and Diastereoselective Alkyl Addition to β,γ-Alkynyl-α-imino Esters with Zinc(II)ate Complexes. Angew. Chem. Int. Ed 2015, 54, 2707–2711.

(12). (a)Plasko DP; Jordan CJ; Ciesa BE; Merrill MA; Hanna JM Visible light-promoted alkylation of imines using potassium organotrifluoroborates. Photochem. Photobiol. Sci 2018, 17, 534–538; [PubMed: 29722411] (b)Cao K; Tan SM; Lee R; Yang S; Jia H; Zhao X; Qiao B; Jiang Z Catalytic Enantioselective Addition of Prochiral Radicals to Vinylpyridines. J. Am. Chem. Soc 2019, 141, 5437–5443; [PubMed: 30866625] (c)Li Y; Zhou K; Wen Z; Cao S; Shen X; Lei M; Gong L Copper(II)-Catalyzed Asymmetric Photoredox Reactions: Enantioselective Alkylation of Imines Driven by Visible Light. J. Am. Chem. Soc 2018, 140, 15850–15858. [PubMed: 30372057]

(13). (a)Shen Z-L; Loh T-P Indium–Copper-Mediated Barbier–Grignard-Type Alkylation Reaction of Imines in Aqueous Media. Org. Lett 2007, 9, 5413–5416; [PubMed: 18052071] b Shen Z-L; Cheong H-L; Loh T-P Indium–Silver- and Zinc–Silver-Mediated Barbier–Grignard-Type

Alkylation Reactions of Imines by Using Unactivated Alkyl Halides in Aqueous Media. Chem. Eur. J 2008, 14, 1875–1880. [PubMed: 18058963]

(14). (a)Garza-Sanchez RA; Tlahuext-Aca A; Tavakoli G; Glorius F Visible Light-Mediated Direct Decarboxylative C–H Functionalization of Heteroarenes. ACS Catal. 2017, 7, 4057–4061; (b)Proctor RSJ; Davis HJ; Phipps RJ Catalytic enantioselective Minisci-type addition to heteroarenes. Science 2018, 360, 419–422; [PubMed: 29622723] (c)Fujiwara Y; Dixon JA; O'Hara F; Funder ED; Dixon DD; Rodriguez RA; Baxter RD; Herlé B; Sach N; Collins MR; Ishihara Y; Baran PS Practical and innate carbon-hydrogen functionalization of heterocycles. Nature 2012, 492, 95–100; [PubMed: 23201691] (d)Gutiérrez-Bonet A; Remeur C; Matsui JK; Molander GA Late-Stage C–H Alkylation of Heterocycles and 1,4-Quinones via Oxidative Homolysis of 1,4-Dihydropyridines. J. Am. Chem. Soc 2017, 139, 12251–12258; [PubMed: 28832137] (e)Patel NP; Kelly CB; Siegenfeld AP; Molander GA Mild, Redox-Neutral Alkylation of Imines Enabled by an Organic Photocatalyst. ACS Catal. 2017, 7, 1766–1770; [PubMed: 28367354] (f)Klauck FJR; James MJ; Glorius F Deaminative Strategy for the Visible-Light-Mediated Generation of Alkyl Radicals. Angew. Chem. Int. Ed 2017, 56, 12336–12339;(g)Ueda M; Miyabe H; Miyata O; Naito T Carbon radical addition to N-sulfonylimines mediated by triethylborane or zinc. Tetrahedron 2009, 65, 1321–1326;(h)Fujii S; Konishi T; Matsumoto Y; Yamaoka Y; Takasu K; Yamada K Radical Aminomethylation of Imines. J. Org. Chem 2014, 79, 8128–8133; [PubMed: 25101967] (i)Fernández-Salas JA; Maestro MC; Rodríguez-Fernández MM; García-Ruano JL; Alonso I Intermolecular Alkyl Radical Additions to Enantiopure N-tert-Butanesulfinyl Aldimines. Org. Lett 2013, 15, 1658–1661; [PubMed: 23484734] (j)Friestad GK Addition of carbon-centered radicals to imines and related compounds. Tetrahedron 2001, 57, 5461–5496;(k)Miyabe H; Ueda M; Naito T Carbon-Carbon Bond Construction Based on Radical Addition to C=N Bond. Synlett 2004, 1140–1157;(l)Fava E; Millet A; Nakajima M; Loescher S; Rueping M Reductive Umpolung of Carbonyl Derivatives with Visible-Light Photoredox Catalysis: Direct Access to Vicinal Diamines and Amino Alcohols via α-Amino Radicals and Ketyl Radicals. Angew. Chem. Int. Ed 2016, 55, 6776–6779.

(15). (a)Primer DN; Molander GA Enabling the Cross-Coupling of Tertiary Organoboron Nucleophiles through Radical-Mediated Alkyl Transfer. J. Am. Chem. Soc, 2017,139, 9847–9850; [PubMed: 28719197] (b)Primer DN; Karakaya I; Tellis JC; Molander GA Single-Electron Transmetalation: An Enabling Technology for Secondary Alkylboron Cross-Coupling. J. Am. Chem. Soc 2015, 137, 2195–2198; [PubMed: 25650892] (c)Tellis JC; Primer DN; Molander GA Single-electron transmetalation in organoboron cross-coupling by photoredox/nickel dual catalysis. Science 2014, 345, 433–437; [PubMed: 24903560] (d)Stache EE; Rovis T; Doyle AG Dual Nickel- and Photoredox-Catalyzed Enantioselective Desymmetrization of Cyclic meso-Anhydrides. Angew. Chem. Int. Ed 2017, 56, 3679–3683;(e)Koike T; Akita M Combination of organotrifluoroborates with photoredox catalysis marking a new phase in organic radical chemistry. Org. Biomol. Chem 2016, 14, 6886–6890. [PubMed: 27282517]

(16). Heinz C; Lutz JP; Simmons EM; Miller MM; Ewing WR; Doyle AG Ni-Catalyzed Carbon–Carbon Bond-Forming Reductive Amination. J. Am. Chem. Soc, 2018, 140, 2292–2300. [PubMed: 29341599]

(17). Trowbridge A; Reich D; Gaunt MJ Multicomponent synthesis of tertiary alkylamines by photocatalytic olefin-hydroaminoalkylation. Nature 2018, 561, 522–527. [PubMed: 30258135]

(18). Chen N; Dai X-J; Wang H; Li C-J Umpolung Addition of Aldehydes to Aryl Imines. Angew. Chem. Int. Ed 2017, 56, 6260–6263.

(19). Koike T; Akita M Visible-light radical reaction designed by Ru- and Ir-based photoredox catalysis. Inorg. Chem. Front 2014, 1, 562–576.

(20). Brønsted and Lewis acid additives are reported to promote the traditional Petasis reaction:Carrera DE The acid promoted Petasis reaction of organotrifluoroborates with imines and enamines. Chem. Commun 2017, 53, 11185–11188;Li Y; Xu M-H Lewis Acid Promoted Highly Diastereoselective Petasis Borono-Mannich Reaction: Efficient Synthesis of Optically Active β,γ-Unsaturated α-Amino Acids. Org. Lett 2012, 14, 2062–2065. [PubMed: 22480132] In situ generated BF3 may also spur the reaction.

(21). See Supporting Information for details.

(22). (a)Chinzei T; Miyazawa K; Yasu Y; Koike T; Akita M Redox-economical radical generation from organoborates and carboxylic acids by organic photoredox catalysis. RSC Adv. 2015, 5, 21297–

21300;(b)Matsui JK; Primer DN; Molander GA Metal-free C-H alkylation of heteroarenes with alkyltrifluoroborates: a general protocol for 1°, 2° and 3° alkylation. Chem. Sci, 2017, 8, 3512–3522. [PubMed: 28507725]

(23). Welsch ME; Snyder SA; Stockwell BR Privileged scaffolds for library design and drug discovery. Curr. Opin. Chem. Biol 2010, 14, 347–361. [PubMed: 20303320]

(24). Huang K; Li X; Yu C; Zhang Y; Mariano P; Wang W Visible-Light-Promoted Nickel- and Organic-Dye-Cocatalyzed Formylation Reaction of Aryl Halides and Triflates and Vinyl Bromides with Diethoxyacetic Acid as a Formyl Equivalent. Angew. Chem. Int. Ed 2017, 56,1500–1505.

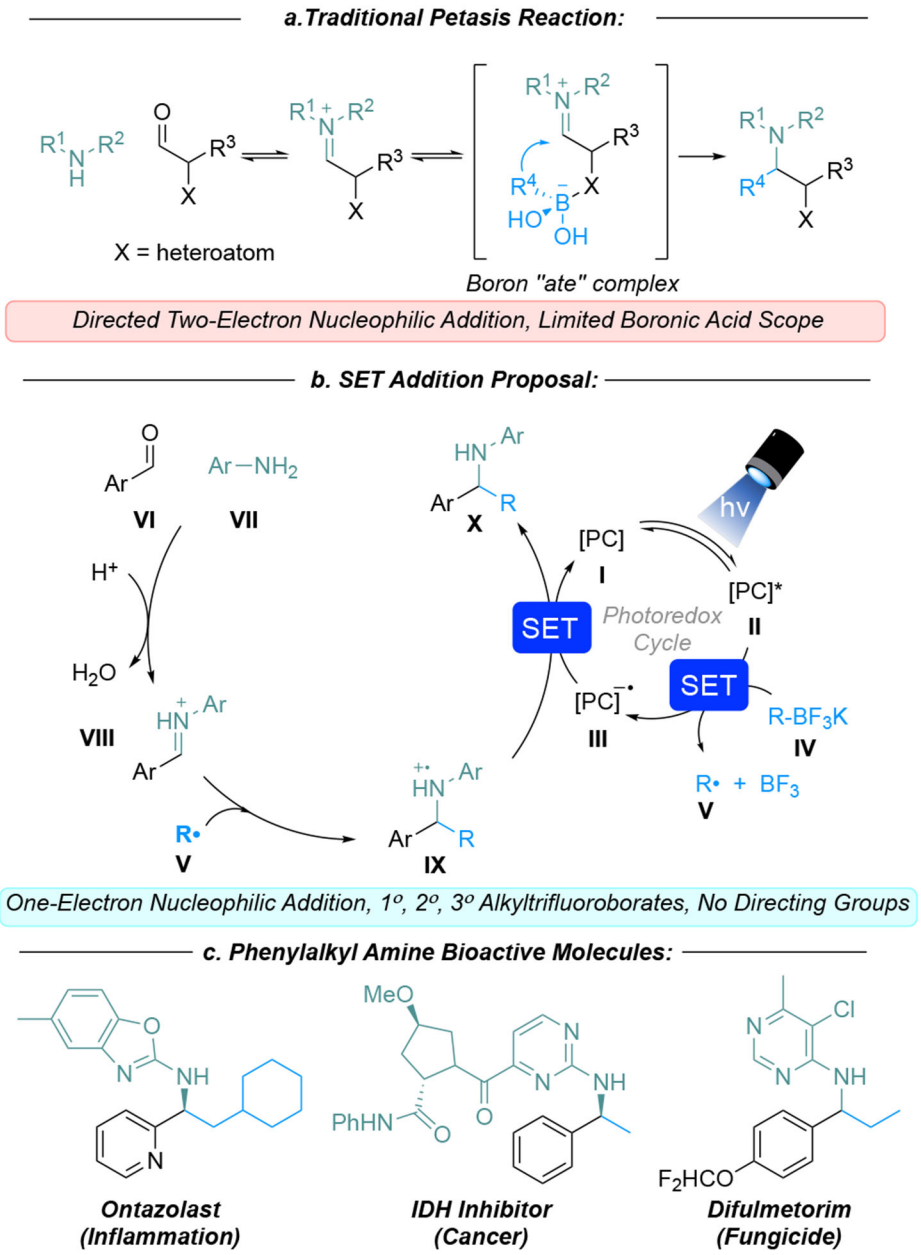
(25). Apnes GE; Didluk MT; Filipski KJ; Guzman-Perez A; Lee ECY; Pfefferkorn JA; Stevens BD; Tu MM Glucagon Receptor Modulators. U.S. Patent 20120202834, 8 9, 2012.

(26). Kronenthal DR; Han CY; Taylor MK Oxidative N-dearylation of 2-azetidinones. p-Anisidine as a source of azetidinone nitrogen. J. Org. Chem 1982, 47, 2765–2768.

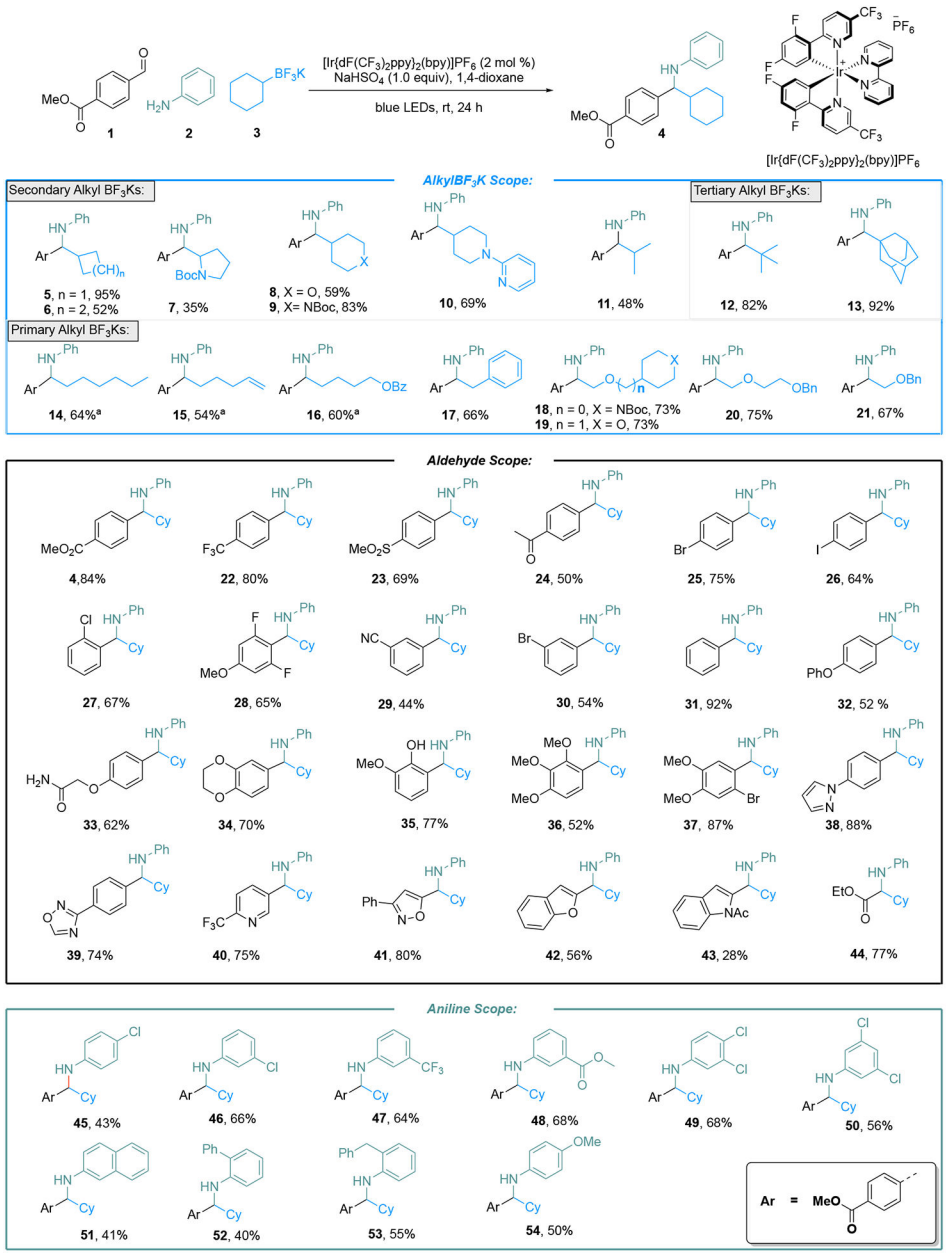
(27). Nakajima M; Fava E; Loescher S; Jiang Z; Rueping M Photoredox-Catalyzed Reductive Coupling of Aldehydes, Ketones, and Imines with Visible Light. Angew. Chem. Int. Ed 2015, 54, 8828–8832.

(28). Roth HG; Romero NA; Nicewicz DA Experimental and Calculated Electrochemical Potentials of Common Organic Molecules for Applications to Single-Electron Redox Chemistry. Synlett 2016, 27, 714–723.

(29). Zhu X; Castleberry SR; Nanny MA; Butler EC Effects of pH and Catalyst Concentration on Photocatalytic Oxidation of Aqueous Ammonia and Nitrite in Titanium Dioxide Suspensions. Environ. Sci. Technol 2005, 39, 3784–3791. [PubMed: 15952386]

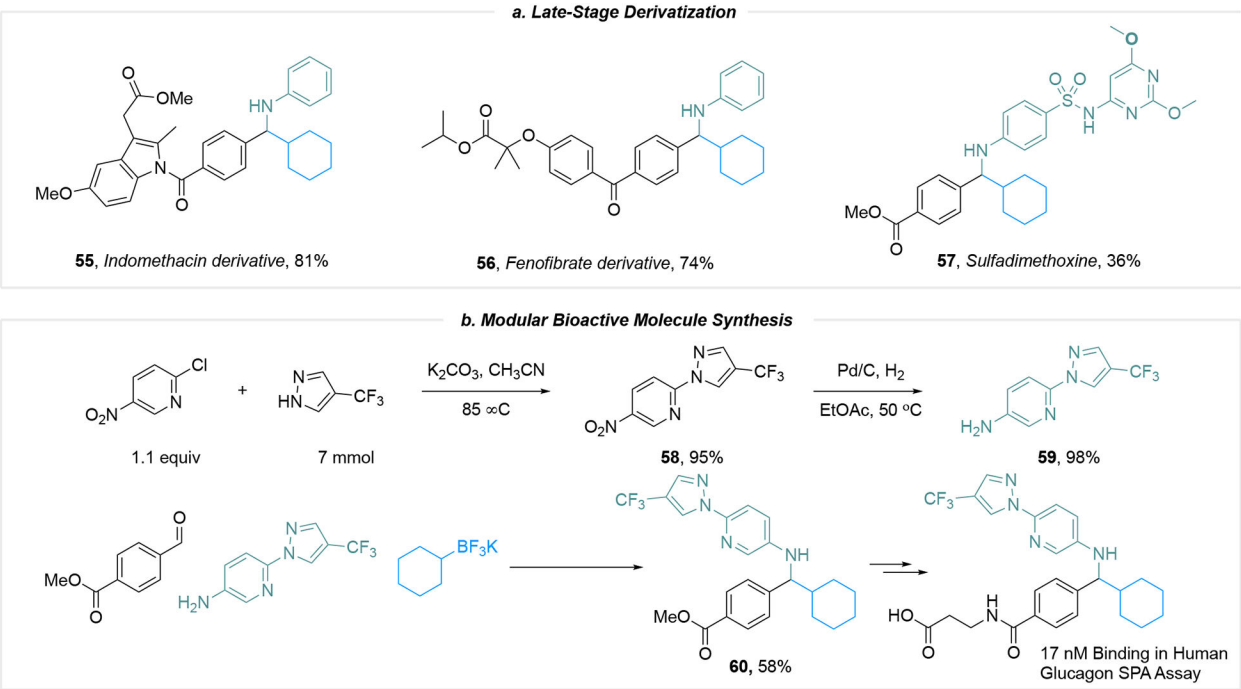


Scheme 1. Mechanistic Rationale: SET-based Petasis reaction and phenylalkyl amine bioactive molecules



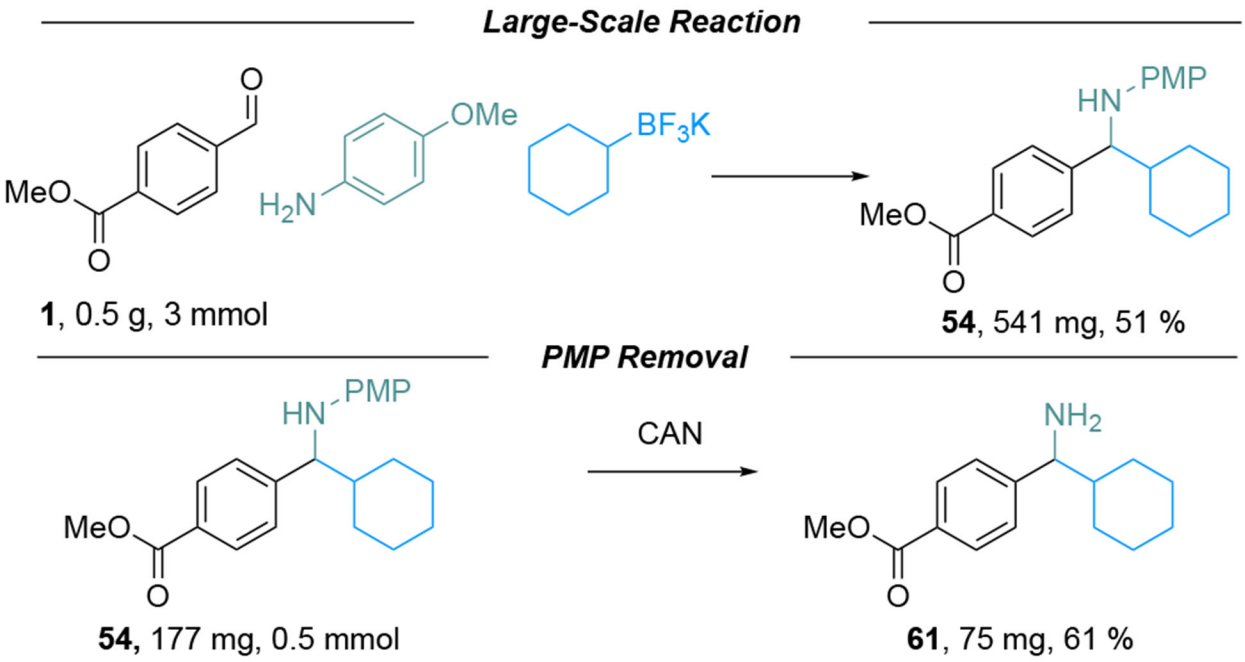
Scheme 2. Scope of alkyltrifluoroborates, aldehydes and anilines[a]

[a] Reaction conditions: aldehyde (0.5 mmol), alkyltrifluoroborate (0.75 mmol), aniline (0.75 mmol), [Ir{dF(CF_3)ppy}$_2$(bpy)]PF_6 (0.01 mmol), $NaHSO_4$ (0.5 mmol) and 1,4-dioxane (5 mL) under blue LED irradiation for 24 h. Isolated yields are given. [b]Irradiated by 34 W Kessil lamp.



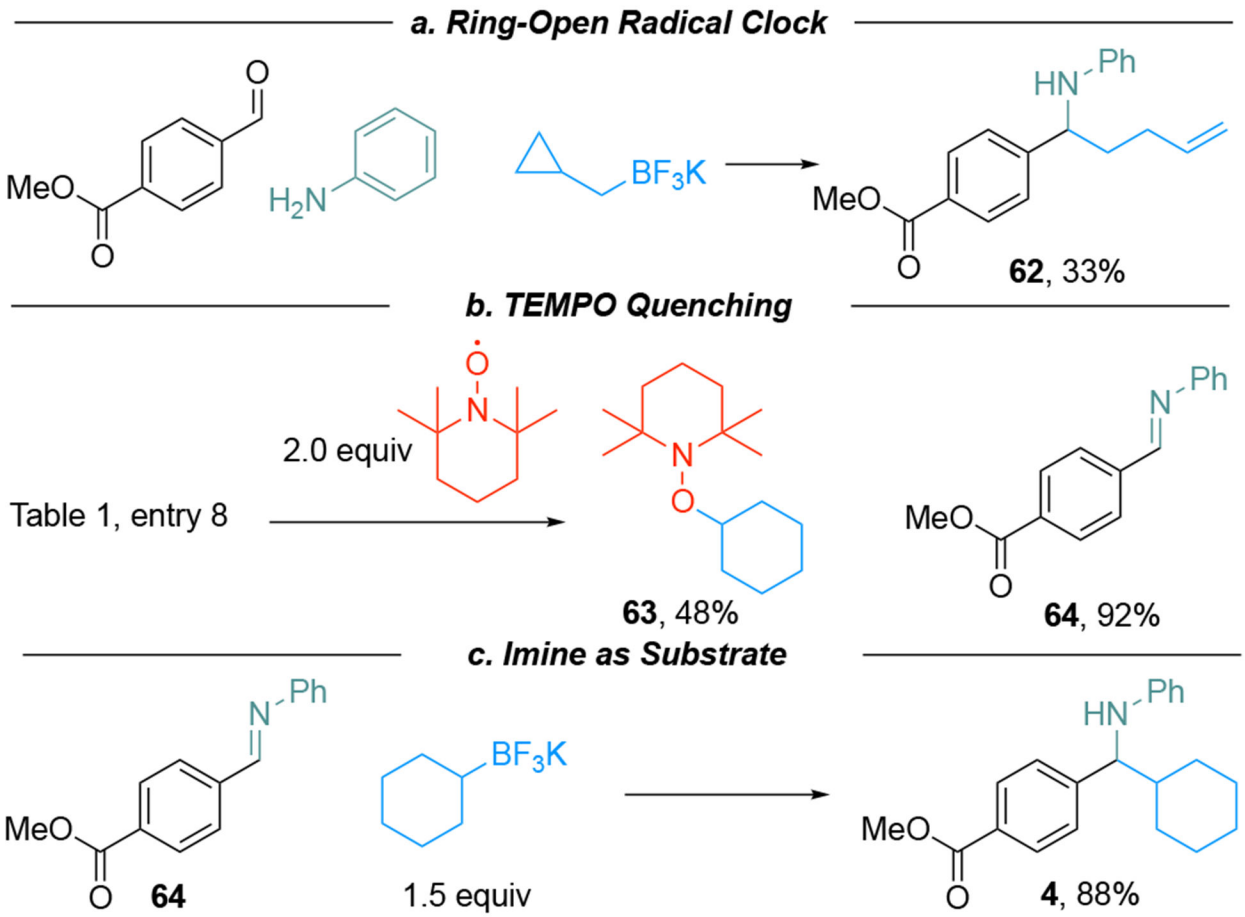
Scheme 3. Late-stage functionalization of pharmaceutical analogues and modular bioactive molecule synthesis[a]

[a] See Supporting Information for details.



Scheme 4. Large-scale reaction and removal of the PMP group[a]

[a]See Supporting Information for details.



Scheme 5. Preliminary mechanistic studies[a]

[a]See Supporting Information for details.