Photomediated Tandem Sulfonyl Addition-Chemoselective N-Cyclization of *o*-Alkenyl Aryl Ureas: Direct Assembly of Functionalized Dihydroquinazolinones

Sakamuri Sarath Babu,[a] Purushothaman Gopinath,[a]*

[a]Department of Chemistry, Indian Institute of Science Education and Research (IISER) Tirupati, Tirupati 517507, India, E-mail: gopi@iisertirupati.ac.in.

Keywords: Photoredox catalysis, chemoselective cyclization, sulfonylation, functionalized quinazolinones, *o*-alkenyl aryl ureas.

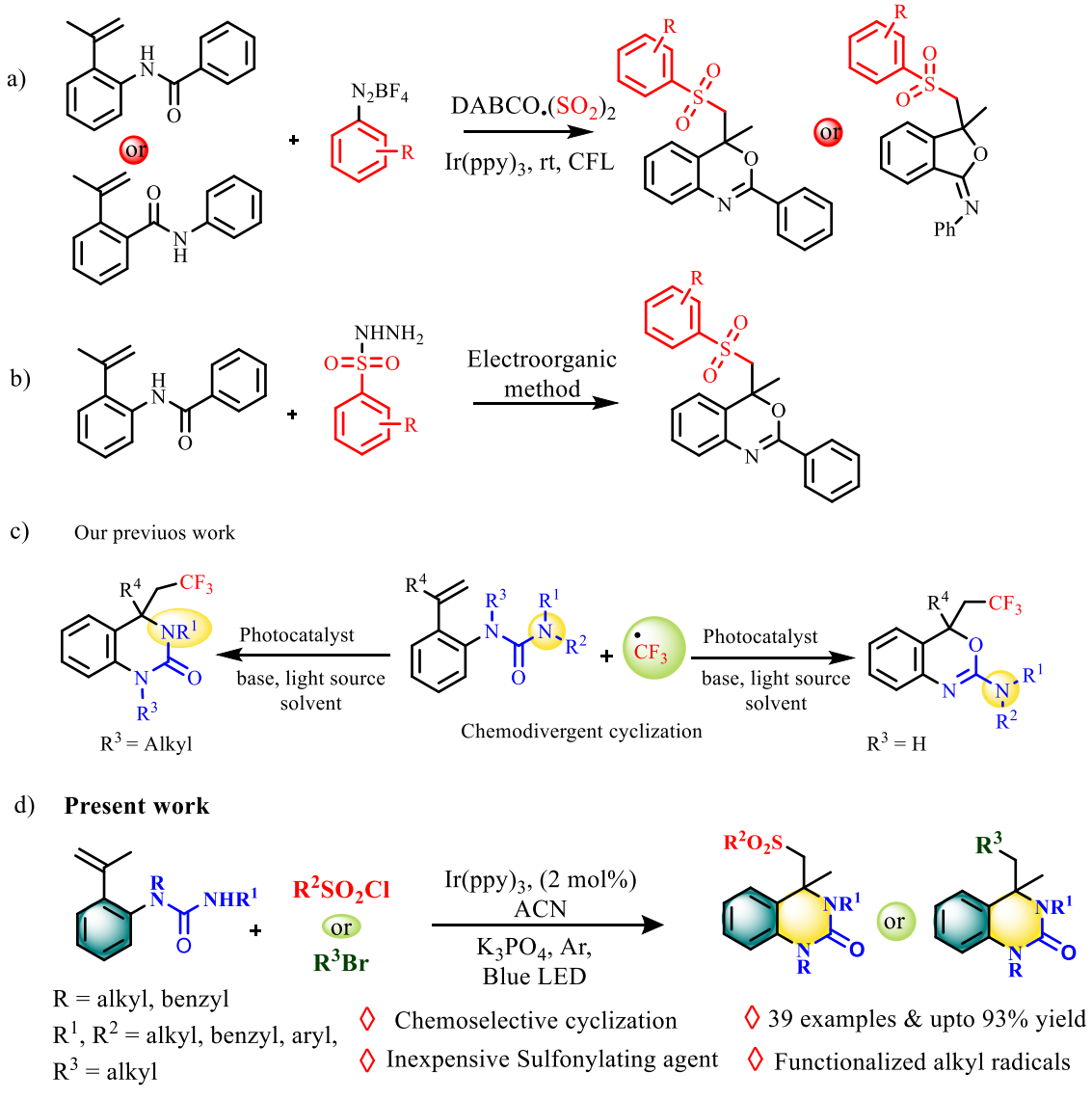
Abstract:

Photoredox mediated tandem addition-chemoselective cyclization of *o*-alkenyl aryl ureas are reported for the synthesis of sulfonyl and other electrophilic radical decorated dihydroquinazolinones. By a careful choice of o-alkenyl aryl urea starting materials, we have achieved chemoselective N-cyclization in the presence of a more reactive amidic oxygen. We have demonstrated the scope of the methodology with a variety of *o*-alkenyl aryl ureas and sulfonyl chlorides including simple aliphatic sulfonyl chlorides, which are less commonly explored. Finally, we also demonstrated the application of our methodology with other electrophilic radicals, which afforded the resultant products in good yields under slightly modified conditions. Quenching studies with TEMPO, revealed a radical mechanism and finally, large-scale synthesis of sulfonyl substituted dihydroquinazolinone showcases the synthetic utility of the methodology.

Introduction:

Photoredox catalysis, an environmentally friendly, mild, and powerful tool for the generation of various radical intermediates, facilitates radical mediated addition reactions in the presence of a suitable radical acceptor. Recently, photomediated tandem radical addition-cyclization reactions have attracted wide attention for their ability to afford functionalized molecular scaffolds in a direct fashion under mild conditions.[1] Although radical cascade addition followed by O-cyclization reactions are common and reported,[2] there are not many reports or studies on radical cascade addition & N-cyclizations[3] of amide/urea type functional groups due to the

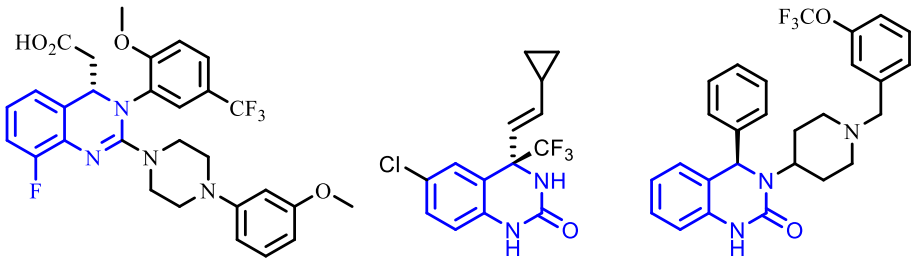
interference of oxygen.[2a] In this direction our group recently reported photoredox catalysed cascade CF_3 addition/annulation of *o*-alkenyl aryl ureas for the construction of 2-amino-1,3-benzoxazines and dihydroquinazolinones in a chemodivergent fashion by controlling the ambident nucleophilicity of aryl ureas via selective N- versus O-cyclization.[4] However, apart from trifluromethyl radicals, other electrophilic radicals were not viable substrates under the reaction conditions due to varied redox potentials and reactivity of different electrophilic radical precursors (**Scheme 1**).



Sulfone moieties are well known functional groups in organic synthesis as they play a vital role in forging carbon-carbon double bonds via Julia olefination.[5] They are commonly found in many natural products, drugs[6] and synthetic intermediates for the construction of interesting molecular scaffolds.[7] Although, the generation of sulfonyl

radicals via conventional methods are known,[8] they have limitations such as the requirement of high reaction temperatures, strong external oxidants, metal additives etc.[9] Sulfonyl chlorides are commercially available inexpensive reagents, which recently are used for the generation of reactive sulfonyl radicals under mild and environmentally friendly conditions using photoredox catalysis via a single electron transfer process.[10]

Dihydroquinazolin-2(1H)-ones on the other hand are an important class of organic molecules found in many bioactive molecules and drugs. For example; DPC-083 is a potent reverse transcriptase inhibitor used for the treatment of HIV infection.[11] Similarly, afacifenacin is used for the treatment of nocturia, which is in phase II clinical trials and Letermovir shows great potential for next generation treatment of HCMV (human cytomegalovirus) infection and has already been approved for phase III clinical trials (**Figure 1**).[12] Given the importance of both dihydroquinazolin-2(1H)-ones and sulfone moieties, it is desirable to develop a mild protocol to access sulfonyl decorated dihydroquinazolin-2(1H)-ones in a single step. In this direction, we designed a tandem addition/chemoselective N-cyclization strategy for the synthesis of sulfonyl functionalized dihydroquinazolinones from *o*-alkenyl aryl ureas mediated by sulfonyl radicals (and other electrophilic radicals) via photoredox catalysis.



letermovir DPC-083 Afacifenacin

Figure 1. Bioactive molecules containing dihydroquinazolinone frameworks.

We started our investigation using N1-benzyl substituted *o*-propenyl phenylurea (**1a, 1.0 equiv.**) as a model substrate and commercially available, inexpensive tosyl chloride (**2a, 1.5 equiv.**) as a sulfonylating agent in the presence of 2.0 mol% $Ru(bpy)_3Cl_2$ photocatalyst and dipotassium hydrogen phosphate (1.5 equiv.) under blue light irradiation in ACN (0.1 M) as solvent. Unfortunately, no expected product

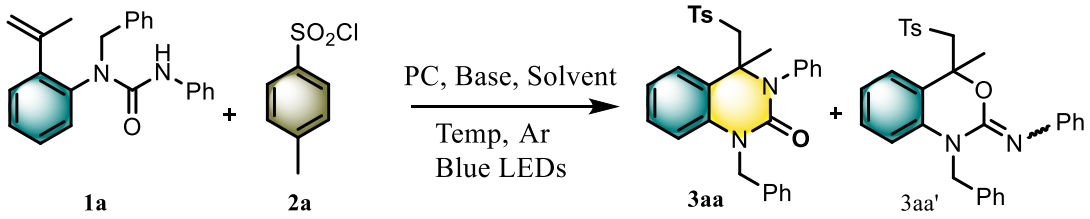
was observed under these conditions. Further screening of photocatalysts, revealed *fac*-Ir(ppy)$_3$ as the optimal catalyst, yielding 42% of dihydroquinazolinone product, **3aa**. Further attempts to increase the yield of **3aa** by changing the solvents resulted in lower yields with complex reaction mixtures (**Table 1, entries 5 & 6**). Finally, reducing the temperature to 14°C improved the yield to 60% (**Table 1, entry 8**). Further reduction of reaction temperature to 5°C didn't help and rendered relatively poor yields (**Table 1, entry 9**). On the other hand, when the reaction was carried out at 8°C with K_3PO_4 (1.5 equiv.) as base, 74% yield of the desired product was obtained (**Table 1, entry 14**). Finally, optimization of base concentration (1.0 equiv.) resulted in 78% yield of the desired product (**Table 1, entry 15**) whereas no desired product was observed in the absence of a base (**Table 1, entry 16**), showing its importance in the desired transformation.

With the optimised condition in hand, we further explored the scope of this tandem addition-chemoselective cyclization protocol with a variety of N1,N2-disubstituted *o*-alkenyl phenylureas **1** and tosylchloride, **2a** (**Scheme 2**). Delightfully, N1-benzyl-N2-alkyl substituted o-alkenyl aryl ureas (**1b-1d**) underwent smooth transformation and furnished the corresponding sulfonyl functionalized dihydroquinazolin-2(1H)-ones (**3ba, 3ca, 3da**) in good yields (74%-81%). Apart from the benzyl substitution at N1, other alkyl substituents such as PMB & ethyl (**1e-1g**) also afforded the resultant products in good yields (**3ea-3ga**). Similarly, N2-aryl substituted-*o*-alkenyl aryl ureas, containing both electron-donating and electron-withdrawing substituents on the phenyl ring afforded the desired products (**3ia-3la**) in moderate to good yields (58%-77%). Notably, an electron-withdrawing substituent on the phenyl ring at the para position (**1l**) rendered relatively lower yields (58%) in comparison to substituents at other positions.

Next we investigated the feasibility of this reaction with regard to a diverse spectrum of aryl sulfonyl chlorides (**2a-2l**) and as expected a wide range of sulfonyl chlorides were well endured under the reaction conditions (**Scheme 3**). For example; aryl sulfonyl chlorides with electron donating groups including simple aryl sulfonyl chloride worked well and offered the desired products (**3aa-3af**) in good yields (71%-

82%). Moreover, electron poor aryl sulfonyl chlorides were also well tolerated irrespective of the substituents position (*o*/*m*/*p*) and gave the corresponding products (**3ag-3aj**) in moderate yields to good yields (60%-69%). Interestingly naphthyl sulfonyl chloride and pyridyl aryl sulfonyl chloride also worked well and afforded 67% & 70% yield of the desired products (**3ak, 3al**) respectively.

Table 1: Screening table

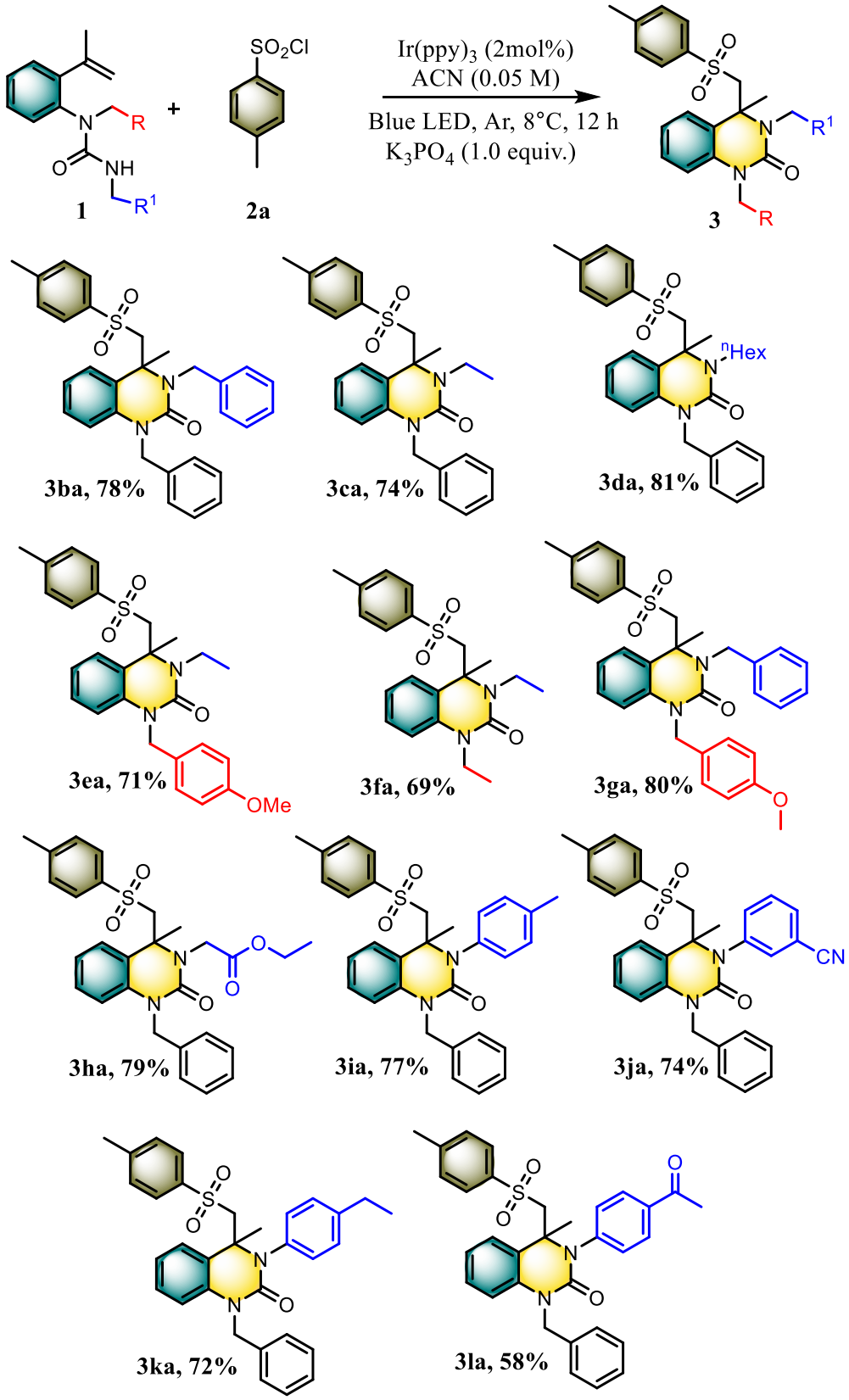


1a 2a 3aa 3aa'

S.No	PC (2 mol%)	Base (1.5 equiv.)	Solvent	Temp.	Yield
1	$Ru(bpy)_3Cl_2$	K_2HPO_4	ACN	rt	-
2	$Ir(ppy)_2(dtbpy)$	K_2HPO_4	ACN	rt	trace
3[b]	CzIPN	K_2HPO_4	ACN	rt	-
4	*fac*-$Ir(ppy)_3$	K_2HPO_4	ACN	rt	42%[c]
5	*fac*-$Ir(ppy)_3$	K_2HPO_4	DCE	rt	34% (20%)[d]
6	*fac*-$Ir(ppy)_3$	K_2HPO_4	DMF	rt	28%
7	*fac*-$Ir(ppy)_3$	K_2HPO_4	ACN	14°C	57% (24%)
8	*fac*-$Ir(ppy)_3$	K_3PO_4	ACN	14°C	60% (22%)
9	*fac*-$Ir(ppy)_3$	K_2HPO_4	ACN	5°C	46% (19%)
10	*fac*-$Ir(ppy)_3$	K_2HPO_4	ACN	8°C	53% (20%)
11[e]	*fac*-$Ir(ppy)_3$	K_3PO_4	ACN	8°C	74% (18%)
12	*fac*-$Ir(ppy)_3$	KH_2PO_4	ACN	8°C	60% (17%)
13	*fac*-$Ir(ppy)_3$	$NaHCO_3$	ACN	8°C	51% (14%)
14	*fac*-$Ir(ppy)_3$	Cs_2CO_3	ACN	8°C	47% (16%)
15[e,f]	*fac*-$Ir(ppy)_3$	K_3PO_4	ACN	8°C	78% (14%)
16	*fac*-$Ir(ppy)_3$	-	ACN	8°C	Complex
17[g]	*fac*-$Ir(ppy)_3$	K_3PO_4	ACN	8°C	-
18	-	K_3PO_4	ACN	8°C	-

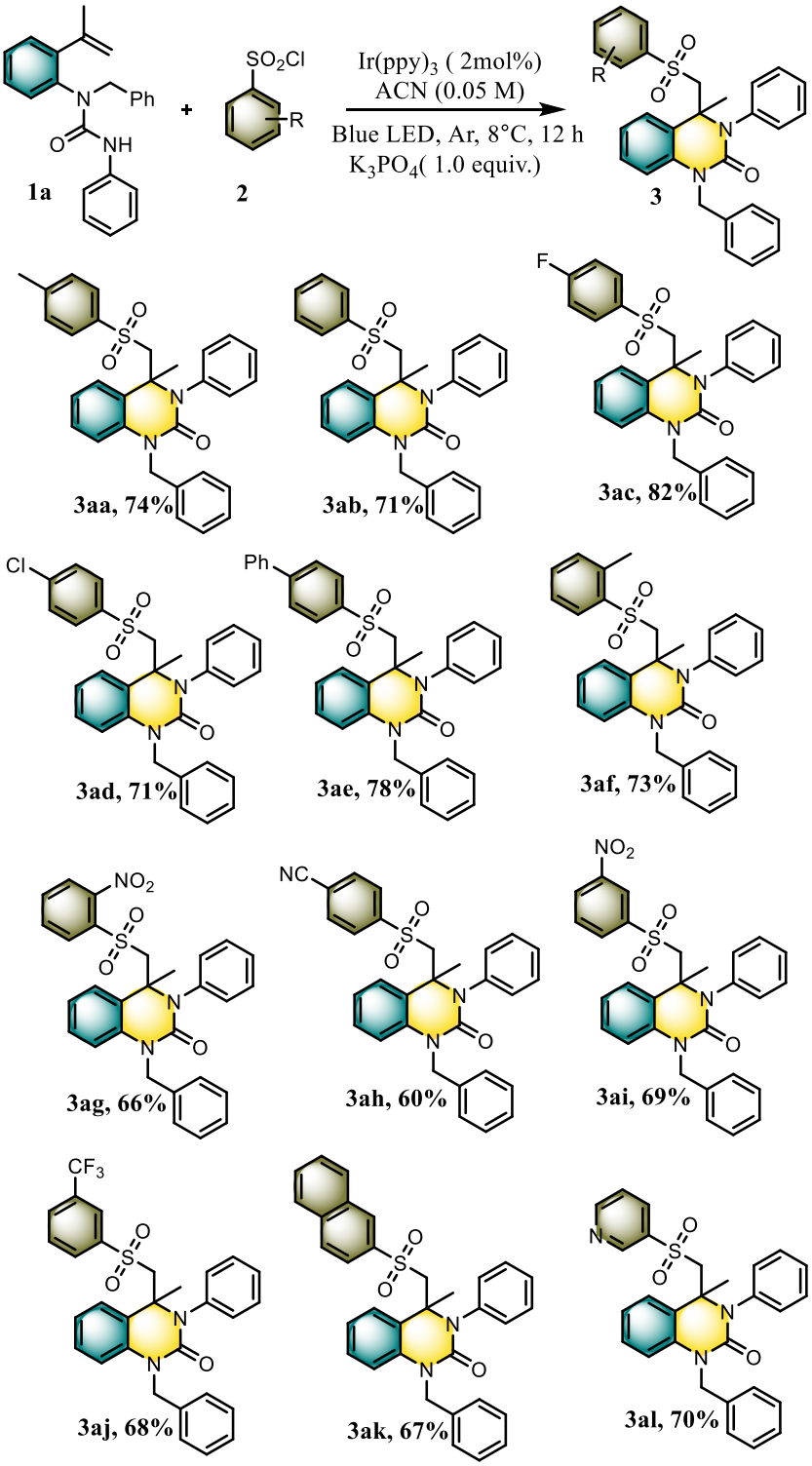
[a]Reaction conditions: 1a (0.1 mmol, 1.0 equiv), 2a (1.5 equiv), base (1.5 equiv), Solvent (0.1 M), 12 h, ^1H NMR yields with 1,1,2,2-tetrachloroethane as internal standard. [b]Reaction performed in presence of DABCO(0.1 equiv). [c]Isolated yield of 3aa. [d]3aa' yield is in the parenthesis. [e]0.05 M ACN. [f]1.0 equiv of base was used. [g]Absence of light.

Scheme 2: Scope of *o*-alkenyl aryl ureas



Reaction conditions: **1** (0.1 mmol, 1.0 equiv), **2a** (1.5 equiv), K_3PO_4 (1.0 equiv), *fac*-Ir(ppy)$_3$ (2 mol%), ACN (0.05 M), blue LEDs at 8°C for 12 h under an argon atmosphere, isolated yields.

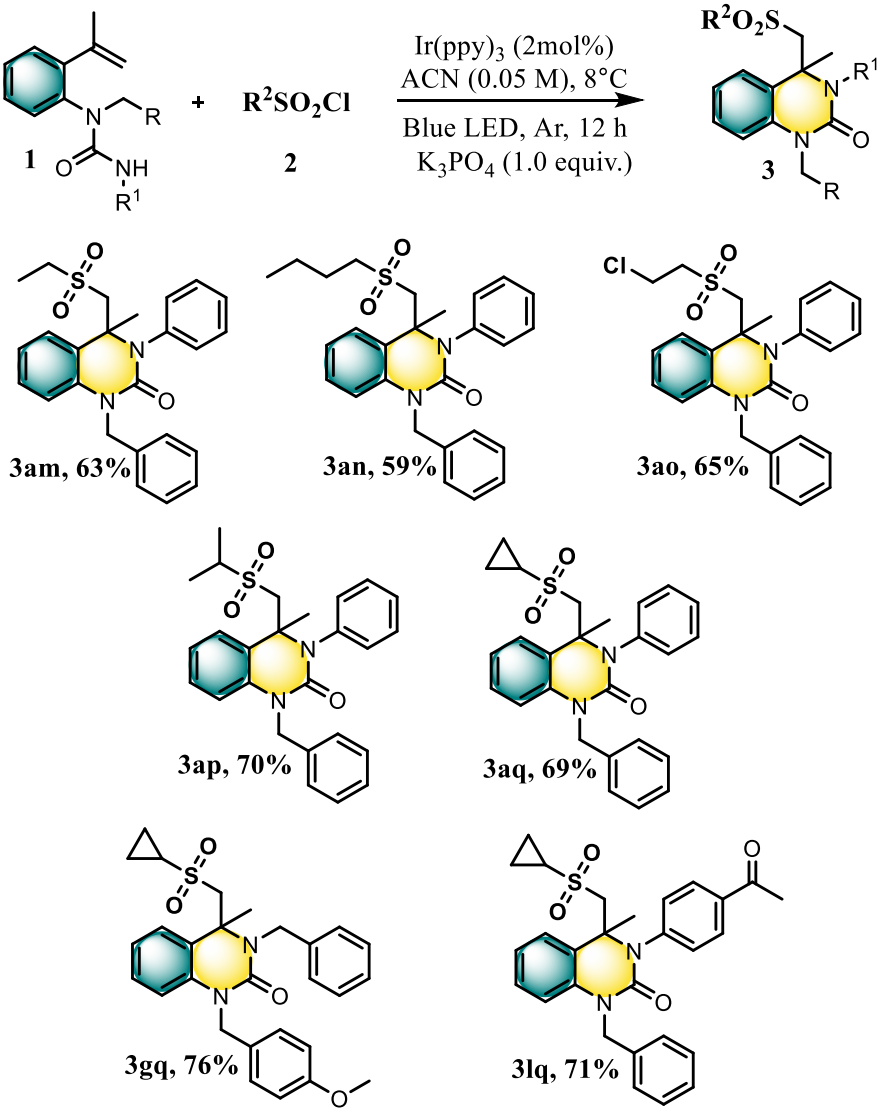
Scheme 3: Scope of aromatic sulfonyl chlorides



Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), **2** (1.5 equiv), K_3PO_4 (1.0 equiv), *fac*-Ir(ppy)$_3$ (2 mol%), ACN (0.05 M), blue LEDs at 8°C for 12 h under an argon atmosphere, isolated yields.

We later studied aliphatic sulfonyl chlorides (ethyl, butyl, 2-chloroethyl, isopropyl and cyclopropyl chlorides) for the desired transformation (**Scheme 4**) and found them to be suitable reacting partners under the standard reaction conditions to afford the products (**3am-3aq, 3gq &3lq**) in moderate to good yields (59%-76%).

Scheme 4: Scope of aliphatic sulfonyl chlorides

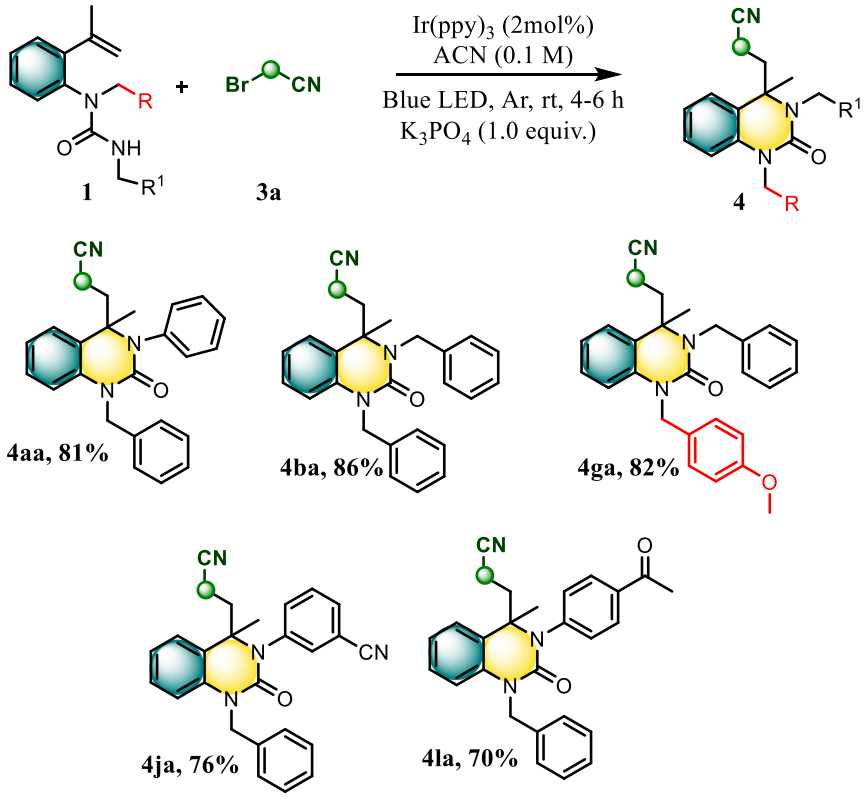


Reaction conditions: **1** (0.1 mmol, 1.0 equiv), **2** (1.5 equiv), K_3PO_4 (1.0 equiv), *fac*-Ir(ppy)$_3$ (2 mol%), ACN (0.05 M), blue LEDs at 8°C for 12 h under an argon atmosphere, isolated yields.

Next, to demonstrate the synthetic utility of this methodology, we focussed our efforts towards the synthesis of functionalized alkyl radicals decorated dihydroquinazolinones via the same chemoselective tandem addition-cyclization strategy (**Scheme 5**). By employing 2-bromoacetonitrile (**3a**) as an alkylating partner

under the standard conditions (with some minor modifications) using **1a** as the alkene partner, we obtained the desired cyanomethyl functionalized dihydroquinazolinone product (**4aa**) in a very good yield (81%). Further, we extended the scope of this method with other *o*-alkenyl aryl ureas (**1a, 1b, 1g, 1j, 1l**) and pleasingly obtained the corresponding cyanomethyl functionalized dihydroquinazolinone products in good yields (**70%-86%**).

Scheme 5: Scope of cyanomethyl functionalized dihydroquinazolin-2(1H)-ones.

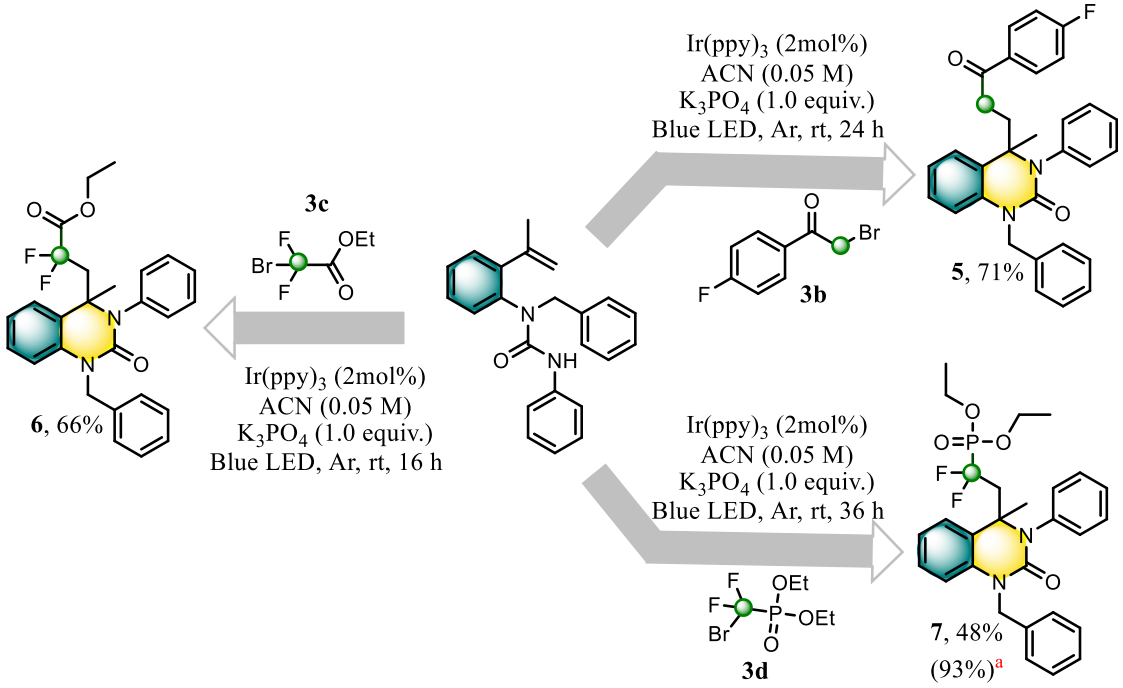


Reaction conditions: **1** (0.1 mmol, 1.0 equiv), **3a** (1.5 equiv), K_3PO_4 (1.0 equiv), *fac*-Ir(ppy)$_3$ (2 mol%), ACN (0.1 M), blue LEDs at room temperature for 4-6 h under an argon atmosphere, isolated yields.

With this interesting results, we next extended this methodology to a variety of other activated alkyl halides (**3b**, **3c** and **3d**) and got the desired dihydroquinazolinones (**5, 6 and 7**) in moderate yields (**Scheme 6**). Later, we performed a scale up experiment and obtained the desired product, **3aa** in almost similar yield (73%) in comparison to the standard (0.1 mmol) scale (**scheme 7**). In order to study the mechanism, we carried out the reaction in the presence of TEMPO, a radical trapping agent, which resulted in no desired transformation with the starting material remaining unreacted, which suggests a radical pathway. To demonstrate the importance of PC and light, we

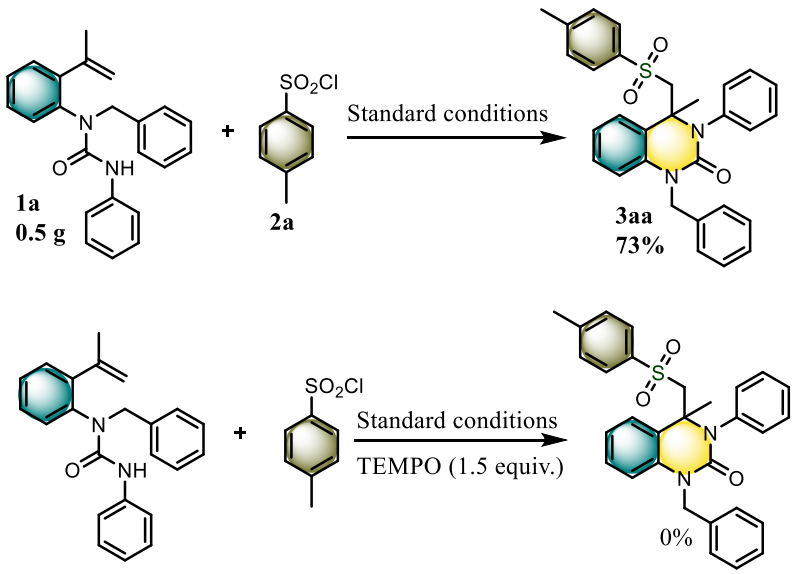
performed control experiments in the absence of PC and light irradiation, and found no desired product in both the cases. Stern-Volmer studies showed the excited $Ir(ppy)_3$ photocatalyst was effectively quenched by sulfonyl chloride, suggesting an oxidative quenching cycle.

Scheme 6: Scope of other alkyl radicals.



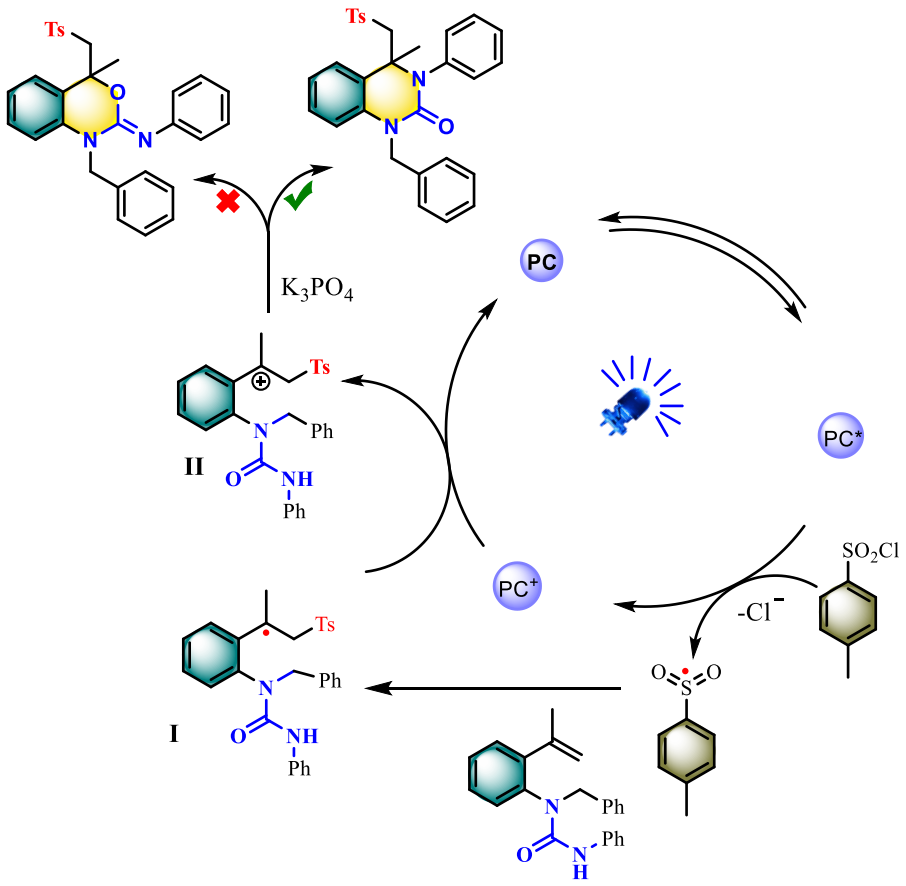
Reaction conditions: **1** (0.1 mmol, 1.0 equiv), **3b/3c/3d** (1.5 equiv), K_3PO_4 (1.0 equiv), *fac*-$Ir(ppy)_3$ (2 mol%), ACN (0.05 M), blue LEDs at room temperature for 16-36 h under an argon atmosphere, isolated yields. [a]Yield based on the starting material recovery.

Scheme 7: Scale up and mechanistic study



Based on these experimental results and previous reports,[10b] we proposed a possible mechanism as shown in figure 2. At first the photoexcited triplet state Ir^{+3} undergoes oxidative quenching with tosyl chloride, resulting in the formation of tosyl radical and Ir^{+4}. The resultant tosyl radical then adds to the double bond of o-alkenyl aryl urea and affords the corresponding benzylic radical intermediate (**I**), which is immediately oxidised to the corresponding benzylic cation (**II**) by the oxidised form of photocatalyst Ir^{+4} to form the ground state photocatalyst, Ir^{+3}. The benzylic cation intermediate (**II**) undergoes chemoselective intramolecular N-annulation followed by deprotonation to afford the desired dihydroquinazolin-2(1H)-one products.

Figure 2: Proposed mechanism



In conclusion, we have demonstrated o-alkenyl aryl ureas as potential precursors for the synthesis of functionalized dihydroquinazolinone analogs. The ambidentate nucleophilicity of aryl ureas was tuned for chemoselective N-cyclization. The versatility of the method has been successfully showcased with different o-alkenyl aryl ureas and sulfonyl chlorides. In order to demonstrate the synthetic utility of the

method a variety of other radical precursors such as cyanobromomethane, α-bromo functionalised carbonyls/phosphates etc. were used to obtain the corresponding functionalized dihydroquinazolinones. Finally, we also demonstrated the method on a large scale using substrate **1a** and the resultant product, **3aa** was obtained in almost similar yields, showing its potential application.

Acknowledgements

This work is supported by the SERB, India. P.G. thanks DST-SERB for a Ramanujan fellowship (SB/S2/RJN-041/2017). S.S.B thanks IISER Tirupati for financial support.

References:

1. (a) Huang, H.-M.; Garduño-Castro, M. H.; Morrill, C.; Procter, D. J., Catalytic cascade reactions by radical relay. *Chem. Soc. Rev.,* **2019**, *48*, 4626-4638; (b) Xu, G.-Q.; Xu, P.-F., Visible light organic photoredox catalytic cascade reactions. *Chem. Commun.,* **2021**, *57*, 12914-12935.
2. (a) Liu, T.; Zheng, D.; Li, Z.; Wu, J., Synthesis of sulfonated benzo [d][1, 3] oxazines by merging photoredox catalysis and insertion of sulfur dioxide. *Adv. Synth. Catal.,* **2018**, *360*, 865-869; (b) He, T.-J.; Zhong, W.-Q.; Huang, J.-M., The synthesis of sulfonated 4 H-3, 1-benzoxazines via an electro-chemical radical cascade cyclization. *Chem. Commun.,* **2020**, *56*, 2735-2738; (c) Deng, Q.-H.; Chen, J.-R.; Wei, Q.; Zhao, Q.-Q.; Lu, L.-Q.; Xiao, W.-J., Visible-light-induced photocatalytic oxytrifluoromethylation of N-allylamides for the synthesis of CF3-containing oxazolines and benzoxazines. *Chem. Commun.,* **2015**, *51*, 3537-3540; (d) Sun, S.; Zhou, C.; Cheng, J., Synthesis of 4-cyanoethylated benzoxazines by visible-light-promoted radical oxycyanomethylation of olefinic amides with bromoacetonitrile. *Tetrahedron Lett.,* **2019**, *60*, 150926; (e) Fu, W.; Han, X.; Zhu, M.; Xu, C.; Wang, Z.; Ji, B.; Hao, X.-Q.; Song, M.-P., Visible-light-mediated radical oxydifluoromethylation of olefinic amides for the synthesis of CF 2 H-containing heterocycles. *Chem. Commun.,* **2016**, *52*, 13413-13416.
3. Gimeno, A.; Cuenca, A. B.; Medio-Simón, M.; Asensio, G., Gold (I)-Catalyzed Reactions of 1-(ortho-Alkynylaryl) ureas: Highly Selective Heterocyclization and Synthesis of Mixed N, O-Acetals. *Adv. Synth. Catal.,* **2014**, *356*, 229-236.
4. Babu, S. S.; Varma, A. A.; Gopinath, P., Photoredox catalyzed cascade CF3 addition/chemodivergent annulations of ortho-alkenyl aryl ureas. *Chem. Commun.,* **2022**, *58*, 1990-1993.
5. (a) Prilezhaeva, E. N., Sulfones and sulfoxides in the total synthesis of biologically active natural compounds. *Russ. Chem. Rev.,* **2000**, *69*, 367-408; (b) El-Awa, A.; Noshi, M. N.; du Jourdin, X. M.; Fuchs, P. L., Evolving organic synthesis fostered by the pluripotent phenylsulfone moiety. *Chem. Rev.,* **2009**, *109*, 2315-2349.
6. (a) Soria, J.-C.; Tan, D. S. W.; Chiari, R.; Wu, Y.-L.; Paz-Ares, L.; Wolf, J.; Geater, S. L.; Orlov, S.; Cortinovis, D.; Yu, C.-J.; Hochmair, M.; Cortot, A. B.; Tsai, C.-M.; Moro-Sibilot, D.; Campelo, R. G.; McCulloch, T.; Sen, P.; Dugan, M.; Pantano, S.; Branle, F.; Massacesi, C.; de Castro, G., First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. *Lancet.,* **2017**, *389*, 917-929; (b) Amri, N.; Wirth, T., Recent advances in the electrochemical synthesis of organosulfur compounds. *Chem. Rec.,* **2021**, *21*, 2526-2537.

7. (a) Feng, M.; Tang, B.; H Liang, S.; Jiang, X., Sulfur containing scaffolds in drugs: synthesis and application in medicinal chemistry. *Curr. Top. Med. Chem.,* **2016**, *16*, 1200-1216; (b) Ilardi, E. A.; Vitaku, E.; Njardarson, J. T., Data-mining for sulfur and fluorine: An evaluation of pharmaceuticals to reveal opportunities for drug design and discovery: Miniperspective. *J. Med. Chem.,* **2014**, *57*, 2832-2842.
8. Zhu, J.; Sun, S.; Xia, M.; Gu, N.; Cheng, J., Copper-catalyzed radical 1, 2-cyclization of indoles with arylsulfonyl hydrazides: access to 2-thiolated 3 H-pyrrolo [1, 2-a] indoles. *Org. Chem. Front.,* **2017**, *4*, 2153-2155.
9. (a) Wu, J.; Zong, Y.; Zhao, C.; Yan, Q.; Sun, L.; Li, Y.; Zhao, J.; Ge, Y.; Li, Z., Silver or cerium-promoted free radical cascade difunctionalization of o-vinylanilides with sodium aryl-or alkylsulfinates. *Org. Biomol. Chem.,* **2019**, *17*, 794-797; (b) Zhu, X.-Y.; Li, M.; Han, Y.-P.; Chen, S.; Li, X.-S.; Liang, Y.-M., Copper-Catalyzed Oxidative Cyclization of Alkynes with Sulfonylhydrazides Leading to 2-Sulfonated 9 H-pyrrolo [1, 2-a] indol-9-ones. *J. Org. Chem.,* **2017**, *82*, 8761-8768.
10. (a) Pagire, S. K.; Kumagai, N.; Shibasaki, M., The Different Faces of [Ru (bpy) 3Cl2] and fac [Ir (ppy) 3] Photocatalysts: Redox Potential Controlled Synthesis of Sulfonylated Fluorenes and Pyrroloindoles from Unactivated Olefins and Sulfonyl Chlorides. *Org. Lett.,* **2020**, *22*, 7853-7858; (b) Rao, W.-H.; Li, Q.; Chen, F.-Y.; Jiang, L.-L.; Xu, P.; Deng, X.-W.; Li, M.; Zou, G.-D.; Cao, X., Visible-Light Photoredox-Catalyzed Sulfonyl Lactonization of Alkenoic Acids with Sulfonyl Chlorides for Sulfonyl Lactone Synthesis. *J. Org. Chem.,* **2021**, *86*, 11998-12007; (c) Zhang, P.; Shi, S.; Gao, X.; Han, S.; Lin, J.; Zhao, Y., Photoredox-catalyzed cascade annulation of N-propargylindoles with sulfonyl chlorides: access to 2-sulfonated 9 H-pyrrolo [1, 2-a] indoles. *Org. Biomol. Chem.,* **2019**, *17*, 2873-2876.
11. Corbett, J. W.; Ko, S. S.; Rodgers, J. D.; Gearhart, L. A.; Magnus, N. A.; Bacheler, L. T.; Diamond, S.; Jeffrey, S.; Klabe, R. M.; Cordova, B. C., Inhibition of clinically relevant mutant variants of HIV-1 by quinazolinone non-nucleoside reverse transcriptase inhibitors. *J. Med. Chem.,* **2000**, *43*, 2019-2030.
12. Goldner, T.; Hewlett, G.; Ettischer, N.; Ruebsamen-Schaeff, H.; Zimmermann, H.; Lischka, P., The novel anticytomegalovirus compound AIC246 (Letermovir) inhibits human cytomegalovirus replication through a specific antiviral mechanism that involves the viral terminase. *J. Virol.,* **2011**, *85*, 10884-10893.