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 alkyalted 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.

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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 access 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 access 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.37 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 conjonuction 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 building blocks or value-added bioactive compounds.\[37-39\] In parallel, there are only few publications entailing photochemical transformation to afford similar compounds. In 2019, Gryko et al. started the investigation from transition metal catalyzed processes to photocatalytic reaction by combining blue-LED irradiation 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 hydrazide and cesium carbonate to generate in situ a diazoalkane intermediate. The cesium carbonate facilitates 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 (Scheme 1b).\[41\]

Despite 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 1c).\[35\]

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 reaction (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 reaction in the dark do not trigger a conversion, allowing to attest that it 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 conditions to various substituted tryptamine derivatives, like N-methyltryptamine (1b) and serotamine (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-, meta- and para-position were evaluated to provide azepino[4, 5b]indoles derivatives with consistent yield between 53-71% irrespective of the nature of the substituent (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 stabilized by the high electron density of the thiophene substituent. In a surprising 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 families 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
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 observed for the synthesis of azepino (4) electron withdrawing group like p- and m-fluoro (5db and 5dg) or p-chloro (5df) on the aryl moieties give access 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 probably linked to the wide electronic radius which makes it less electronegative, respectively less electron withdrawing.

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 characteristic 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 whether by flash chromatography, crystallization 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
able to observe a characteristic peak related to the formation of the carbene 3c and the final azepino 4 (Scheme 5). Only in a second attempt to blue LED the carbene 3c was formed. The free carbene immediately attacks on the C2-C3 double bond of indole, through cyclopropanation, and result in the formation of the key intermediate 3d via a transition state. Whether the substituent R1 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 transferred 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 has little or no impact on the formation of the cyclopropane ring.

2.2 Blue LED Mediated intramolecular N-H insertion

During the assessment 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 additional investigation, we discovered that around 5–10% of a by-product was formed. After purification and characterization, we came to the conclusion that this impurity was the product of the N-H intermolecular insertion (Scheme 6).

Since a one-pot methodology was developed for the C2/C3-H insertion, we can easily conceive that unreacted phenyl diazoester and tryptamine could afford the undesired by-product. Except reaction on amide, benzotriazolocarbene, carbazole, pyrazoles, and sulfonamides,[41,42] there is only few reports of the N-H insertion of indoles with aryl diazoesters[43,44,45] in presence of blue-LED (Scheme 1d-e). In 2019 and 2020, Koenigs et al. developed metal free carbene N-carbazolation with visible light and in presence of aryl diazoesters.[44] This first methodology was followed by a functionalization with tosylhydrazine 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 clopidogel a platelet aggregation inhibitor drug.[41]

During the same period, in 2020, Jurberg 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 structures.[42] Therefore, we investigate the N-H insertion of unprotected indole derivatives into aryl diazosters 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, cooled 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 measuring the UV absorption 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 key intermediates 3a to 3d was submitted in Scheme 5, when the diazo intermediate 3b is submitted to blue LED the carbene 3c was formed. The free carbene is efficient and the absorption peak is diminished over the time (Figure 2A to C). Based on these preliminary results, DCM and ACN were selected to optimize the reaction condition in batch mode (Table 2). For both solvents, in presence of 1 equiv of 2a, the reduction of the reaction temperature 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 towards 1f from 1.0 to 2.5 allow to slightly 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.

By contrast, methanol (MeOH, polar protic) discloses the weakest absorption 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 results, DCM and ACN were selected to optimize the reaction condition in batch mode (Table 2). For both solvents, in presence of 1 equiv of 2a, the reduction of the reaction temperature 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 towards 1f from 1.0 to 2.5 allow to slightly 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 pursue the process optimization, 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 group, 3-methyl indole (1g), one with an electron withdrawing group, 3-acetyl indole (1f), and in presence of aryl diazoesters.
ing group, 3-cyanoindole (1h), and finally the indole (1f), with the optimized 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 beginning 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 rationally 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 commit 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, respectively 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

![Scheme 5. Mechanism of formation of azepino (4) and spiropiperidino (6) derivatives](image)

![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.](image)

| 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     | 1.5b      | 25     | 51         |
| 6     | DCM     | 2.0b      | 25     | 55         |
| 7     | DCM     | 2.5b      | 25     | 51         |

*a* Isolated yield; *b* Compound was added in portions to the reaction mixture.
flow rate of 3 mL/h and a residence time of 2 h (Table 3, Entry 4). By increasing 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 optimized reaction condition for batch and flow processes (Scheme 9). All-embracing, we can conclude that the flow methodology gives access to better yields over batch. As we already observe 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-methyldindole (1g) and 3-phenylimidindole (1j) give access to the desired products, 7ga and 7jb to 7jk, with but 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 position. The only impurity observed during the development of both methodologies is the dimerized diazo compound. Finally, we applied the developed blue-LED methodology to the synthesis of the 3-(1H-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 Hammett’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 was plotted against the deviation in the chemical shift of N-H protons 1g-i wrt. 1f. As expected, a linear relationship was observed. The plot of the log(k/kₐ) against the reported Hammett’s substitution constant with substituent at the meta position delight a similar linear relationship. These results fervently suggests that the calculated deviation in the chemical shift of N-H protons is equivalent to the Hammett’s substitution constant.

Before quantum chemical calculations 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 condition only traces of the N-H-inserted product were obtained. Second, a kinetic isotope study (KIE) of 1f and its deuterated analogue in presence of 2a allow us to determine the apparent KIE (Kₐ/Kₕ) 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 initial step of the chemical transformation involve the formation of a carbene at the sp² carbon center of 2a. Then the carbene reacts with the C3 position of the indole core to obtain the desired product 7fa [59].

### 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-friendliness 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...
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 (CH₃CN) and diethyl ether (Et₂O), 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 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 11a (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 in 65~78% yield. Similarly, 2,4-dimethyl pyrrole 9d afforded a nearly 1:1 regioisomers 10ca-ca' as inseparable mixture. 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 in 65~78% yield. Similarly, 2,4-dimethyl pyrrole 9d, afforded a 2:1 mixture of mono and disubstituted products 11aa-da and 11fa-ja in 65~78% yield. Various families of polycyclic indole, a class of natural compounds, like azepino[4,5-b]indoles and spiropropyrroles 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 (CH₃CN) and diethyl ether (Et₂O), 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 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).

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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 2:1 C3 monoalkylated compounds 11la-la', 11ma-ma' and 11na-na' with 10a (Scheme 11). These were inseparable mixtures where C3-alkylated products 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. 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 of mono and disubstituted products 11aa-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 monosubstituted 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 2:1 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).
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. Moreover, part of the compounds generated through these strategies are presently being screened against various phenotypes to identify their biological activity.

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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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