An Approach to Alkyl Azetidines for Medicinal Chemistry

Oleksandr P. Datsenko,[a] Andrii Baziievskyi,[a] Iryna Sadkova,[a] Bismarck Campos,[b] James T. Brewster II,*[b] John Kowalski,[b] Ronald J. Hinklin,*[b] and Pavel K. Mykhailiuk*[a]

[a] Enamine Ltd, Winston Churchill St. 78, 02094 Kyiv, Ukraine.
E-mail: Pavel.Mykhailiuk@gmail.com; Web: https://www.mykhailiukchem.org
[b] Pfizer Boulder Research and Development, 3200 Walnut St., Boulder, CO 80023, USA.
Email: jmsbrewster2@gmail.com, ronhinklin@yahoo.com

ABSTRACT: Alkyl azetidines have been prepared by photochemical modifications of azetidine-2-carboxylic acids *in batch* and *in flow*. The reaction has been realized in mg-, g-, and even multigram quantities. The obtained azetidines are valuable building blocks for drug discovery.

Introduction. The azetidine ring has gained significant popularity in drug discovery campaigns over the past decade. Today, at least seven approved drugs contain the residue of azetidine (Figure 1), and dozens of other azetidine-containing bioactive molecules are now at different stages of clinical trials.[1] Continued adoption of this motif requires new synthetic methodologies enabling access to building blocks with more diverse functionalities.

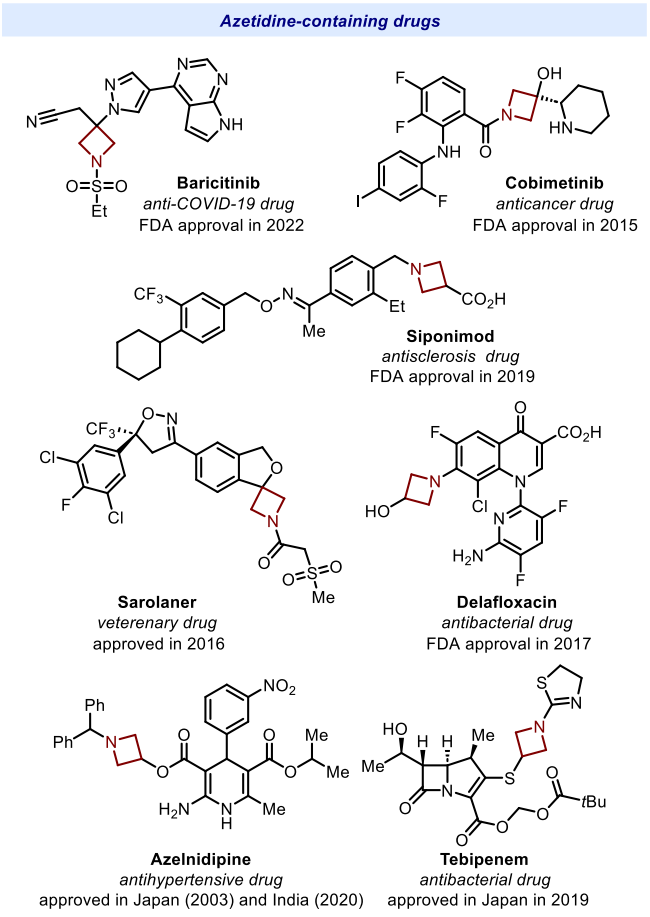
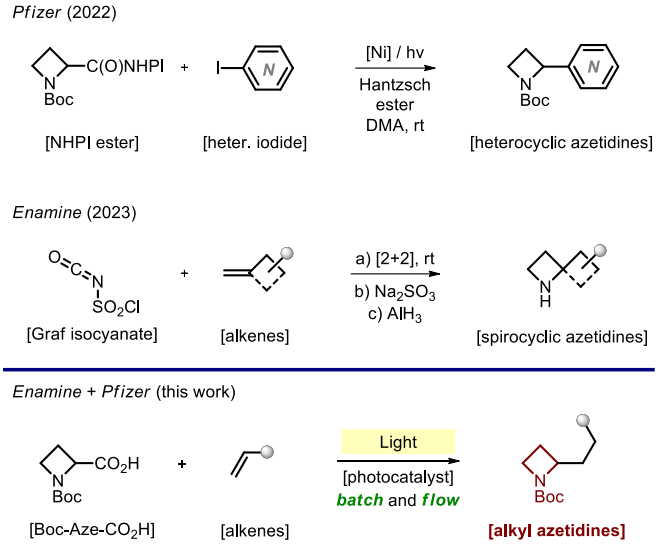


Figure 1. Small molecule azetidine-containing drugs.

It is thus not surprising that significant efforts have been put toward the preparation of substituted azetidines.[2] Most of these approaches, however, focus on the preparation of 3-substituted azetidines,[2,3] whereas 2-substituted isomers are rare.[4]

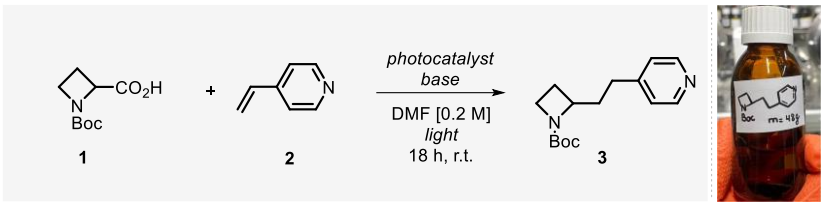


Scheme 1. Preparation of 2-substituted azeditines for medicinal chemistry: previous and this study. NHPI: *N*-hydroxyphtalimide.

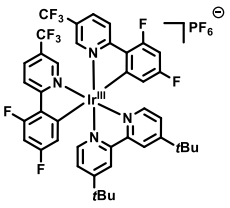
Our laboratories have been interested in applying different strategies towards accessing diversely substituted azetidines for medicinal chemistry. For example, in 2022, *Pfizer* reported on the [Ni]-catalyzed decarboxylative (hetero)arylation of the azetidine-containing redox-active ester to form 2-(hetero)aryl-azetidines (Scheme 1).[5] In 2023, *Enamine* developed the practical synthesis of 2-spirocyclic azetidines employing the formal [2+2]-cycloaddition between Graf isocyanate and exocyclic alkenes (Scheme 1).[6]

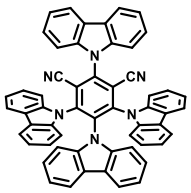
Here, we present our collaborative studies between *Enamine* and *Pfizer* aimed at the direct photochemical modifications of azetidine-2-carboxylic acids with alkenes. This reaction has been realized *in batch* and *in flow*, enabling the preparation of alkyl azetidines for medicinal chemistry in mg-, g-, and even multigram quantities.

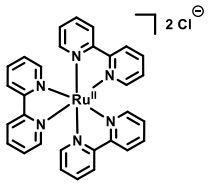
This is the first systematic study on the topic.

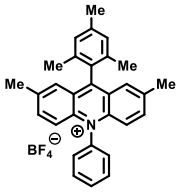


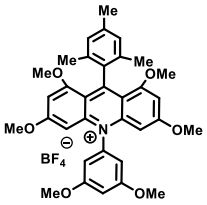
Entry	Catalyst	Base	Light	Yield
1	[Ir]	K_2CO_3	450 nm	39%
2	[Ir]	BTMG	450 nm	30%
3	[Ir]	K_3PO_4	450 nm	< 25%
4	[Ir]	LiOH-H_2O	450 nm	**76%**
5	[Ir]	2,4,6-collidine	450 nm	< 5%
6	4CzIPN	LiOH-H_2O	365 nm	**66%**
7	TiO_2 anatase	LiOH-H_2O	365 nm	< 5%
8	$Ru(bpy)_3Cl_2$	LiOH-H_2O	450 nm	< 5%
9	[Acr] 1	LiOH-H_2O	450 nm	< 5%
10	[Acr] 2	LiOH-H_2O	450 nm	< 10%
11	[Acr] 3	LiOH-H_2O	450 nm	< 5%
12	[Os] 1	LiOH-H_2O	660 nm	< 5%
13	[Os] 2	LiOH-H_2O	660 nm	< 5%
14	[Ir]	LiOH-H_2O	no light	n.d.
15	4CzIPN	LiOH-H_2O	no light	n.d.
16	4CzIPN, in flow [48 g of product]	LiOH-H_2O	365 nm	**61%**

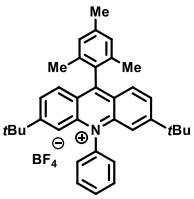


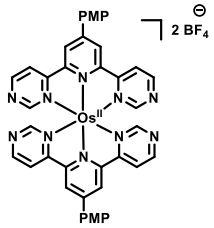


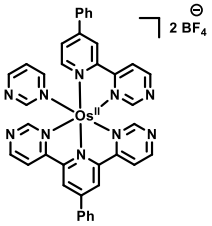








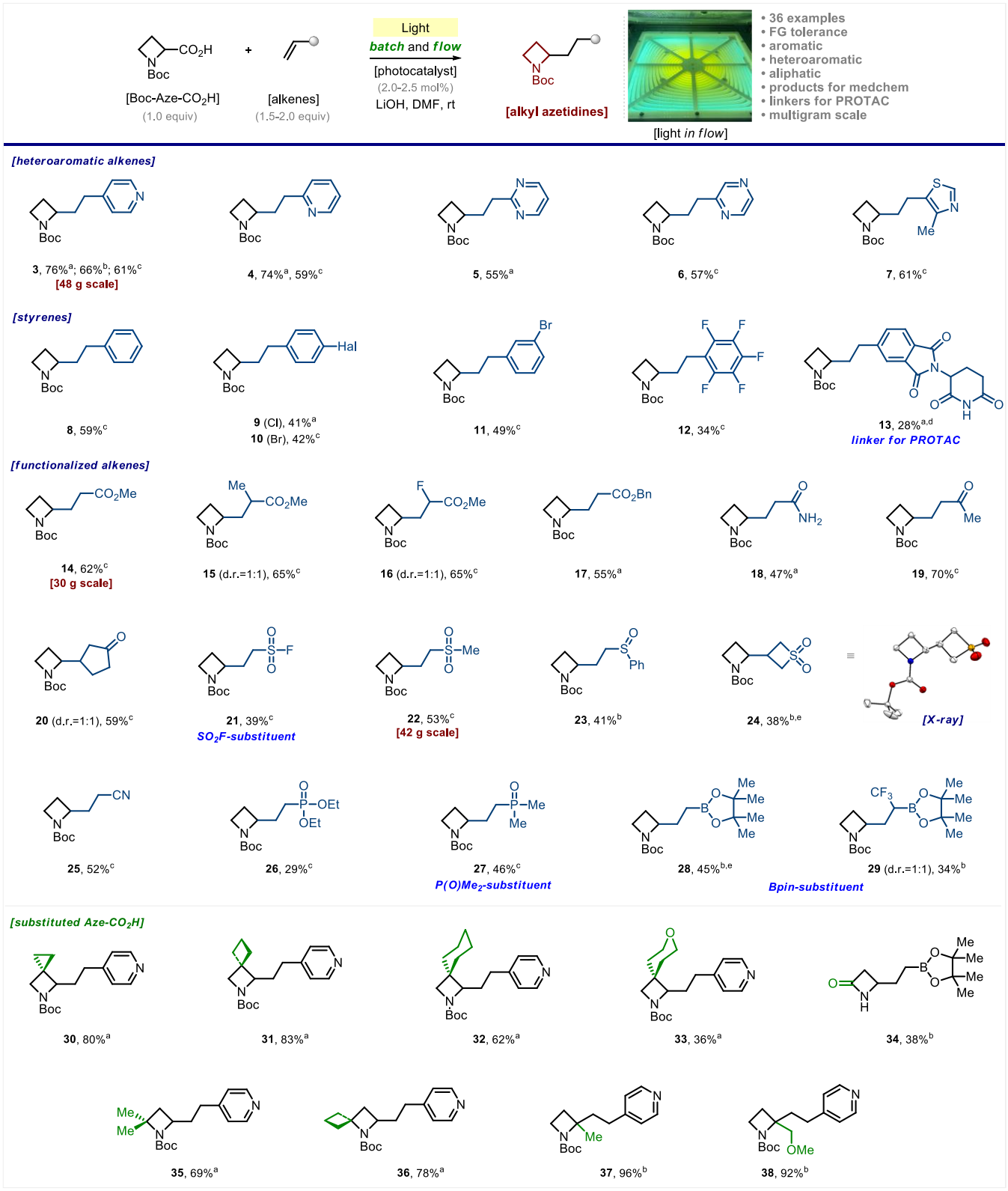




Scheme 2. Optimization of the reaction. Batch synthesis: azetidine carboxylic acid **1** (150 mg, 745 µmol, 1.0 equiv), 4-vinylpyridine (**2**) (157 mg, 1.49 mmol, 2.0 equiv), photocatalyst (2.5 mol%, 18.6 µmol), LiOH-H_2O (34.4 mg, 820 µmol, 1.1 equiv) in DMF [0.2 M]. Isolated yields after HPLC purification. (a) 365 nm. (b) 450 nm. (c) 660 nm. Flow synthesis: azetidine carboxylic acid **1** (1.0 equiv), 4-vinylpyridine (**2**) (1.5 equiv), 4CzIPN (2.0 mol%), LiOH-H_2O (1.1 equiv) in DMF [0.2 M], 365 nm, 30 mL/min. BTMG: 1,1,3,3-tetramethylguanidine. PMP: *para*-methoxyphenyl. *N.d.*: not determined.

Results and Discussion. *Optimization*. The photochemical reaction between amino acids and alkenes was known.[7,8] Surprisingly, azetidine-containing substrates were not present in those studies. On the other hand, rare azetidine-containing compounds non-systematically occurred in various radical reactions.[9,10] We thus initiated our studies by pursuing conditions for the direct photochemical reaction between the commercially available *N*-Boc azetidine-2-carboxylic acid (**1**) with a commercially available Michael acceptor - 4-vinyl pyridine (**2**). Optimal reaction conditions were found by varying base, photocatalyst, and light wavelength (Scheme 1). We found that utilizing (Ir[dF(CF_3)ppy]$_2$(dtbpy))PF_6 in dimethylformamide under irradiation with 450 nm, azetidine **1** underwent the reaction with vinyl pyridine in the presence of multiple bases, such as potassium carbonate (entry 1, Scheme 2), 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (entry 2), potassium phosphate tribasic (entry 3), and lithium hydroxide monohydrate (entry 4) in 39%, 30%, <25%, and 76% yield, respectively. The use of 2,4,6-collidine failed to give the product (entry 5). Changing the metal-containing photocatalyst to the organic one, 4CzIPN, and performing the reaction at 365 nm (entry 6) also provided product **3** with a reasonable 66% yield. Attempts to further change the photocatalyst to TiO_2 *anatase* (entry 7), $Ru(bpy)_3Cl_2$ (entry 8), acridinium photocatalysts (entry 9-11), and osmium(II) photocatalysts (entry 12-13) yielded little to no isolable product. A solvent screen aimed at replacing dimethylformamide gave varying results with tetrahydrofuran and acetonitrile resulting in decreased yields (please, see SI for full details of the optimization). Control experiments revealed that without light the reaction did not proceed (entries 14, 15).

Scaled-up synthesis. Previously, we used the photochemistry *in flow* for the multigram scale preparation of bicyclo[1.1.1]pentanes for medicinal chemistry.[11] Here, we wanted to use this knowledge for the multigram scale preparation of azetidines for medicinal chemistry. Therefore, having identified optimal batch reaction conditions (entries 4 and 6), we next performed the reaction *in flow* using the cheaper organic catalyst - 4CzIPN (entry 17). Pleasingly, under these conditions, 48 g of product **3** was easily obtained in 61% yield in one run (Scheme 2).



Scheme 3. Reaction scope: variation of alkenes, and substitution at the azetidine ring. Isolated yields. Reaction conditions: [a]azetidine carboxylic acid (1.0 equiv), alkene (2.0 equiv), (Ir[dF(CF$_3$)ppy]$_2$(dtbpy))PF$_6$ (2.5 mol%), LiOH-H$_2$O (1.1 equiv) in DMF [0.2 M], 450 nm, 18h, rt, batch. [b]Azetidine carboxylic acid (1.0 equiv), alkene (2.0 equiv), 4CzIPN (2.5 mol%), LiOH-H$_2$O (1.1 equiv) in DMF [0.2 M], 365 nm, 12-18h, rt, batch. [c]Azetidine carboxylic acid (1.0 equiv), alkene (1.5 equiv), 4CzIPN (2.0 mol%), LiOH-H$_2$O (1.1 equiv) in DMF [0.2 M], 365 nm, in flow, 20-30 mL/min. [d]1.2 equiv. of styrene was used. [e]Cs$_2$CO$_3$ instead of LiOH. X-ray crystal structure of compound **24** (carbon – grey, nitrogen – blue, oxygen – red, sulfur - orange). Ellipsoids are shown at a 50% probability level.

Scope. With optimized conditions in hand, we explored the utility of this chemistry in accessing diversely substituted azetidines (Scheme 3). In studying the reaction scope, we allowed some flexibility using both metal-containing [Ir] and organic (4CzIPN) catalysts in batch. Many azetidine products were also subsequently prepared on scale *in flow* using the organic catalyst.

A variety of heteroaryl styrenes, such as 2-vinylpyridine, 2-vinylpyrimidine, 2-vinylpyrazine, and the corresponding vinyl thiazole underwent the addition giving azetidines **4**-**7** in 55-74% yield. Reaction with substituted styrenes also worked well to provide the corresponding azetidines **8**-**12** in good yields. As a demonstration of the potential utility of this chemistry, we also explored the reaction with 5-vinyl thalidomide, which yielded a new E3 ubiquitin ligase recruiter building block **13** in 28% yield. More traditional Michael acceptors (methyl acrylate, methyl vinyl ketone, *etc*) furnished azetidines **14**-**20** in 47-70% yield. Reaction with CH_2=$CHSO_2F$ gave product **21**. To the best of our knowledge, this is the first example of preparing sulfonyl fluoride directly from non-activated amino acids.[12]

Reaction with vinyl sulfones, acrylonitrile, and a $PO(OEt)_2$-containing alkene gave the corresponding azetidines **22**-**26** in 29-53% yield. The $MeSO_2$-moiety is common within approved drugs,[13] and in this context, the $MeSO_2$-substituted product **22** is especially interesting. The structure of sulfone **24** was proven by X-ray analysis.[14] It is also worth noting the synthesis of $P(O)Me_2$-substituted azetidine **27**. In 2016, the FDA approved the anticancer drug *Brigatinib*,[15] and since then the $P(O)Me_2$-containing building blocks have become common in medchem campaigns.[16]

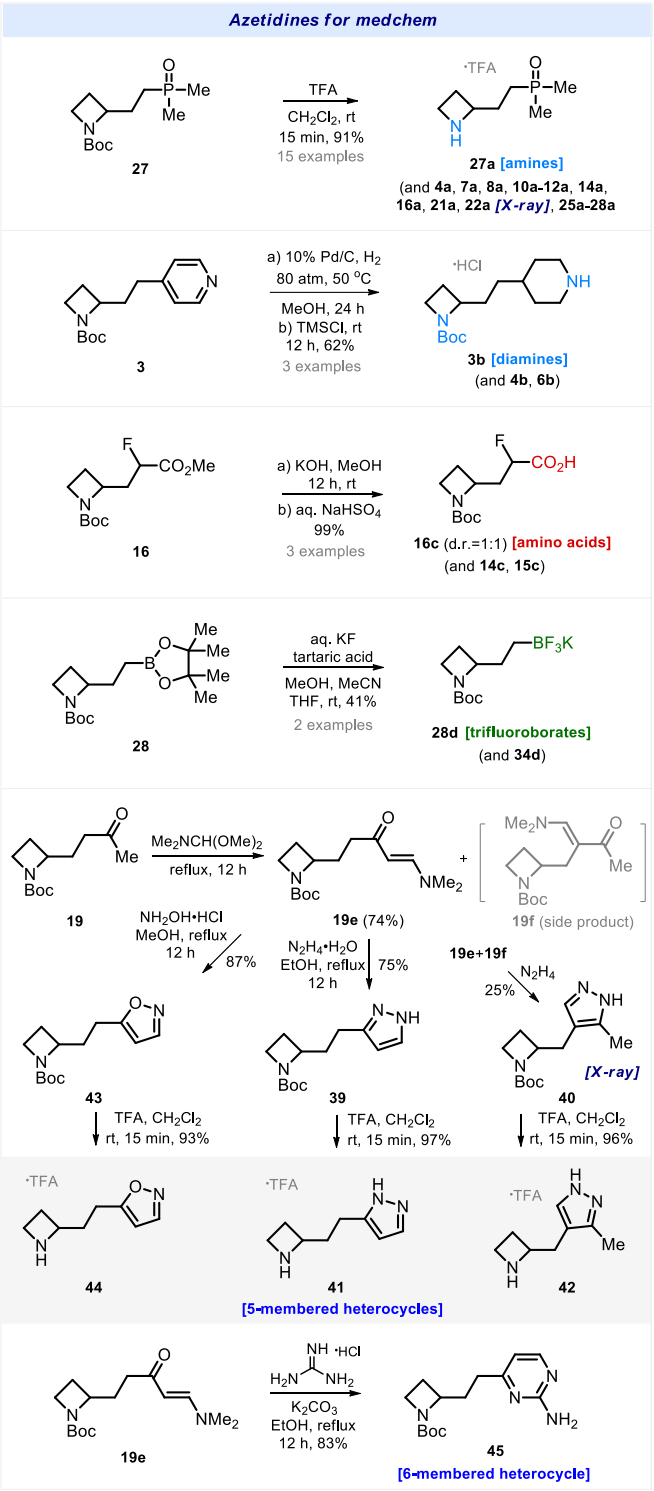
Reaction with vinyl boronates gave the Bpin-substituted azetidines **28** and **29** in 34-45% yield.

Various substituted *N*-Boc azetidine-2-carboxylic acids having aliphatic and ethereal functionalities also proved suitable in the reaction giving azetidines **30**-**36** in 36%-80% yield. Interestingly, quaternary azetidine-2-carboxylic acids underwent direct decarboxylative reaction with 4-vinyl pyridine to smoothly yield products **37** and **38** in 96% and 92%, respectively.

Limitations. The developed approach towards 2-alkyl azetidines was not without limitations. Our conditions failed to give good yield with (a) intrinsically sterically hindered β-substituted acrylates ($MeCH$=$CHCO_2Me$, Me_2C=$CHCO_2Me$), (b) non-polarized alkenes (*N*-Bn maleimide, butadiene sulfone), and (c) electron-rich alkenes ($EtOCH$=CH_2, 2-thiophene-CH=CH_2). For a full list of non-reactive alkenes, please, see SI, p 29. The lack of reactivity of the electron-rich alkenes suggests a nucleophilic character of the intermediate *N*-Boc azetidine radical.[17]

Functionalizations. With a practical and scalable protocol toward 2-alkyl azetidines in hand, we converted various products into value-added, multi-functional azetidine-containing building blocks (compounds with one or two functional groups) for use in medicinal chemistry. The standard acidic *N*-Boc deprotection gave amines "a" (Scheme 4). The structure of amine **22a** was proven by X-ray analysis.[14] Reduction of the pyridine/pyrazine ring with H_2/Pd in methanol under heating provided diamines "b."

Saponification of the ester group resulted in the formation of interesting amino acids "c." The reaction of the Bpin-compounds with potassium fluoride in an acetone/water mixture smoothly gave trifluoroborates "d." The reaction of compound **19** with $Me_2NCH(OMe)_2$ led to the formation of a mixture of two



Scheme 4. Synthesis of azetidine-containing building blocks for medicinal chemistry.

isomeric products **19e**:**19f**=3:1, from which the pure isomer **19e** was isolated in 74% yield by column chromatography. The cyclization of **19e** with hydrazine hydrate provided pyrazole **39** in 75% yield. We also obtained the isomeric pyrazole **40** via the reaction of **19e**+**19f** with hydrazine hydrate and the separation of the isomeric products by column chromatography. The structure of compound **40** was proven by X-ray analysis.[14] Acidic deprotection of the *N*-Boc group formed unique isomeric scaffolds **41** and **42**. Cyclization of **19e** with hydroxylamine allowed isolating isoxazole **43** in 87% yield. Acidic *N*-Boc

deprotection of the latter provided scaffold **44**. Condensation of compound **19e** with guanidine smoothly afforded pyrimidine **45** in 83% yield.

Conclusions. We have developed a unified set of conditions for the direct photochemical functionalization of azetidine-2-carboxylic acids with alkenes. The reaction has been realized *in batch* and *in flow* allowing the rapid preparation of alkyl azetidines in mg-, g-, and even multigram quantities. The obtained products, - sulfonyl fluorides, boropinacolates, potassium, trifluoroborates, P(O)Me_2-derivatives, PROTAC-linkers, *etc* - are valuable building blocks for drug discovery.

Conflicts of interest. OPD, AB, IS and PKM are employees of Enamine. JTB, BC, JK, and RJH were employees of Pfizer.

Acknowledgments. This work was sponsored by Enamine and Pfizer.

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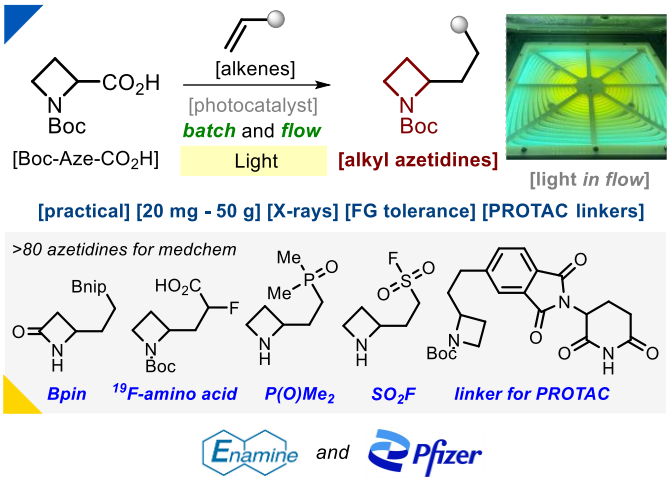
An Approach to Alkyl Azetidines for Medicinal Chemistry

Oleksandr P. Datsenko,[a] Andrii Baziievskyi,[a] Iryna Sadkova,[a] Bismarck Campos,[b] James T. Brewster II,*[b] John Kowalski,[b] Ronald J. Hinklin,*[b] and Pavel K. Mykhailiuk*[a]

[a] Enamine Ltd, Winston Churchill St. 78, 02094 Kyiv, Ukraine.
[b] Pfizer Boulder Research and Development, 3200 Walnut St., Boulder, CO 80023, USA.



Alkyl azetidines have been prepared by photochemical modifications of azetidine-2-carboxylic acids *in batch* and *in flow*. The reaction has been realized in mg-, g-, and even multigram quantities. The obtained azetidines are valuable building blocks for drug discovery.