Photochemical Access to Drug-Like Alkyl Azetidines: Batch and Flow Strategies

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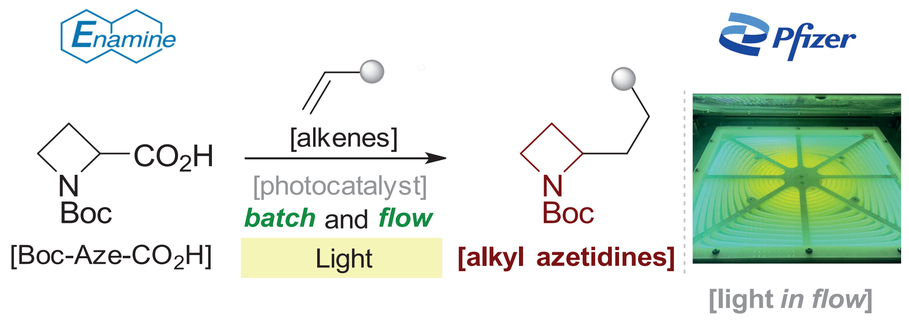
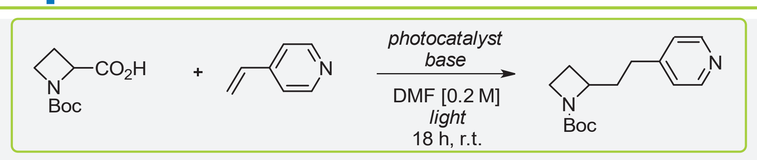
Introduction and Aim

Azetidines are strained four-membered nitrogen heterocycles that have gained growing interest in medicinal chemistry due to their distinct structural and physicochemical features. At least seven approved drugs already contain azetidine units, with many more in clinical development. Despite this relevance, most synthetic methods target 3-substituted azetidines[1], while 2-substituted variants remain underexplored.[2] Here, we report two scalable photochemical strategies to access alkyl-substituted azetidines. The first enables ring construction from aliphatic ketones and vinyl azides; the second introduces a direct, systematic method for the photochemical functionalization of azetidine-2-carboxylic acids with alkenes. Both are compatible with batch and flow setups, allowing efficient synthesis from milligram to multigram scale – offering valuable tools for drug discovery.[3]

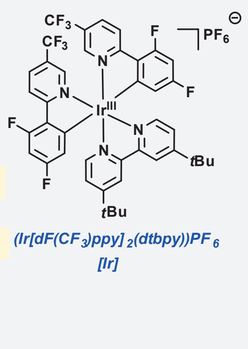


[practical] [20 mg - 50 g] [X-rays] [FG tolerance] [PROTAC linkers]

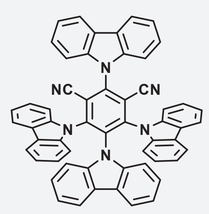
Reaction optimization



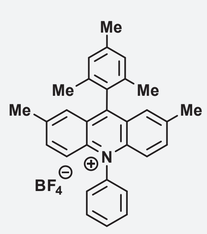
Entry	Catalyst	Base	Light	Yield
1	[Ir]	K_2CO_3	450 nm	39%
2	[Ir]	BTMG	450 nm	30%
3	[Ir]	K_3PO_4	450 nm	< 25%
4	[Ir]	LiOH-H_2O	450 nm	76%
5	[Ir]	2,4,6-collidine	450 nm	< 5%
6	4CzIPN	LiOH-H_2O	365 nm	66%
7	TiO_2 anatase	LiOH-H_2O	365 nm	< 5%
8	$Ru(bpy)_3Cl_2$	LiOH-H_2O	450 nm	< 5%
9	[Acr] 1	LiOH-H_2O	450 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%



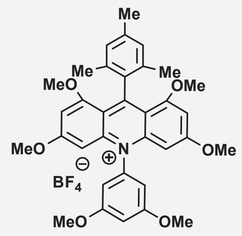
(Ir[dF(CF3)ppy]2(dtbpy))PF6
[Ir]



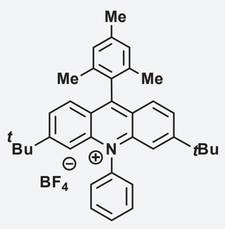
4CzIPN



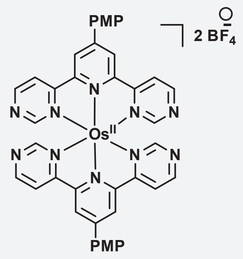
Acridinium catalyst 1
[Acr] 1



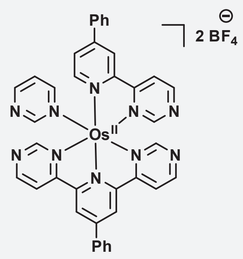
Acridinium catalyst 2
[Acr] 2



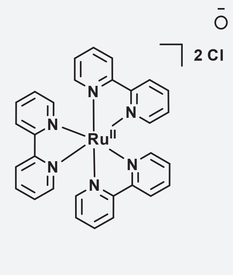
Acridinium catalyst 3
[Acr] 3



[Os] catalyst 1

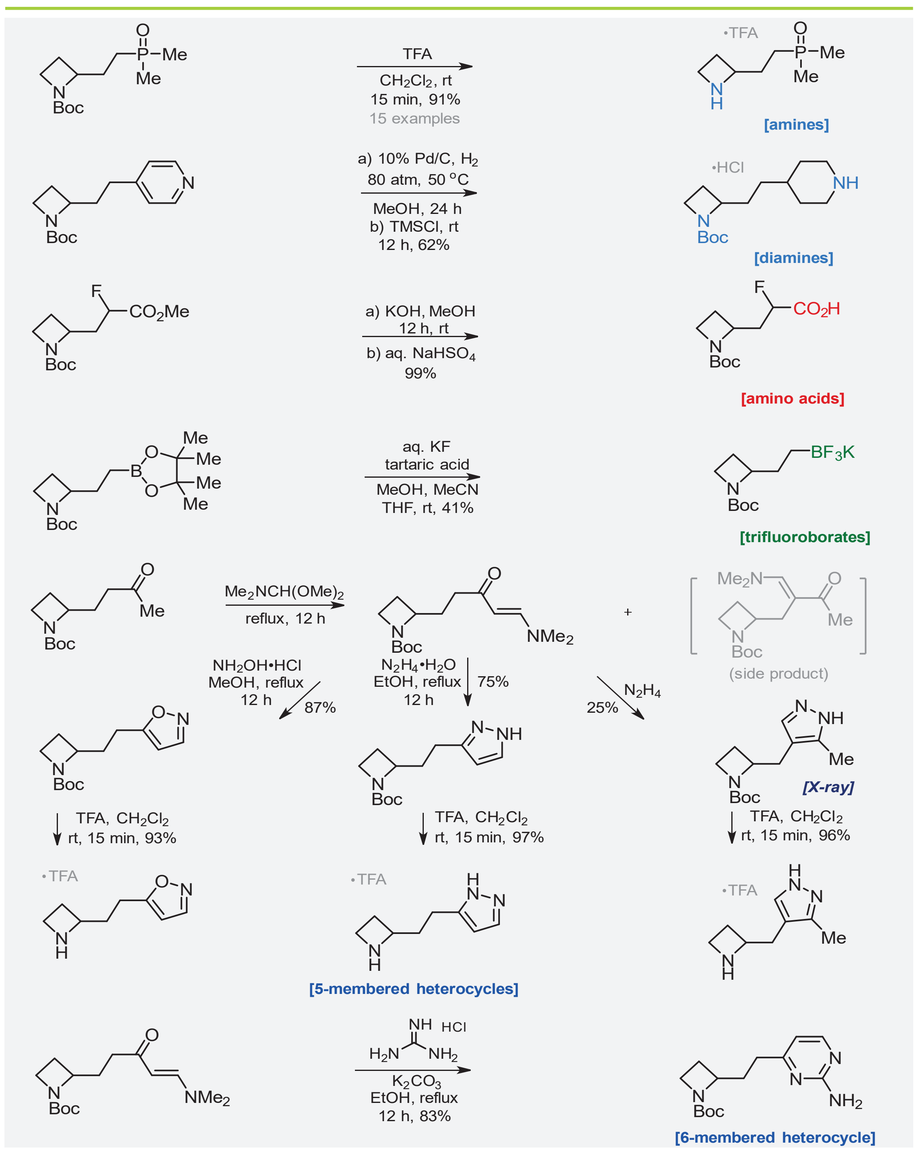


[Os] catalyst 2



$Ru(bpy)_3Cl_2$

Azetidines for medchem



Results

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References

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2.R. Gianatassio, D. Kadish, *Org. Lett*,. **2019**, *21*, 2060–2063.
3.Oleksandr P. Datsenko et al., *Org. Lett.*, 2025.