doi:10.2533/chimia.2022.483 Chimia 76 (2022) 483–492

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Blue LED Mediated C-H and N-H Insertion of Indoles into Aryldiazoesters and Iodonium Ylides

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Abstract: Herein we have discussed projects related to blue LED mediated C-H and N-H insertion reaction in indoles and related heterocycles with aryl diazoesters and iodonium ylides as sources of carbenes. Blue LED effectively facilitates these conversions and was optimized from the option of numerous other LED lights. No metal catalysts were required. The reactions provide formation of differently alkylated indoles, pyrroles and furans. Control experiments and DFT calculation were used to understand the mechanism of reactions. As an application compounds bearing azepino[4, 5-b]indole and spiropiperidino indole building blocks were synthesized from the alkylated products.

Keywords: Blue LED · C-H insertion · N-H insertion · Aryldiazoesters· Iodonium ylides

In 2012, Ludovic received his Ph.D. under the supervision of Prof. Alexandre Alexakis at the University of Geneva. In 2013, he joined BASF Pharma Evionnaz as Process R&D chemist. In 2015, Ludovic became Head of Process R&D Laboratories at Siegfried Evionnaz SA. In 2018, he was appointed as Head of Development Department and member of the Steering Committee. Since 2019, Ludovic is Associate Professor at the HES-SO University of Applied Sciences and Arts Western Switzerland - HEIA-FR.

Dr. Subhabrata Sen, is a Professor in the Department of Chemistry, Shiv Nadar University, Gautam Buddha Nagar India, UP, India. He has about a decade long experience in pharmaceutical industry, from 2002–2012, in companies like BASF-India, Pfizer-VMPS, Chemocentryx etc. until he moved to academia in Shiv Nadar University in 2013. He is the recipient of the prestigious SIEBOLD Collegium Award from University of Würzburg, Germany in 2017 and has been nominated as the fellow of the Royal Society of Chemistry, London in 2021. He has received the research fellowship in 2022 from the University of Paris, France.

Introduction

By the virtue of their presence in varied natural compounds, receptors, proteins, and drug molecules, indoles derivatives are key building blocks for synthetic organic chemists as well as for medicinal chemist and pharmaceutical scientists.[1-17] When we start our investigation on active scaffold, we observed a lack of efficient methodologies to acces to polycyclic indole derivatives while indole alkaloids, polycyclic indolines or simply polycyclic compounds are large families of natural poroducts (NPs) particularly attractive for their complex scaffolds that possess C-C or C-N bonds. In this context, functionalization of indoles species give acces to a wide range of effective motifs for drug discovery (for diverse biological target), dyes, fragrance & flavor, if we consider examples already described in the scientific literature (Figure 1).[18-34]

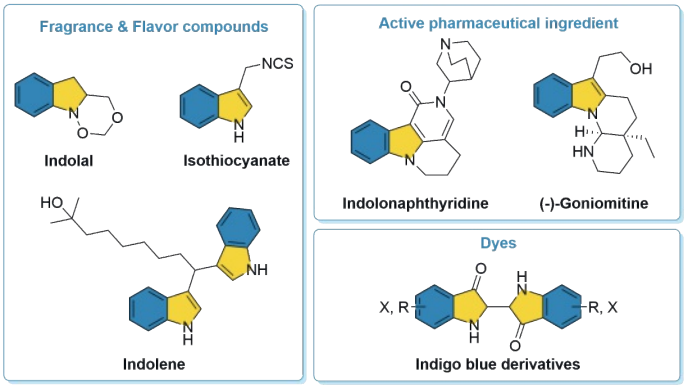


Figure 1. Structure of value-added polycyclic indole compounds.

Based on this assumption, the research group of Prof. Sen and Prof. Gremaud have started to work together in 2019 that resulted in the publication of few research articles about the use of sustainable photochemical reaction *via* blue LED method, to mediate: i) intramolecular C2/C3-H functionalization and cyclopropanation of tryptamines;[35] ii) C-H functionalization of indole, pyrroles and furans with iodonium ylides,[36] both to afford a variety of azepino[4,5-b] indoles; and iii) N-H insertion of indoles to obtain *N*-alkylated product.[31] The reaction of indole core to the C2/C3-H or N-H position give easy access to a wide range of polycyclic indoles derivatives with attractive properties. The conjounction between green chemical transformation and bioactive compounds with efficacious medicinal, smelly or tinting properties have impel in the last decade to forceful effort among the organic chemists community. Admidst all the effort, it was interesting to note that the application of blue LED on C2/C3 substituted indoles with diazoesters or hypervalent idoine (HVI) to generate value-added scaffolds was limited (Scheme 1).

Herein, we report various methodologies using mild blue LED-mediated batch or flow synthetic strategies for C-H and N-H insertion of indole derivatives with diazoesters and iodonium ylides.

2. Results and Discussion

2.1 *Blue LED Mediated intramolecular C2/C3-H functionalization and cyclopropanation of tryptamines*

Transition metal are usually used to catalyze C2/C3-H activation of indoles to afford key bulding blocks or value-added bioactive compounds.[37-39] In parallel, there are only few publications entailing photochemical transforamtion to afford similar compounds. In 2019, Gryko *et al.* started the investigation from transtion metal catalyzed processes to photocatalytic reaction by combining blue-LED irradation and ruthenium ($Ru(bpy)_3Cl_2$) to obtain C2-H functionalization (Scheme 1a).[40] In 2020, Koenigs *et al.* use the Bamford-Stevens reaction in presence of tosyl hydrazone and cesium carbonate to generate *in situ* a diazoalkane intermediate. The cesium carbonate facilitate the formation of diazoalkane which in presence of blue-LED form a carbene intermediate. It then reacts with indole derivatives to generate the C3-H functionalized or cyclopropanated product (Scheme1b).[41] Despit these methodologies there is a room for improvement to develop green and efficient strategies to obtain C2/C3-H activation of indoles, and their application to access various natural product inspired building block such as azepino[4, 5b]-indoles. Thus, we focused our effort on a blue-LED methodology that allow intramolecular C-H functionalization of tryptamine derivatives to afford azepino or spiropiperidino indoles (Scheme 1f).[35] We initially investigate this chemical transformation by screening various types of solvents and LED's in order to establish the most appropriate condition to generate azepino[4, 5b]indoles in presence of tryptamine (1a), phenyl acetate (2a), 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU) and *p*-acetamido benzenesulfonyl azide (*p*-ABSA) (Table 1). With chlorinated or alcoholic solvent only low to moderate yield were obtained after 24h of rection (Table 1, Entry 1 to 5). As acetonitrile (ACN) was known to be beneficial for similar transformation a 3:1 mixture of ACN with water was tested as well as with only acetonitrile. No conversion was observed with ACN:H_2O mixture (Table 1, Entry 6) while with ACN a yield of 92% was obtained (Table 1, Entry 7). To conclude this first round of investigation various light sources were evaluated and as expected switching from Blue LED to white, green or red-LED's the yield drops down to 5 % (Table 1, Entry 9 to 11). As expected, the rection in the dark do not trigger a conversion, allowing to attest that is necessary to have a light source to initiate the formation of the carbene and the following intramolecular cyclization to obtain the desired product (Table 1, Entry 12).

Applying the optimized reaction conditons to various substitued tryptamine derivatives, like *N*-methyltrypatamine (1b) and serotonine (1c), in the intramolecular C2-H functionalization give access to 4ba and 4ca with respectively 61% and 55% yield (Scheme 2). In parallel, various alkyl or aryl acetate with electron donating or withdrawing groups in *ortho*-, *metha*- and *para*-position were evaluated to provide azepino[4, 5b]indoles devrivatives with consistent yield between 53-71% irrespective of the nature of the subsituent (Scheme 2).

However, a trend indicate that arenes are higher yielding than substituted arene, except for the thiophene derivatives (4ad and 4cd) where better yield were obtained. This results are explained through the electron deficiency of the carbene 3c which is stabilzed by the high electron density of the thiophene substituent. In a surprinsing way, when instead of N-methyl tryptamine the N-acetyl or N-Boc protected tryptamine were used a new class of spiropepiridino product (6) was observed after Boc-deprotection with 10% TFA in DCM (Scheme 3).

It was quite impressive to observe two diametrically different famillies of product, azepino (4) vs. spiropiperidino (6), only by substitution of a small and not chelating protecting group by various carbonyl derivatives protecting group. With this initial results in our hand, we decide to investigate in a deeper way the

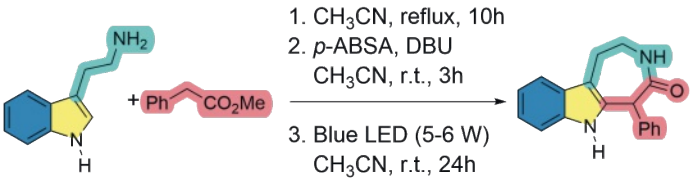
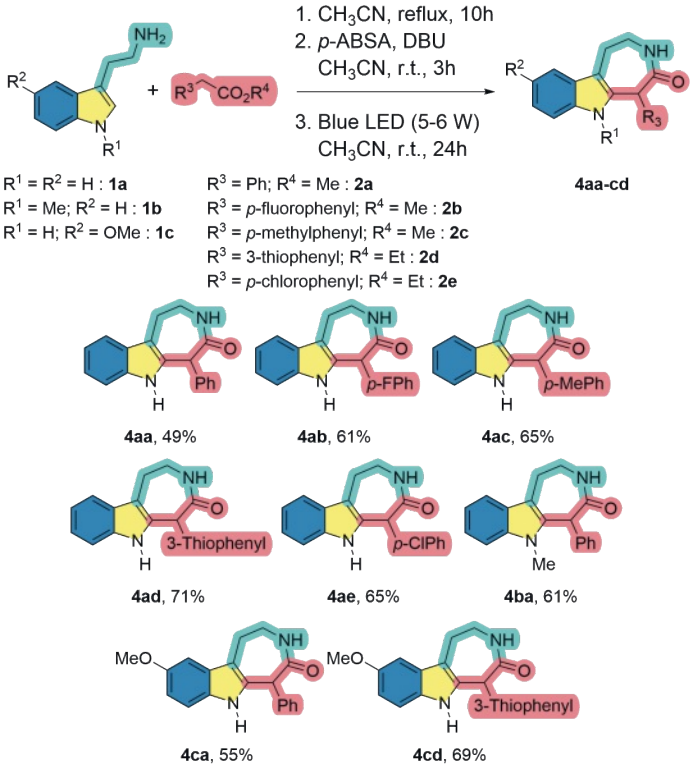


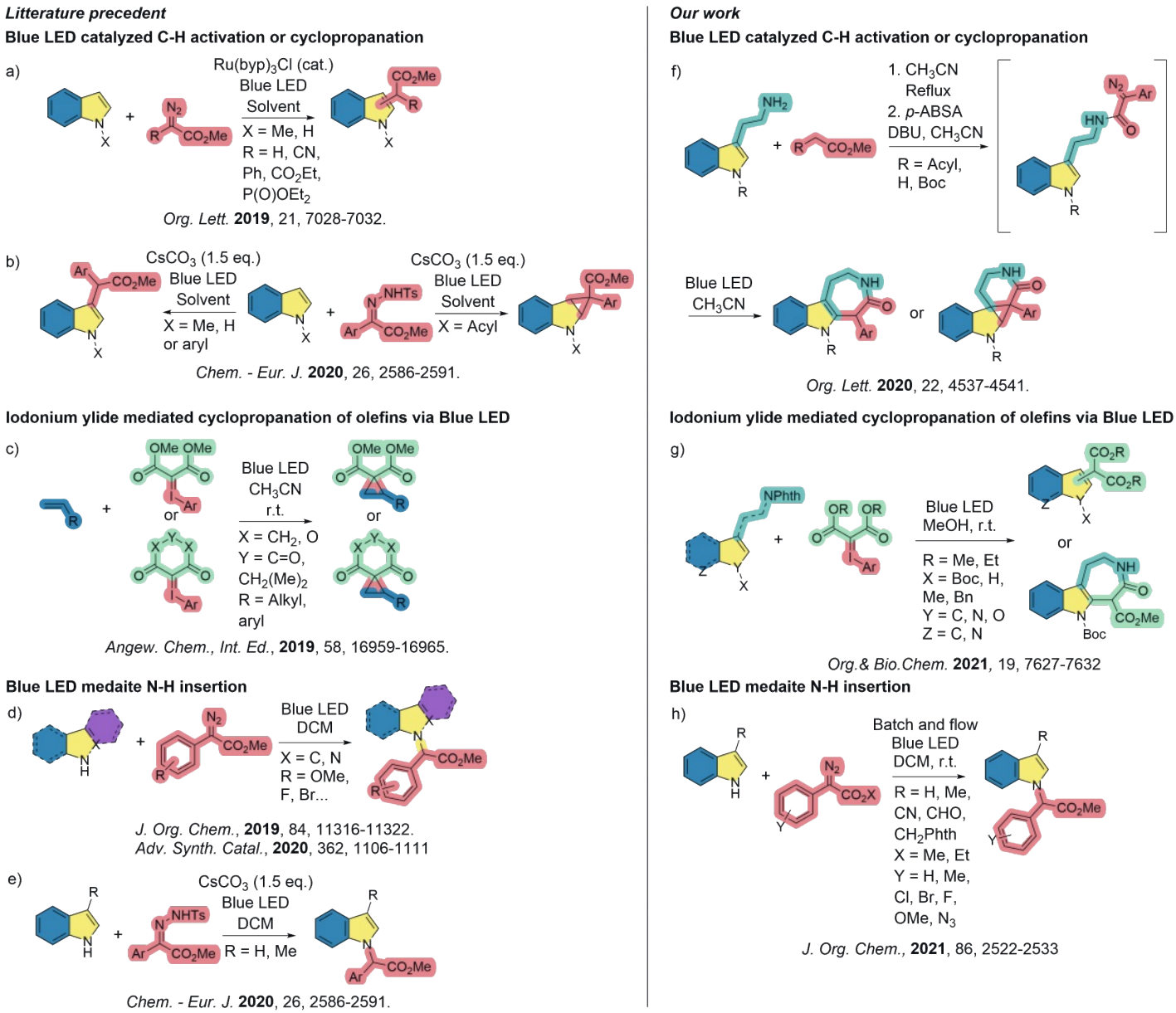
Table 1. Screening of reaction conditions.

Entry	Solvent	Light Source	Yield [%][a]
1	DCM	Blue LED	80
2	DCE	Blue LED	78
3	MeOH	Blue LED	20
4	EtOH	Blue LED	30
5	TFE	Blue LED	20
6	ACN:H_2O[b]	Blue LED	0
7	ACN[c]	Blue LED	92
8	ACN[c,d]	Blue LED	81
9	ACN[c]	Red LED	5
10	ACN[c]	Green LED	5
11	ACN[c]	White LED	60
12	ACN[c]	Dark	0

[a] Isolated yield; [b] ACN.H2O 3:1; [c] Anhydrous; [d] Reaction time for step 3: 12h

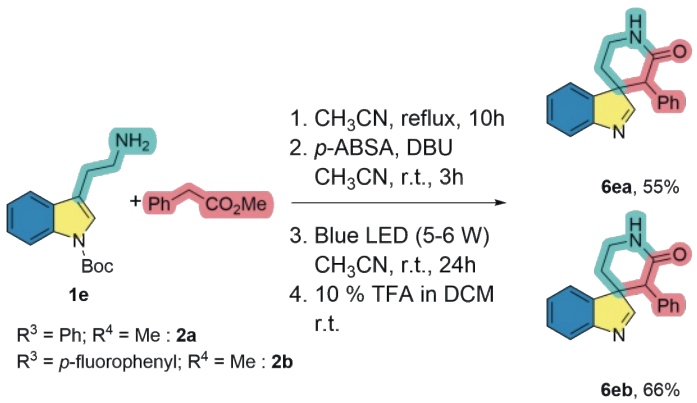


Scheme 2. Synthesis of azepino indole molecules.



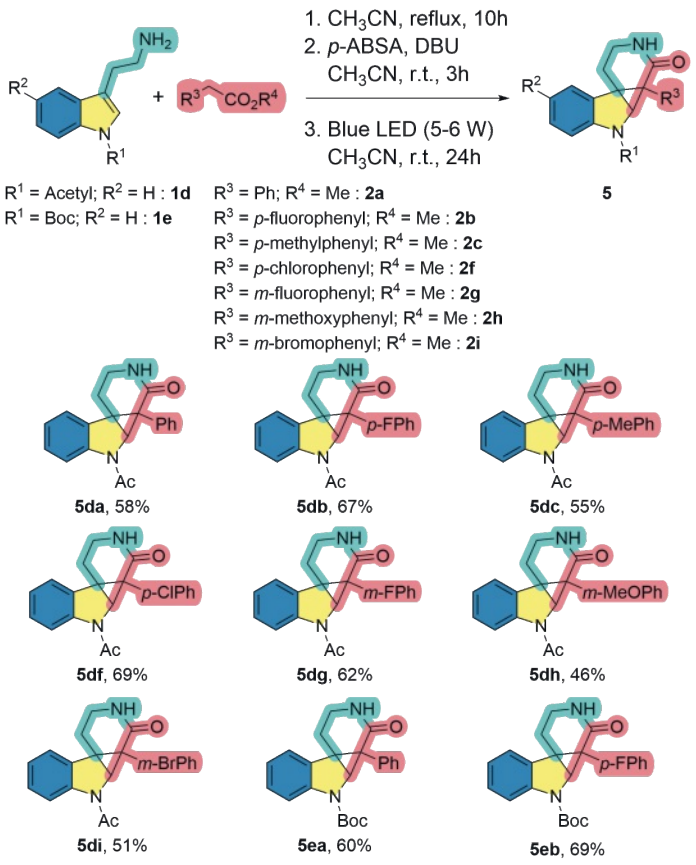
Scheme 1. Previous reports vs. our work on green Blue LED methodologies for C-H and N-H activation.

formation of cyclopropane fused polycyclic compounds, an intermediate for spiropepiridino product, especially by screening various alkyl and aryl acetate (Scheme 4). Contrary to what has been observe for the synthesis of azepino (4) electron withdrawing group like p- and m-fluoro (5db and 5dg) or p-chloro (5df) on the aryl moities give aces to better yield, respectively 62% to 69%, than the electron donating group like p-methyl (5dc) or m-methoxy (5dh) where yields from 46% to 55% were obtained for the synthesis of spiropiperidino (5). The result obtained for the m-bromo derivatives (5di) do not follow the trend of other electron withdrawing group. This observation is probablly linked to the wide electronic radius which makes it less electronegative, respectively less electron withdrawing.



Scheme 3. Synthesis of spiropiperidino indoles.

With all these experimental results in our hand, we decide to investigate the mechanisms of transformation for the two families of product. One of our hypothesis related to the moderate yield of this project was linked to the unstable nature of the diazo intermediate. First, to support our work, the reaction was followed by LC-MS. The formation of the intermediate 3a was quantitative and a caracteristic peak was well detected at 279.1586 m/z $[3a+H]^+$ (Scheme 5). Then, the reaction mixture was cooled down to 25±3 °C and *p*-ABSA as well as DBU were sequentially added to the reaction mixture followed by three hours of stirring after which the TLC showed a complete conversion to the diazo intermediate 3b. We concluded that 3b is unstable since we were not able to isolate this intermediate from the crude reaction mixture wether by flash chromatography, crystalization or other isolation method. Thus, the reaction were telescoped and the reaction mixture with 3b was subjected to blue LED. By LC-MS we were

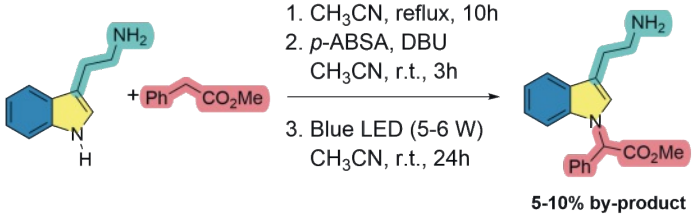


Scheme 4. Synthesis of cyclopropane fused polycyclic compounds an intermediate for spiropiperidino indoles.

able to observe a caracteristic peak related to the formation of the carbene 3c and the final azepino 4 (Scheme 5). Only in a second working package a density functional theory study (DFT) was carried out. As we already observe with the LC-MS in-process control, compounds 4, 5 and 6 are connected to one another by the key intermediates 3a to 3d. As stated in the mechanism proposed in Scheme 5, when the diazo intermediate 3b is submit to blue LED the carbene 3c was formed. The free carbene immediately attacks on the C2-C3 double bond of indole, through cycloprpanation, and result in the formation of the key intermediate 3d via a transtion state. Whether the substituent R^1 is H or Me, the lone pair of electrons on the indole nitrogen open the cyclopropyl ring to give access of 3e. The proton on C2 position of the indole ring was transfered to the adjacent carbocation position and leads to the formation of azepino product 4. In the case of the intermediate 3d, another possible chemical pathway is also observed. The proton on nitrogen can also migrated to the adjacent C2 of indole and opened up the three-membered ring and lead to the formation of spiropepiridino compiunds 6. But compared to the formation of azepino 4, the transition state energy barriers are much higher. Acetyl substitution on nitrogen has little or no impact on the formation of the cyclopropane ring with an analogous attack on the C2-C3 positon of the indole by the carbene to give access to 3d. In the same way the reaction is barrierless and with a highly exothermic reaction energy. The slight energetical difference can be explain by the conjugation of the lone paire on the indole nitrogen and the acetyl moiety, which allow to obtain a more stable cyclopropane ring.[35]

2.2 *Blue LED Mediated intramolecular N-H insertion*

During the assesment of the blue LED-mediated intramolecular C2/C3-H activation of indoles to yield varieties of azepino[4, 5b]-indoles moderate yields were observed. After additionnal investigation, we discovered that aroud 5–10% of a by-product was



Scheme 6. Side product from C2/C3-H activation

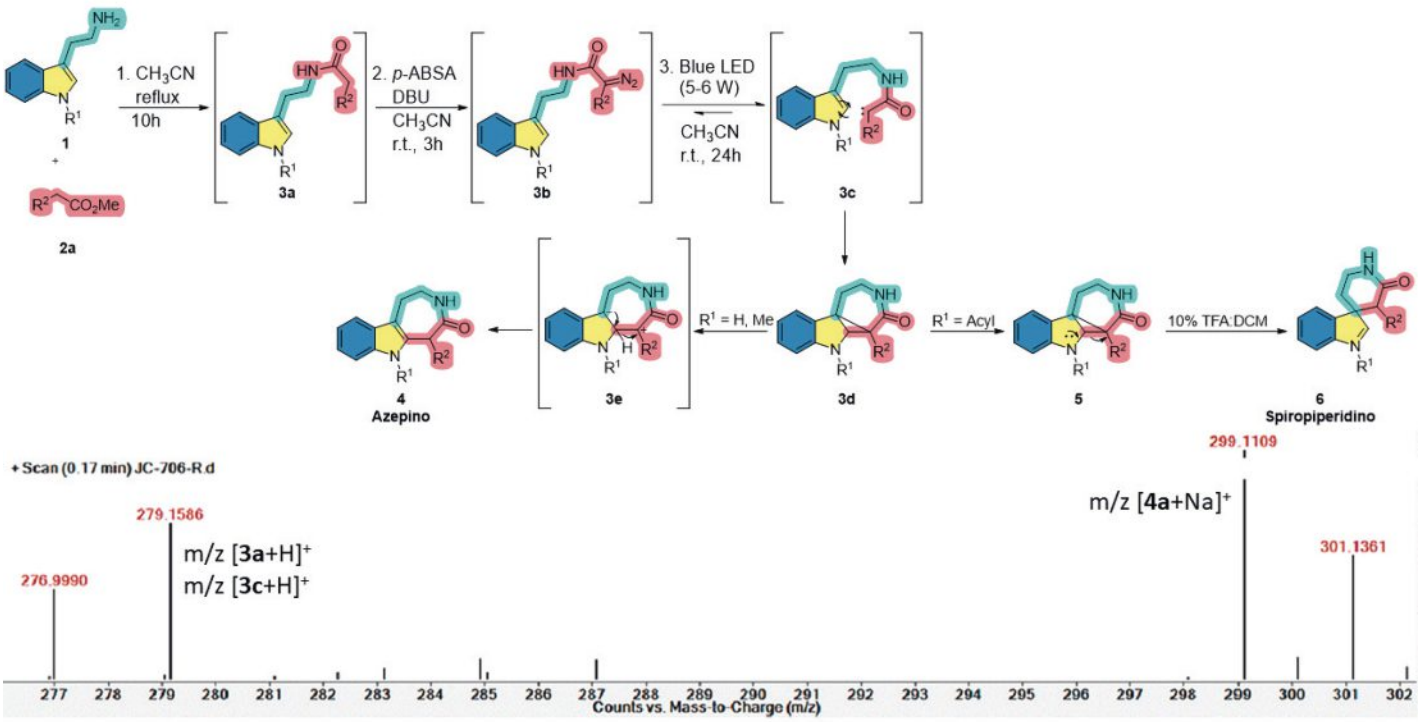
formed. After purification and characheterization, we come to the conculsion that this impurity was the product of the N-H intermolecular insertion (Scheme 6).

Since a one-pot methodology was developped for the C2/C3-H insertion, we can easly conceive that unreacted phenyl diazoester and tryptamine could afford the undesired by-product.

Except reaction on amide, benzotriarzole, carbene, carbazole, pyrazoles, and sulfonamides[41-45] there is only few reports of the N-H insertion of indoles with aryl diazoesters[46-49] in presence of blue-LED (Scheme 1d-e). In 2019 and 2020, Koenigs *et al.* developped metal free carbene *N*-carbazolation with visible light and in presence of aryl diazoesters.[44] This first methodology was followed by a functionalization with tosylhydrazone in presence of cesium carbonate as a base to promote the N-H insertion of unprotected *N*-heterocycles like indoles, tetrahydroquinoline or thienopiperidine. The last one give access to biologically active molecule and enables the direct synthesis of an analogue of clopridogel a platelet aggregation inhibitor drug.[41] During the same period, in 2020, Jurgberg *et al.* reported a blue LED methodology to promote the N-H insertion of carbazoles, pyroles and 1,2,3-triazoles into aryl diazoacetates to access also to bilogically relevant strcutures.[42] Therfore, we investigate the N-H insertion of unprotected indole derivatives into aryl diazoesters in presence of blue LED in batch and flow mode. The latter was performed with an home made photo-flow reactor consisting of 6.3 mL of perfluoroalkoxy alkane tubing capillary reactor, with an internal diameter (ID) 2 mm, coiled around the outer wall of a glass cylinder in combination with a 3-4 W blue LED light strip (with spectral range of 435–445 nm) taped on the inner wall of the cylinder. We started the investigation by mesuring the UV absoption over the time of the phenyldiazoacetate in various solvent in presence of the blue LED with a spectral range between 435–445 nm. We chose solvents coming from various classes of solvents but where phenyldiazoacetate was soluble. For dichloromethane (DCM, non polar) and acetonitrile (ACN, polar – aprotic) the formation of the resulting carbene is efficient and the absorbtion peak is diminishing over the time (Figure 2A to C).

By contrast, methanol (MeOH, polar protic) discolse the wekeast absoption energy. Potentially, the resulting carbene could get quenched by the MeOH or by the water present in MeOH (Figure 2A to C). Based on these preliminary resluts, DCM and ACN were selected to optimze the reaction condition in batch mode (Table 2). For both solvents, in presence of 1 equiv of 2a, the reduction of the reaction temperture increase the yield from 21% to 42% with ACN (Table 2, Entry 1–2) and from 39% to 45% in DCM (Table 2, Entry 3–4). For DCM, the increase in efficiency is less significant, especially because the temperature drop between the two trials is less important than for the ACN. Increasing the number of equivalent of 2a twoards 1f from 1.0 to 2.5 allow to slighty increase the yield (Table 2, Entry 4–7). The best result was obtained in DCM at 25 °C and in presence of 2.0 equivalent of 2a (Table 2, Entry 6) with 55% yield.

To pursuse the process optimzation, a deeper understanding of the kinetics of the N-H insertion reaction was performed. Indeed, three substituted indoles were tested, one with an electron donating groupe, 3-methyl indole (1g), one with an electron withdraw-



Scheme 5. Mechanism of formation of azepino (4) and spiropiperidino (6) derivatives

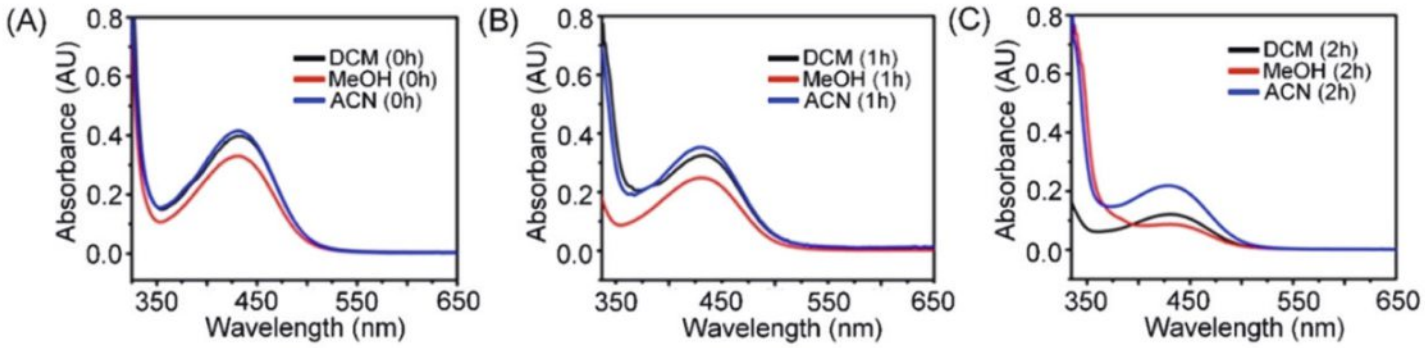


Figure 2. UV absorption of phenyl diazoacetate in various solvents and at different time (A) at 0 h; (B) at 1 h; and (C) at 2 h.

ing group, 3-cyanoindole (1h), and finally the indole (1f), with the optimzed conditions. As for the C2/C3-H insertion the reactions were followed by LC-MS with sample injection every 10 min the first 2 h and every 1 h for the following 6 h. As you can see on Scheme 7B-D, right from the begenning of the reaction the rate of formation of the 7ha is faster than vis-à-vis 7fa and 7ga. This observation is even more striking on Scheme 7E-F. On the same plot, we can rationnaly observe that over the whole period of 8 h the formation of 7fa is faster than 7ga. Thus, the indole substrate substituted in position three by an electron-withdrawing group (R=CN, 1h) has more favorable initial rate and conversion than a neutral group (R=H, 1f) which itself has more favorable initial rate and conversion than an electron-donating group (R=Me, 1g).

Based on the results of the process optimization and kinetic studies, we comit onself to transfer the batch methodology to a flow technology. To start our investigation, we explore various concentration of both substrates (1g and 2a), internal diameter of the tubing capillary reactor as well as the flow rate, respectivelly the residence time (Table 3). With a reaction concentration of 0.1 M for both substrate in a tubing capillary reactor with an ID of 2.0 mm various flow rate and residence time were evaluated (Table 3, Entry 1-4). The best yield (64%) was obtained with a

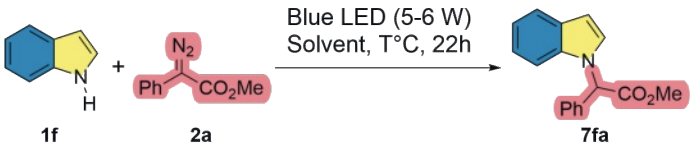
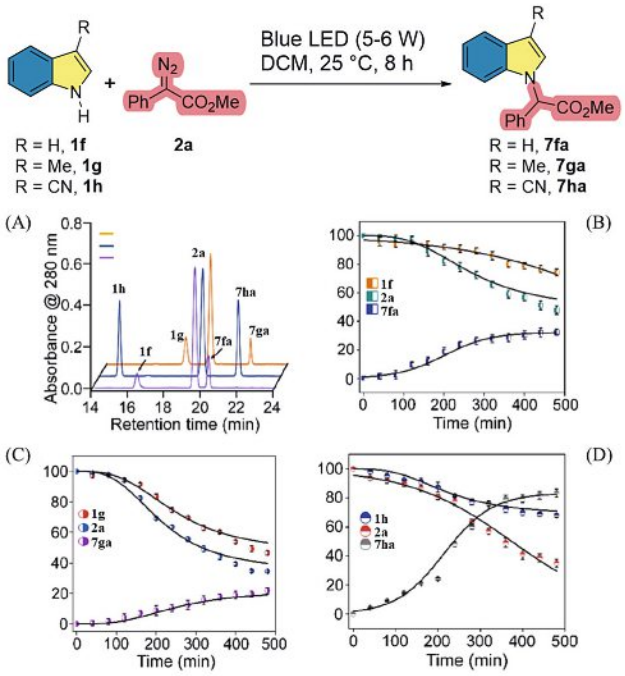


Table 2. Optimization of N-H insertion in batch mode.

Entry	Solvent	2a [equiv]	T [°C]	Yield [%][a]
1	ACN	1.0	78	21
2	ACN	1.0	25	42
3	DCM	1.0	40	39
4	DCM	1.0	25	45
5	DCM	1.5[b]	25	51
6	DCM	2.0[b]	25	55
7	DCM	2.5[b]	25	51

[a] Isolated yield; [b] Compound was added in portions to the reaction mixture



Scheme 7. Reaction kinetics of N-H insertion with various indoles.

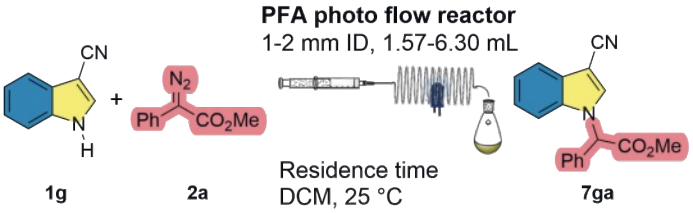


Table 3. Optimization of N-H insertion in flow mode.

Entry	Conc. **1c/2a** [M]	Q[a] [mL/h]	ID [mm]	RT[b] [h]	η[c] **7ga** [%]
1	0.1/0.1	6.0	2.0	1.00	12
2	0.1/0.1	4.5	2.0	1.40	23
3	0.1/0.1	3.5	2.0	1.80	39
4	0.1/0.1	3.0	2.0	2.00	56
5	0.1/0.2	3.0	2.0	2.20	64
6	0.1/0.2	2.0	2.0	3.15	71
7	0.1/0.2	1.5	2.0	4.20	69
8	0.1/0.2	2.0	2.5	4.90	62
9	0.1/0.2	2.0	1.5	1.80	51
10	0.1/0.2	2.0	1.0	0.80	43

[a] Flow rate; [b] Residence time; [c] Isolated yield

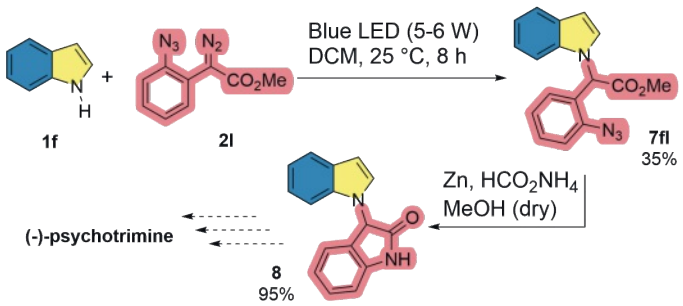
flow rate of 3 mL/h and a residence time of 2 h (Table 3, Entry 4). By incresing the concentration of 2a to 0.2 M, and changing the flow rate, the ID of the tubing capillary reactor and the residence time, the optimum yield of 71% was achieved with a flow rate of 2 mL/h, an ID of 2 mm and a residence time of 3.15 h (Table 3, Entry 6).To stick to our previous results, we evaluated the robustness of the N-H insertion by reacting various 3-substituted indoles 1f-j, with various aryl diazoesters substituted on the phenyl ring 2a–k using the optimzed reaction conditon for batch and flow processes (Scheme 9). All-embracing, we can conclude that the flow methodology give access to better yields over batch. As we already obeserve during the initial experiment, electron-withdrawing group at the C3 carbon of indole like 3-cyanoindole (1h) and 3-carbaldehydeindole (1i) promote the N-H insertion with good yields (≥69 %) to form the desired product, respectively 7ha to 7hk and 7ia to 7ik (Scheme 9).

In a similar trend, indoles substituted by electron-donating group at the C3 position, i.e. 3-methylindole (1g) and 3-phtalimidoindole (1j) give access to the desired products, 7ga and 7jb to 7jk, but with poorer yield (≤66 %). Nevertheless, electron-donating and electron-withdrawing substituent allow to access to the product of interest without formation of by-product of reaction like insertion at the C2/C3-H position or cyclopropanation even when the indole was not substituted at the C3 postion. The only impurity observed during the development of both methodologies is the dimerized diazo compoud. Finally, we applied the developped blue-LED methodology to the synthesis of the 3-(1*H*-indolyl-1-yl)indolin-2-ones (8), a key intermediate for the synthesis of (-)-psychotrimine.[50-54] Indole 1f was reacted with the diazoester 2l under the optimized batch conditions to afford the product 7fl. In situ treatment of the intermediate with zinc dust and ammonium formate give access by lactamization to the key intermediate 8 with an overall yield of 33% (Scheme 8). To highlight the the effect of the substituent at the C3 position of indole, we explore the relationship between chemical shift change of the N-H protons and the related rate of reaction all via a Hamett's plot.[55-58] We observed that for the indole the more electron-donating the C3 substituent is, the more upfield the N-H protons are and accordingly the slower is the rate of the reaction. Finally, the logarithmic ratio of the initial rate of the chemical transformation of 1g-i and 2a *vs.* 1f and 2a was ploted against the deviation in the chemical shift of N-H protons 1g-i *wrt.* 1f. As expected, a linear reltionship was observed. The plot of the $\log(k/k_0)$ against the reported Hamett's substitution constant with substituent at the meta position delight a similar linear relationship. These resluts fervently suggests that the calculated deviation in the chemical shift of N-H protons is equivalent to the Hamett's substitution constant.

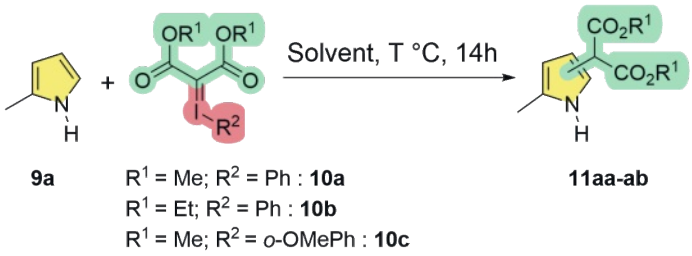
Before quantum chemical caluculations to understand the mechanism of the reaction, few control experiments were performed. First, 1f and 2a were mixed in the absence of blue LED. With this dark reaction condtion only traces of the N-H-inserted product were obtained. Second, a kinetic isotope study (KIE) of 1f and its deutarated analogue in presence of 2a allow us to determine the aparente KIE ($K_H/K_D = 1.32$) with 35% of deuteration at the quaternary carbon center. All these results confirm the implication of the N-H bond of indole in the rate-limiting step of the reaction. Next few calculation were performed. The initail step of the chemical transformation involve the formation of a carbene at the sp^2 carbon center of 2a. Then the carbene reacts with the C3 position of the indole core to obtain the desirec product 7fa.[31]

2.3 *Blue LED Mediated C-H functionalization of indole, pyrroles and furans with iodonium ylides*

Hypervalent iodine compounds are one of the most interesting chemical species that are used as reagents and catalysts for numerous organic transformations. The fact that they mimic metals and are environmentally sustainable makes them extremely valuable. Among these myriad applications, C-H functionalization of ylides (with metal catalysts) is noteworthy.[59-60] To improve the eco-friendlyness of iodine ylide mediated C-H functionalization we recently reported the reaction devoid of any metal catalyst under blue LED at r.t. in methanol (Scheme 1g). Our reported



Scheme 8. Synthesis of 8 a key intermediate for the synthesis of (-)-psychotrimine



Entry	Ratio 1a/4	HVI	Solvent	T [°C]	η[a] [%]
1	1/1	4a	DCM	25	30
2	1/1	4a	MeOH	25	34
3	1/1	4b	DCM	25	25
4	1/1	4b	MeOH	25	29
5	1/1	4c	DCM	25	25
6	1/1	4c	MeOH	25	30
7[b]	1.5/1	4a	MeOH	25	61
8[b]	2/1	4a	MeOH	25	68
9[b]	2.5/1	4a	MeOH	25	68
10[c]	2.5/1	4a	DCM	25	-[d]
11	2.5/1	4a	DCM	40	27

[a] Isolated yield; [b] with blue LED; [c] Dark cond.; [d] no reaction

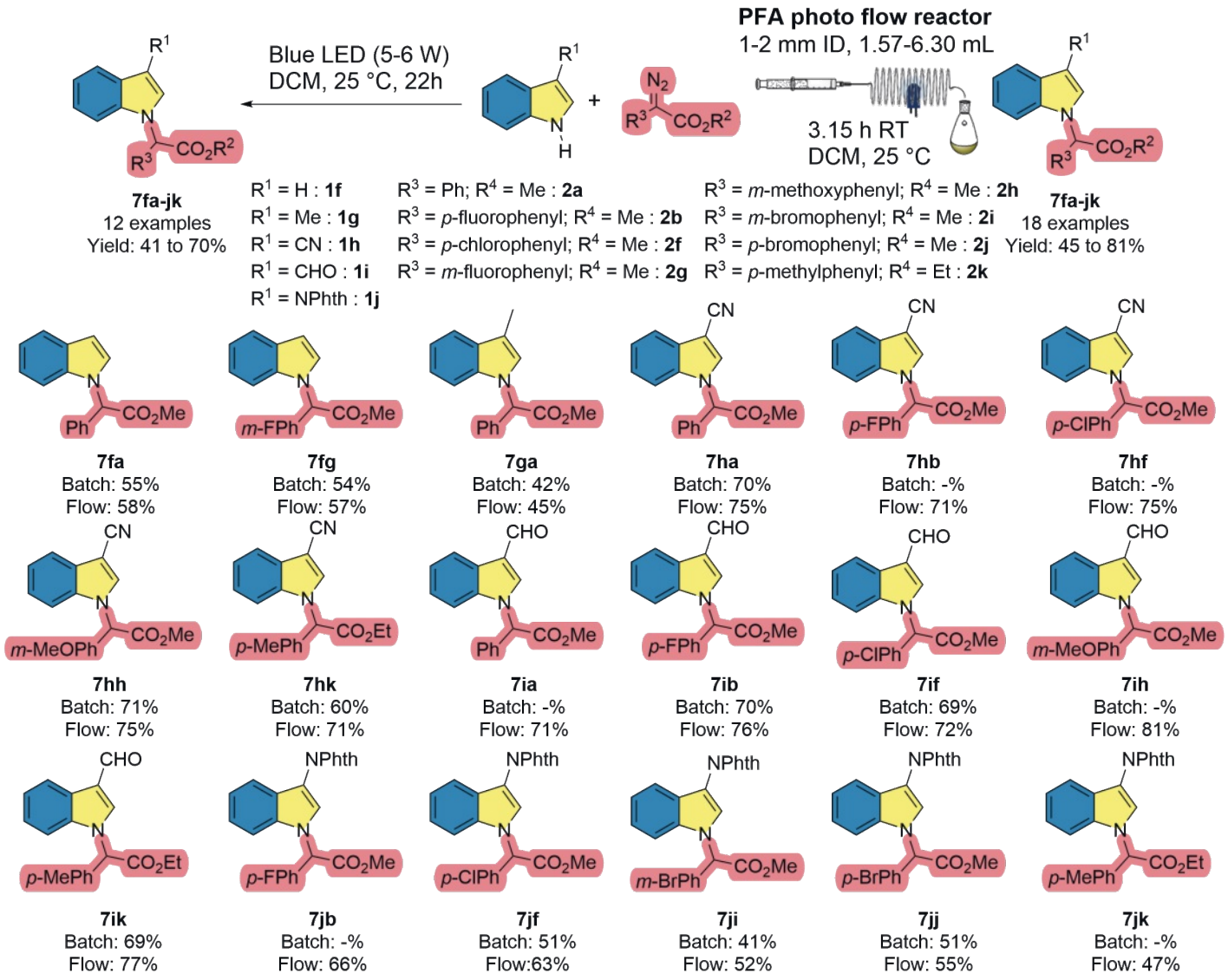
protocol could facilitate C-H functionalization among pyrroles, indoles and furans. The strategy was also applied for the generation of azepino[4, 5-b]indole scaffolds. At the outset the optimization reaction included 2-methyl pyrrole 9a and iodonium ylides 10a and 10b as the reaction partner (Table 4). The reactions were performed under blue LED, dark at 25 °C and under thermal conditions at 40 °C (Table 4). Various solvents were screened for the purpose (Table 4). From the preliminary screening in solvents like dichloromethane (DCM), methanol, acetonitrile (CH_3CN) and diethyl ether (Et_2O), with 1:1 ratio of 9a:10a, at 25°C in blue LED (Table 4, Entry 1–4) it was observed that the reactions in DCM and MeOH (Table 4, Entry 1–2) were the best through the yield of the desired product **r** in 25 and 30% yield in DCM and MeOH respectively (Table 4, Entry 5–6). Next, increasing the equivalent of **9a** to 1.5 and 2 in comparison to 10a, improved the yield significantly to 68% (Table 4, Entry 7–8). Further increment of 9a to 2.5 equivalent however did not improve the yield (Table 4, Entry 9). Additionally, the reaction in dark did not afford any product and the reaction under thermal heating at 40 °C afforded only 27% of 11aa (Table 4, Entry 10–11). Finally, the reaction with 2:1, 9a:10a at 25°C in methanol under blue LED was selected as the optimized protocol.

With the optimized condition in hand diversely substituted pyrroles, indoles and furans underwent C-H functionalization with iodonium ylides 10a and 10b to afford the alkylated products in moderate yields (Scheme 11). The pyrroles 9a-d and 9f-j (both NH free and substituted) when reacted with 10a and 10b afforded 11aa-da and 11fa-ja in 65–78% yield (Scheme 11). 2-methylpyrrole 9a and pyrrole 9b, afforded monosubstituted products 11aa-ba and 11bb with 10a-b in 64–71% yield. However, 3-methyl pyrrole **9c** afforded a nearly 1:1 regiomers 10ca-ca' as inseparable mixture. Similarly, 2, 4-dimethyl pyrrole 9d, afforded a 2:1 mixture of mono and disubstituted products 11da-da' (Scheme 11). It is noteworthy that electron poor 2-cyano pyrrole 9f failed to provide any desired alkylated product 11fa (Scheme 11). The corresponding *N*-Boc and *N*-benzylated pyrroles 9g-j afforded the expected monoalkylated products 11ga-ja in 70 to 78% yield (Scheme 11). Indoles, were the next heterocycles that underwent C-H functionalization under the optimized condition. Unsubstituted indole and its derivatives 9l-n afforded a mixture of C2:C3 monoalkylated compounds 11la-la', 11ma-ma' and 11na-na' with 10a (Scheme 11). These were inseparable mixtures where C3-alkylated product were major. As expected, 3-methylindole **9o** and indole-3-methylacetate 9p afforded the C2 alkylated products 11oa and 11pa in 66 and 63% yield respectively. Interestingly azindole 9q provided the C3 alkylated compound 11qa exclusively in 71% yield. There was ~15% unreacted starting material after about 14h of reaction but no formation of C2 substituted product was observed. It is noteworthy that *N*-Boc indole derivatives 9r-t and N-methyl indole 9w provided the C3 alkylated products 11ra-ta and 11wa exclusively with 10a in 61–69% yield (Scheme 11). Similarly, the 3-substituted *N*-Boc indoles 9u-v afforded C2 alkylated compounds 11ua-va in 68 and 60% yield respectively. Finally, furan 9a and 2-methyl furan 9k afforded the desired C2 substituted products 11ea and 11ka in 61% yield (Scheme 11). Overall, electron rich indoles, pyrroles and furans were more amenable to our protocol though the scope in furan was less extensive.

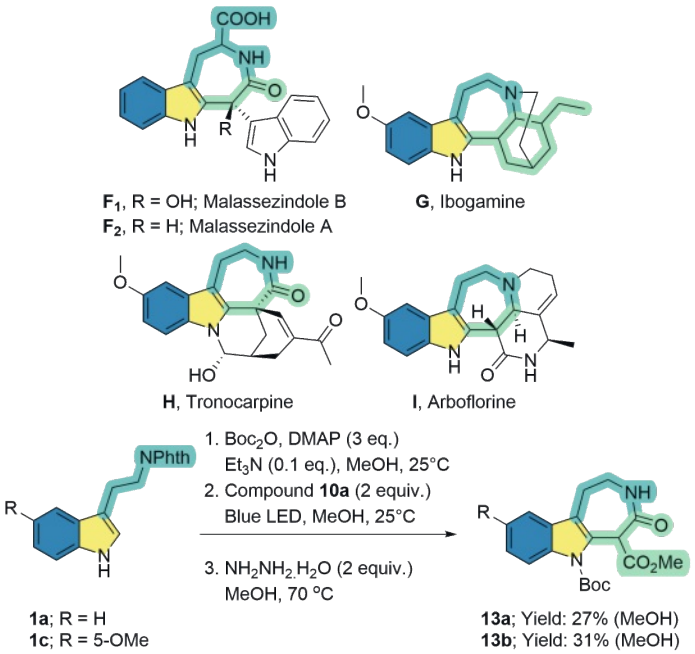
Next few control experiments were performed to understand the mechanism of the transformation. Literature study had indicated radical reaction pathway for iodonium ylides like 10a-c during their cyclopropane formation reactions with olefins. We too investigated the same. Accordingly spin trapping reaction with PBN and reaction in presence of radical scavenger TEMPO confirmed that mechanistically ours too, follow the radical pathway.[36]
Finally, application of the strategy was demonstrated by the synthesis of azepino[4, 5-b]indole from tryptamine derivatives 1a and 1c (Scheme 10). It was a one pot three step reaction sequence in methanol, where N-Boc protection of phthalimido tryptamine derivatives 1a and 1c followed by C2 alkylation with 10a in blue LED and finally phthalimide deprotection with hydrazine hydrate that prompted in situ cyclization to the desired azepino[4, 5-b] indole compounds 13a-b (Scheme 10).

3. Conclusions

Herein, we have developed three new sustainable blue-LED C-H and N-H functionalization methodologies, in batch and/or flow mode, with indoles, tryptamines, furans and pyrroles derivatives in presence of aryl diazoesters or dialkyl malonate derived iodonium ylide. Products were obtained in moderate to excellent yield in mild reaction conditions. Control experiments, HPLC-based kinetics study, DFT calculations, KIE investigation, and Hamett's plot allow us to understand and postulate mechanisms. Various famillies of polycyclic indole, a class of natural compounds, like azepino[4, 5-b]indoles and spiropi-



Scheme 9. Synthesis of N-alkylated indoles under batch and flow mode.



Scheme 10. Synthesis of azepino[4, 5-b]indole scaffolds.

peridino indoles were obtained. The mild reaction conditions developed, with various donor-acceptor substituent, were applied to the synthesis of a key intermediate like the natural product (-)-Psychotrimine for the N-H insertion methodology. Morover, part of the compounds generated through these strategies are presently being screened against various phenotypes to identify their biological activity.

Acknowledgements

We thank Shiv Nadar University, University of applied Sciences and Arts Western Switzerland - HEIA-FR as well as the Leading House South Asia and Iran, Zurich University of Applied Sciences for the financial support. We acknowledge the financial and the MAGUS supercomputing support provided by Shiv Nadar University.

Received: March 28, 2022

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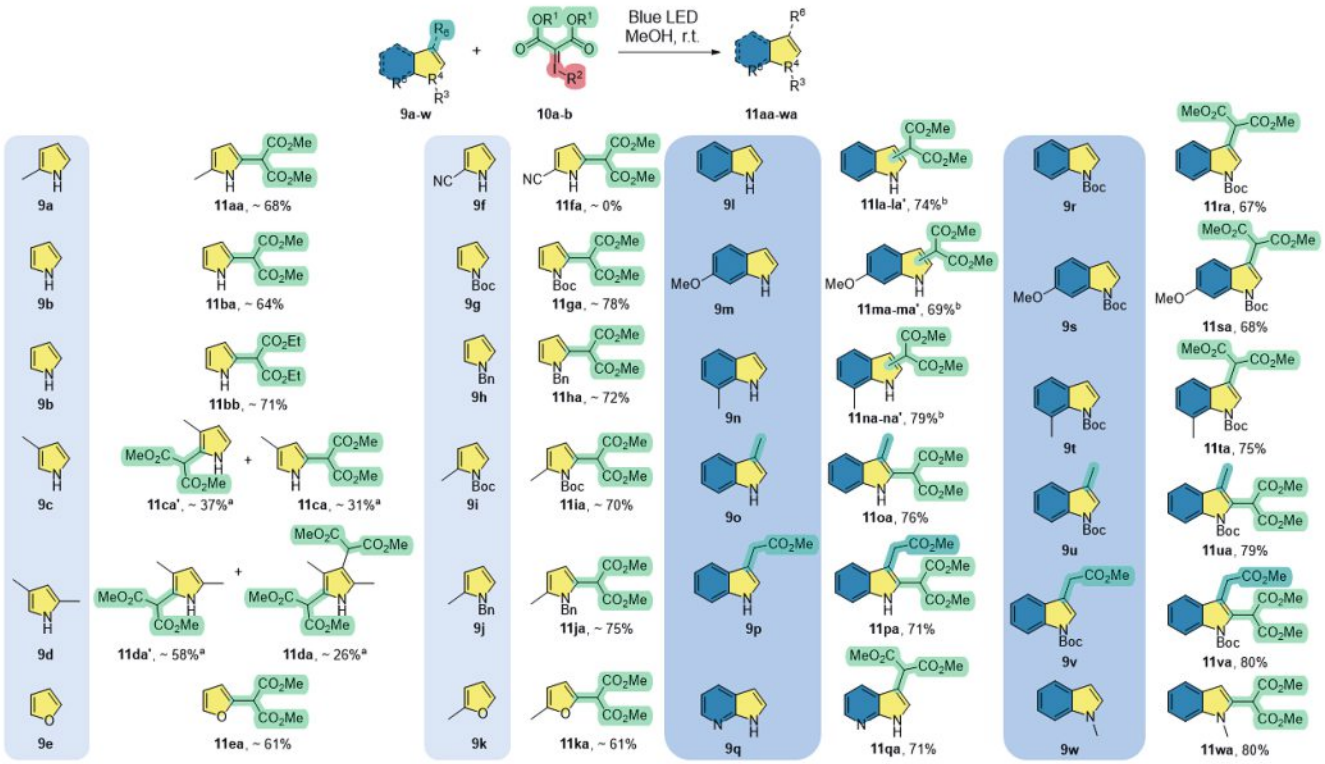

Scheme 11. Blue LED induced CH functionalization of pyrrole, indole and furan derivatives with iodinium ylide; a Separated by chromatography; b 1:1 inseparable mixture.

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