

FH HES

Universities of Applied Sciences

Fachhochschulen – Hautes Ecoles Spécialisées

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

Ludovic Gremaud*, and Subhabrata Sen*

*Correspondence: Ludovic Gremaud – University of Applied Sciences Western Switzerland, Faculty of Engineering and Architecture, Department of Chemistry, Pérolles 80, Fribourg 1700, Switzerland; orcid.org/0000-0002-0630-932X; Email: ludovic.gremaud@hefr.ch. Subhabrata Sen – Department of Chemistry, School of Natural Sciences, Shiv Nadar University, Greater Noida, Uttar Pradesh 201314, India; orcid.org/0000-0002-4608-5498; Email: subhabrata.sen@snu.edu.in

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 spiro piperidino 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 access to polycyclic indole derivatives while indole alkaloids, polycyclic indolines or simply polycyclic compounds are large families of natural products (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]

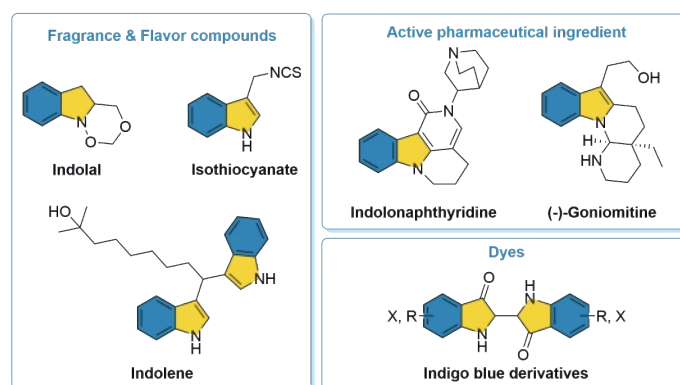


Figure 1. Structure of value-added polycyclic indole compounds.

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.^[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 conjunction 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)₃Cl₂) 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 (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 spiro-piperidino 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 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:H₂O 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 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 serotonin (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 spiro-piperidino 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. spiro-piperidino (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

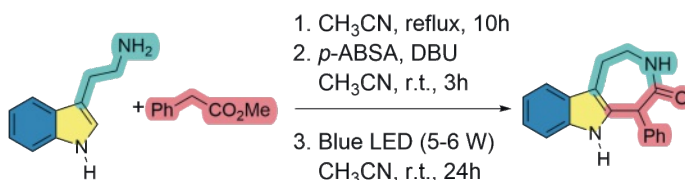


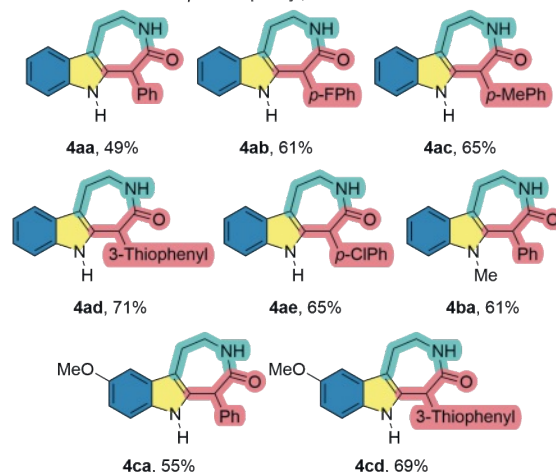
Table 1. Screening of reaction conditions.

| 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 ₂ O ^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



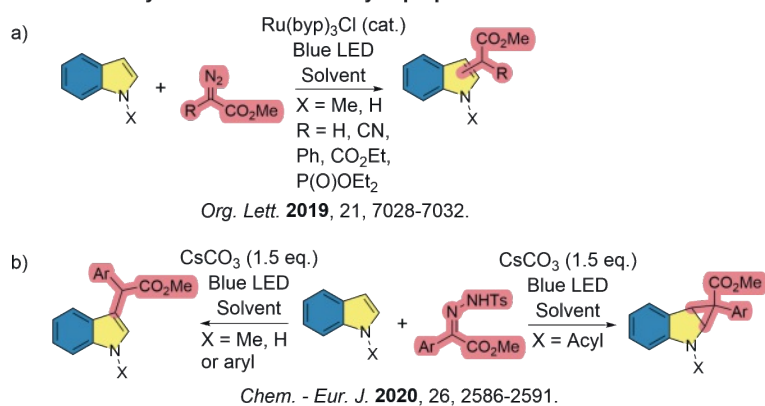
R¹ = R² = H : 1a
 R¹ = Me; R² = H : 1b
 R¹ = H; R² = OMe : 1c
 R³ = Ph; R⁴ = Me : 2a
 R³ = *p*-fluorophenyl; R⁴ = Me : 2b
 R³ = *p*-methylphenyl; R⁴ = Me : 2c
 R³ = 3-thiophenyl; R⁴ = Et : 2d
 R³ = *p*-chlorophenyl; R⁴ = Et : 2e



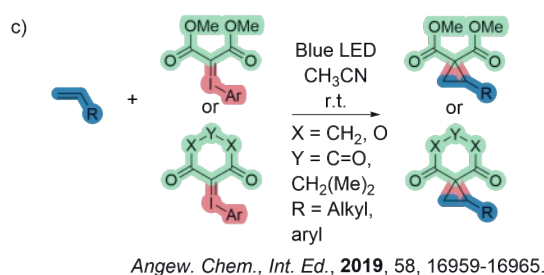
Scheme 2. Synthesis of azepino indole molecules.

Literature precedent

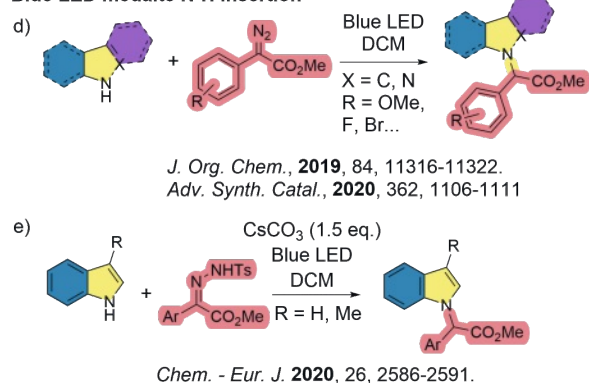
Blue LED catalyzed C-H activation or cyclopropanation



Iodonium ylide mediated cyclopropanation of olefins via Blue LED

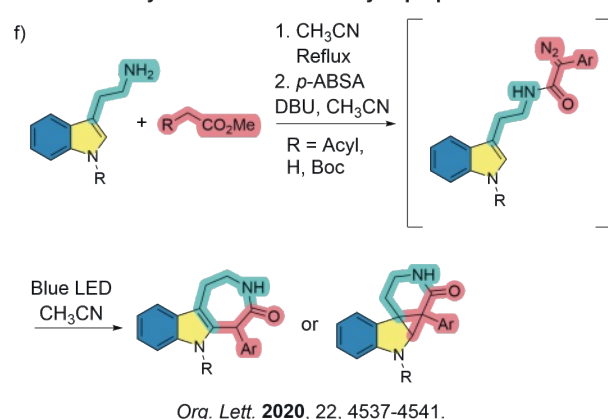


Blue LED mediated N-H insertion

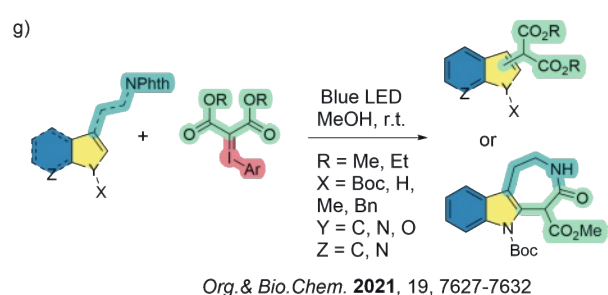


Our work

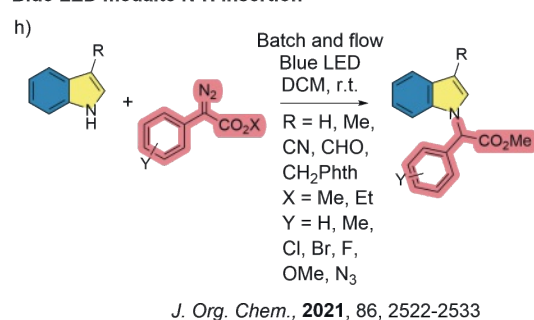
Blue LED catalyzed C-H activation or cyclopropanation



Iodonium ylide mediated cyclopropanation of olefins via Blue LED

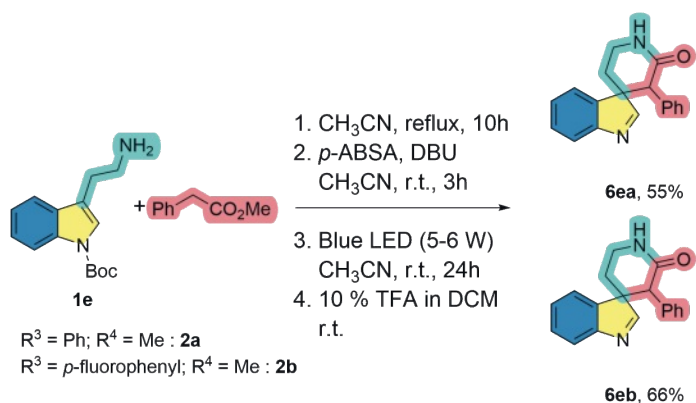


Blue LED mediated N-H insertion



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

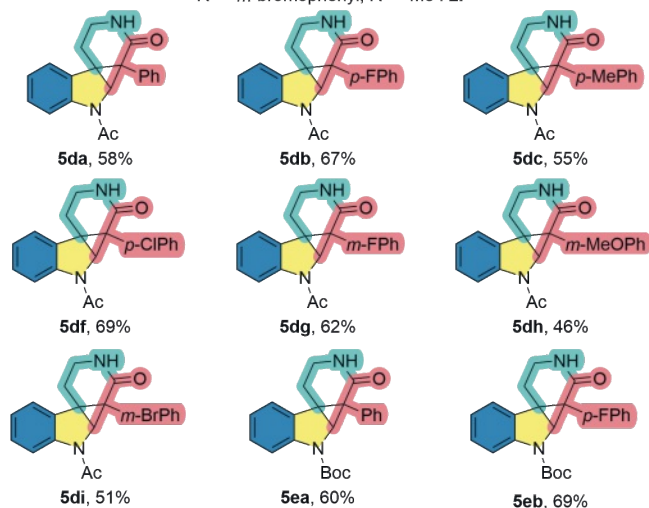
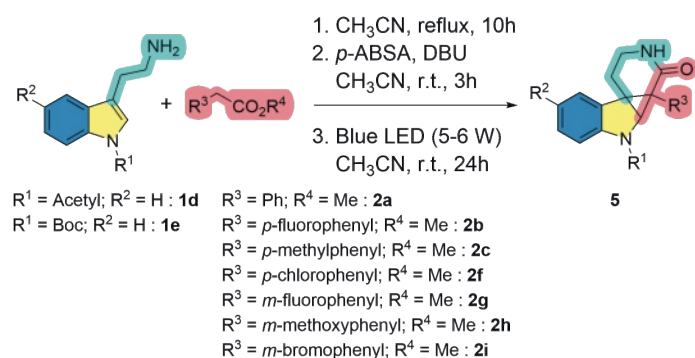
formation of cyclopropane fused polycyclic compounds, an intermediate for spiropeperidino product, especially by screening various alkyl and aryl acetate (Scheme 4). Contrary to what has been observed for the synthesis of azepino (4) electron withdrawing group like *p*- and *m*-fluoro (5db and 5dg) or *p*-chloro (5df) on the aryl moieties give access to better yield, respectively 62%



Scheme 3. Synthesis of spiropeperidino indoles.

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 spiropeperidino (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

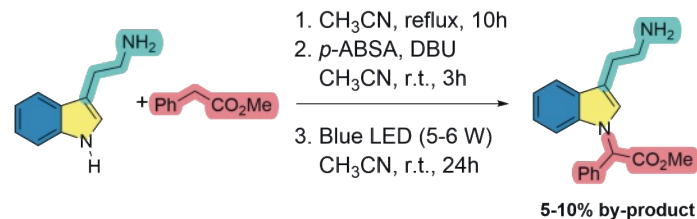


Scheme 4. Synthesis of cyclopropane fused polycyclic compounds an intermediate for spiroperidino indoles.

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 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 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 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 spiroperidino compounds **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 position 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 pair 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 additional investigation, we discovered that around 5–10% of a by-product was



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

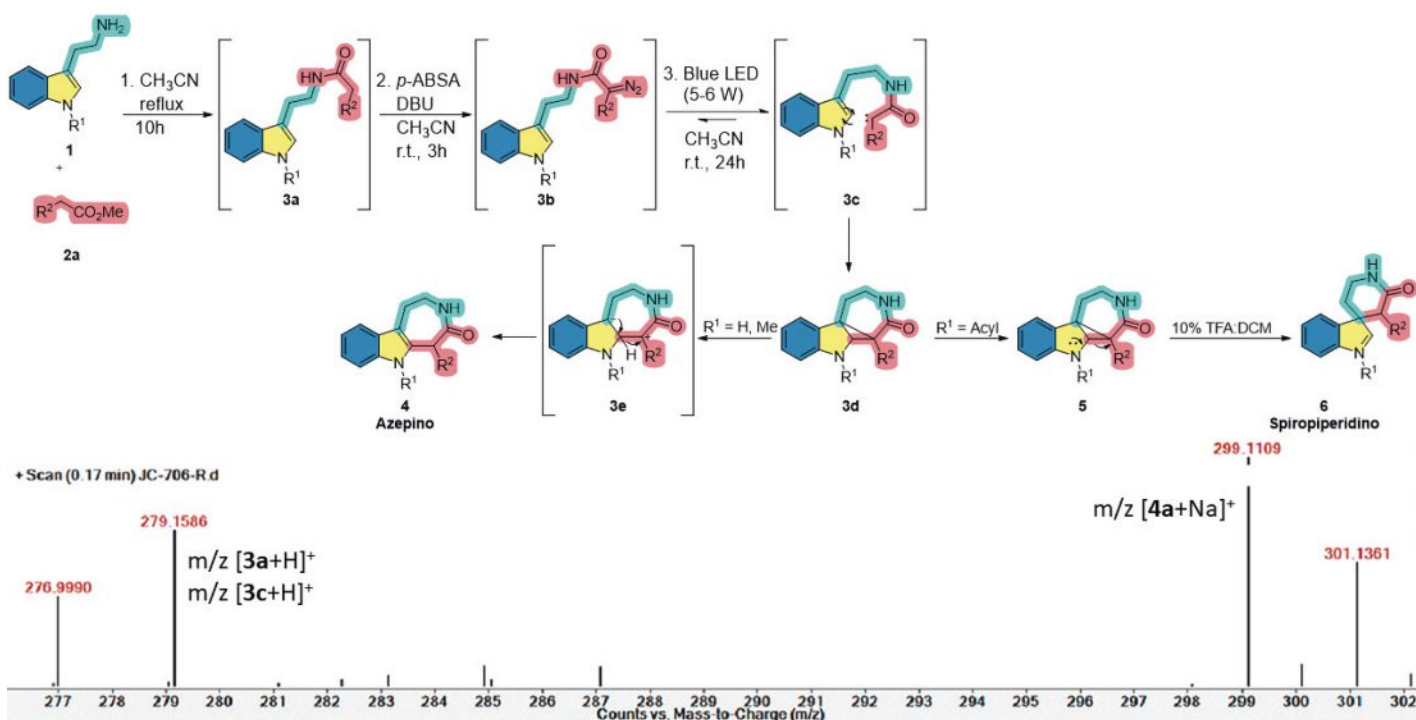
formed. After purification and characterization, we come to the conclusion that this impurity was the product of the N-H intermolecular insertion (Scheme 6).

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, benzotriazole, 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.* 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 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 clopidogrel a platelet aggregation inhibitor drug.^[44] During the same period, in 2020, Jurgberg *et al.* reported a blue LED methodology to promote the N-H insertion of carbazoles, pyrroles and 1,2,3-triazoles into aryl diazoacetates to access also to biologically relevant structures.^[42] Therefore, 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 a 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 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 resulting carbene is efficient and the absorption peak is diminishing over the time (Figure 2A to C).

By contrast, methanol (MeOH, polar protic) discolse 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 withdraw-



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

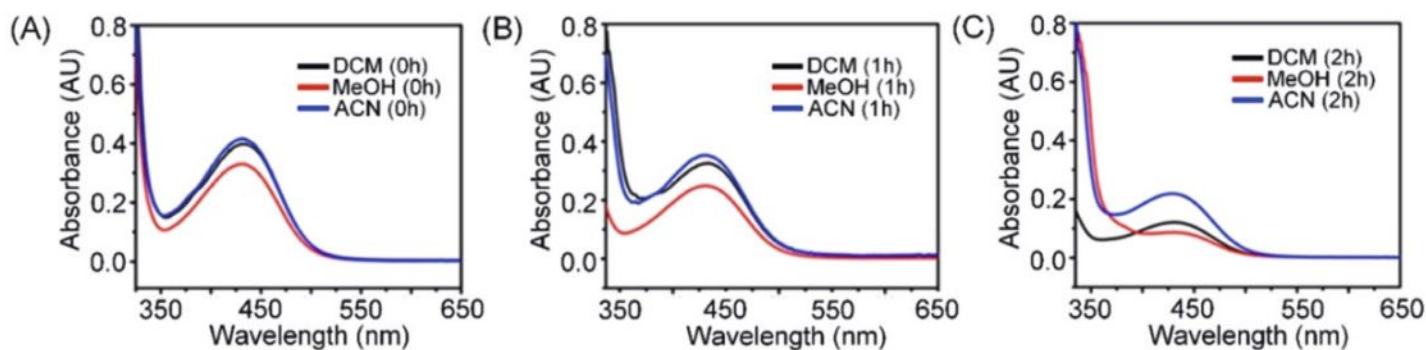


Figure 2. UV absorption of phenyl diazoacetate in various solvents and at different time (A) at 0 h; (B) at 1 h; and (C) at 2 h.

ing group, 3-cyanoindole (1h), and finally the indole (1f), with the 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 ourself 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

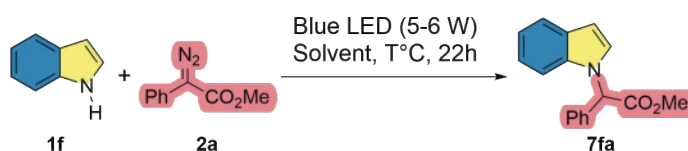
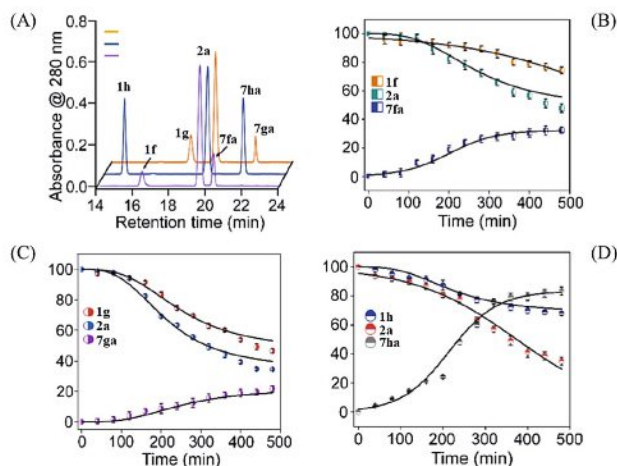
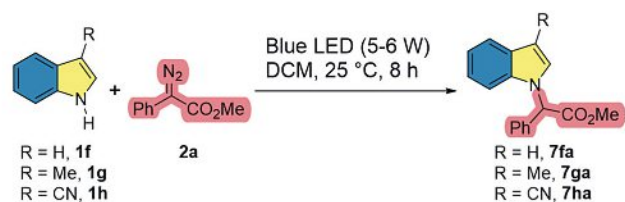


Table 2. Optimization of N-H insertion in batch mode.

| 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.

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 give 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 ($\geq 69\%$) 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-phthalimidindole (**1j**) give access to the desired products, **7ga** and **7jb** to **7jk**, but with poorer yield ($\leq 66\%$). 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-(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 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 up-field 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**

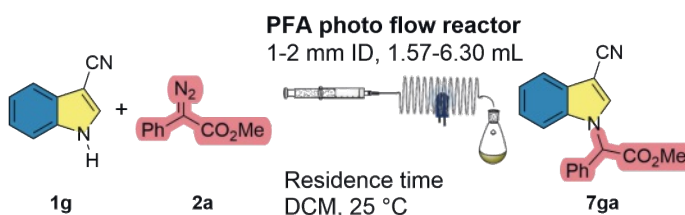


Table 3. Optimization of N-H insertion in flow mode.

| 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 |

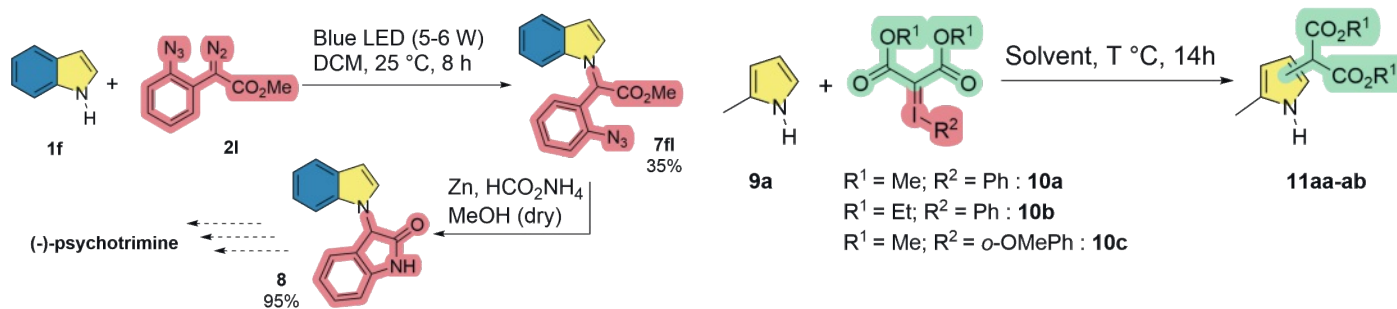
^a Flow rate; ^b Residence time; ^c Isolated yield

was plotted against the deviation in the chemical shift of N-H protons **1g-i** *vs.* **1f**. As expected, a linear relationship was observed. The plot of the $\log(k/k_0)$ 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 ($K_H/K_D = 1.32$) 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 initial 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 desired product **7fa**.^[31]

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

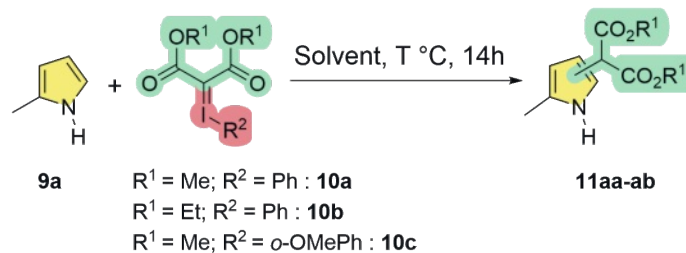
Hypervalent iodine compounds are one of the most interesting chemical species that are used as reagents and catalysts for numerous organic transformations. The fact that they mimic metals and are environmentally sustainable makes them extremely valuable. Among these myriad applications, C-H functionalization of ylides (with metal catalysts) is noteworthy.^[59-60] To improve the eco-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



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

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 **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).



| 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 |

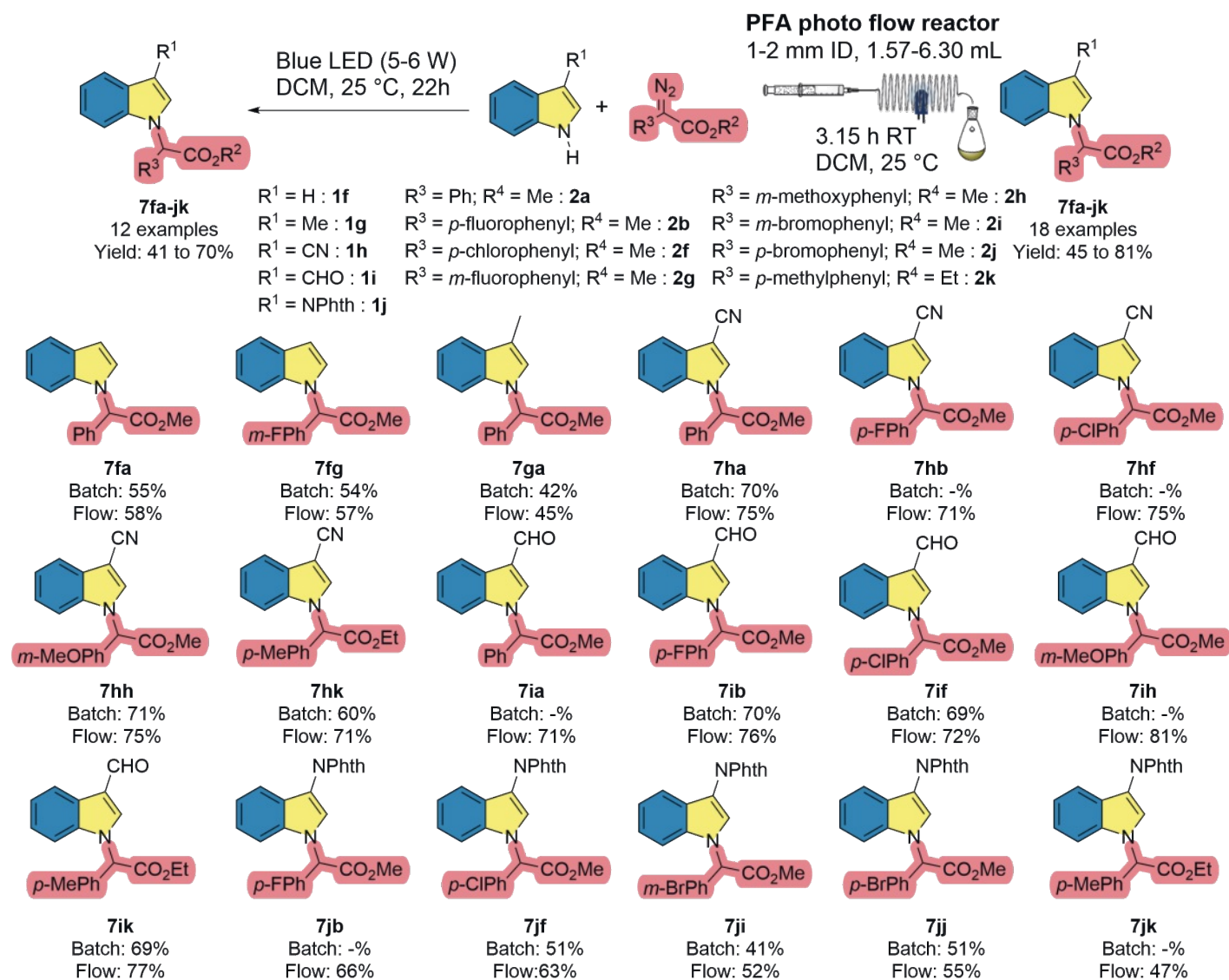
^a Isolated yield; ^b with blue LED; ^c Dark cond.; ^d no reaction

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.

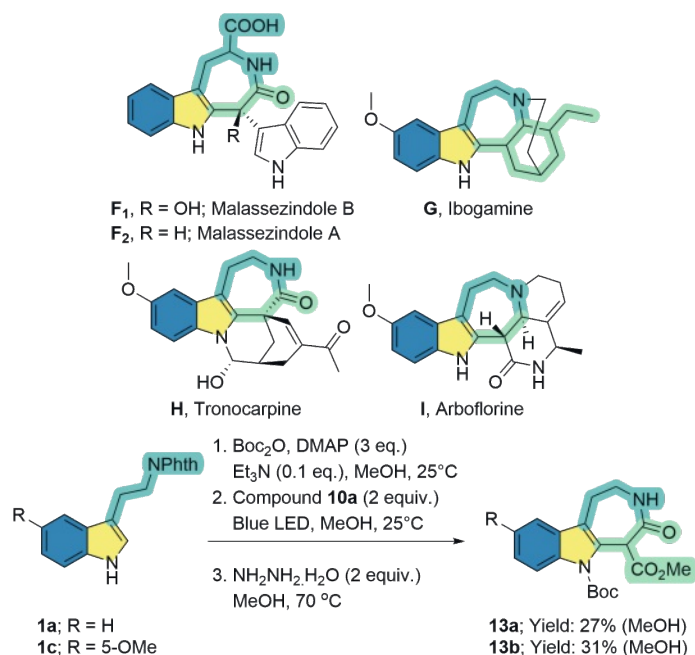
Next few control experiments were performed to understand the mechanism of the transformation. Literature study had indicated radical reaction pathway for iodonium ylides like 10a-c during their cyclopropane formation reactions with olefins. We too investigated the same. Accordingly spin trapping reaction 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 families 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.

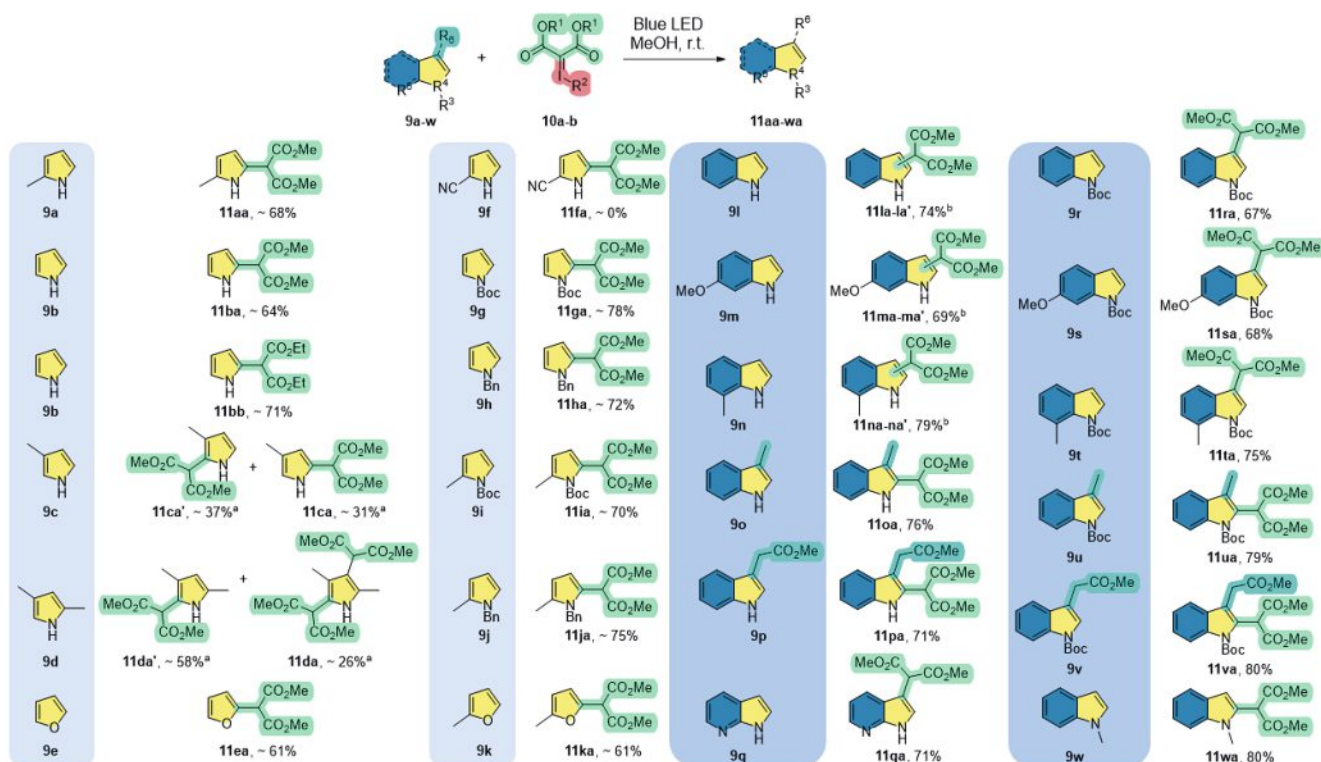
peridino indoles were obtained. The mild reaction conditions developed, with various donor-acceptor substituent, were applied to the synthesis of a key intermediate like the natural product (-)-Psychotrimine for the N-H insertion methodology. Moreover, part of the compounds generated through these strategies 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

- [1] I. S. Johnson, J. G. Armstrong, M. Gorman, J. P. Burnett, *Canc. Res.* **1963**, 23, 1390, <https://doi.org/10.1038/newbio231237a0>.
- [2] S. H. Ferreira, S. Moncada, J. R. Vane, *Nature New Biol.* **1971**, 231, 237, <https://doi.org/10.1351/pac200173091459>.
- [3] G. Bacher, T. Beckers, P. Emig, T. Klenner, B. Kutscher, B. Nickel, *Pure Appl. Chem.* **2001**, 73, 1459, <https://doi.org/10.1351/pac200173091459>.
- [4] A. Duflos, A. Kruczynski, J.-M. Barret, *Curr. Med. Chem.: Anti-Cancer Agents* **2002**, 2, 55, <https://doi.org/10.2174/1568011023354452>.



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.

- [5] T. Beckers, S. Mahboobi, *Drugs Future* **2003**, *28*, <https://doi.org/10.1358/dof.2003.028.08.744356>.
- [6] C. Won, X. Shen, K. Mashiguchi, Z. Zheng, X. Dai, Y. Cheng, H. Kasahara, Y. Kamiya, J. Chory, Y. Zhao, *Proc. Natl. Acad. Sci.* **2011**, *108*, 18518, <https://doi.org/10.1073/pnas.1108436108>.
- [7] S. Samala, R. K. Arigela, R. Kant, B. Kundu, *J. Org. Chem.* **2014**, *79*, 2491, <https://doi.org/10.1021/jo402783p>.
- [8] T. Beckers, S. Baasor, T. Klenner, S. Mahboobi, H. Pongratz, M. Frieser, H. Hufsky, J. Hockemeyer, H. H. Fiebig, A. Burger, F. D. Bohmer, WO 2001082909 A2, April 27, **2001**.
- [9] L. B. Diss, S. D. Robinson, Y. Wu, S. Fidalgo, M. S. Yeoman, B. A. Patel, *ACS Chem. Neurosci.* **2013**, *4*, 879, <https://doi.org/10.1021/cn4000617>.
- [10] B. L. Flynn, G. P. Flynn, E. Hamel, M. K. Jung, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2341, [https://doi.org/10.1016/S0960-894X\(01\)00436-X](https://doi.org/10.1016/S0960-894X(01)00436-X).
- [11] B. L. Flynn, E. Hamel, M. K. Jung, *J. Med. Chem.* **2002**, *45*, 2670, <https://doi.org/10.1021/jm020077t>.
- [12] R. Gastpar, M. Goldbrunner, D. Marko, E. von Angerer, *J. Med. Chem.* **1998**, *41*, 4965, <https://doi.org/10.1021/jm9802281>.
- [13] M. Medarde, A. Ramos, E. Caballero, R. P.-L. d. Clairac, J. L. López, D. G. Grávalos, A. S. Feliciano, *Eur. J. Med. Chem.* **1998**, *33*, 71, [https://doi.org/10.1016/S0223-5234\(99\)80078-6](https://doi.org/10.1016/S0223-5234(99)80078-6).
- [14] S. A. Patil, P. R., D. D. Miller, *Future Med. Chem.* **2012**, *4*, 2085, <https://doi.org/10.4155/fmc.12.141>.
- [15] K. Yamamoto, K. Noda, A. Yoshimura, M. Fukuoka, K. Furuse, H. Niitani, *Cancer Chemother. Pharmacol.* **1998**, *42*, 127, <https://doi.org/10.1007/s002800050795>.
- [16] S. N. Young, *J. Neurophysiarty Clin. Neurosci.* **2007**, *32*, 394.
- [17] M.-Z. Zhang, N. Mulholland, D. Beattie, D. Irwin, Y.-C. Gu, Q. Chen, G.-F. Yang, J. Clough, *European Journal of Medicinal Chemistry* **2013**, *63*, 22, <https://doi.org/10.1016/j.eurjme.2013.03.006>.
- [18] A. Baeyer, *Justus Liebig's Ann. Chem.* **1866**, *140*, 295, <https://doi.org/10.1002/jlac.18661400306>.
- [19] J. Barluenga, C. Valdés, *Mod. Heterocycl. Chem.* **2011**, *377*, <https://doi.org/10.1002/9783527637737.ch5>.
- [20] R. Gali, J. Banothu, R. Gondru, R. Bavantula, Y. Velivela, P. A. Crooks, *Bioorg. Med. Chem. Lett.* **2015**, *25*, 106, <https://doi.org/10.1016/j.bmcl.2014.10.100>.
- [21] K. Karrouchi, S. Radi, Y. Ramli, J. Taoufik, Y. N. Mabkhot, F. A. Al-aizari, M' h. Ansar, *Molecules* **2018**, *23*, <https://doi.org/10.3390/molecules23010134>.
- [22] N. K. Kaushik, N. Kaushik, P. Attri, N. Kumar, C. H. Kim, A. K. Verma, E. H. Choi, *Molecules* **2013**, *18*, <https://doi.org/10.3390/molecules18066620>.
- [23] D. Kumar, N. Maruthi Kumar, M. P. Tantak, M. Ogura, E. Kusaka, T. Ito, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 5170, <https://doi.org/10.1016/j.bmcl.2014.09.085>.
- [24] P. O. Patil, S. B. Bari, *Arabian J. Chem.* **2016**, *9*, 588, <https://doi.org/10.1016/j.arabj.2013.08.027>.
- [25] D. F. Taber, P. K. Tirunahari, *Tetrahedron* **2011**, *67*, 7195, <https://doi.org/10.1016/j.tet.2011.06.040>.
- [26] G. Wang, C. Li, L. He, K. Lei, F. Wang, Y. Pu, Z. Yang, D. Cao, L. Ma, J. Chen, Y. Sang, X. Liang, M. Xiang, A. Peng, Y. Wei, L. Chen, *Bioorg. Med. Chem. Lett.* **2014**, *22*, 2060, <https://doi.org/10.1016/j.bmcl.2014.02.028>.
- [27] X. Zhen, Z. Peng, S. Zhao, Y. Han, Q. Jin, L. Guan, *Acta Pharm. Sin. B* **2015**, *5*, 343, <https://doi.org/10.1016/j.apsb.2015.01.008>.
- [28] L. Zheng, R. Hua, *Front. Chem.* **2020**, *8*, <https://doi.org/10.3389/fchem.2020.580355>.
- [29] C. Hui, F. Chen, F. Pu, J. Xu, *Nat. Rev. Chem.* **2019**, *3*, 85, <https://doi.org/10.1038/s41570-018-0071-1>.
- [30] A. Y. Chen, Q. Lu, Y. Fu, R. Sarpong, B. M. Stoltz, H. Zhang, *J. Org. Chem.* **2018**, *83*, 330, <https://doi.org/10.1021/acs.joc.7b02731>.
- [31] D. Maiti, R. Das, S. Sen, *J. Org. Chem.* **2021**, *86*, 2522, <https://doi.org/10.1021/acs.joc.0c02649>.
- [32] Z. Wang, L. Chen, Y. Yao, Z. Liu, J.-M. Gao, X. She, H. Zheng, *Org. Lett.* **2018**, *20*, 4439, <https://doi.org/10.1021/acs.orglett.8b01720>.
- [33] S. Guha, S. Gadde, N. Kumar, D. S. Black, S. Sen, *J. Org. Chem.* **2021**, *86*, 5234, <https://doi.org/10.1021/acs.joc.1c00141>.
- [34] G. S. Clark, *Perfum. Flavor.* **1995**, *20*, 21, <https://doi.org/10.1016/B978-012397720-5/50003-7>.
- [35] J. Chauhan, M. K. Ravva, L. Gremaud, S. Sen, *Org. Lett.* **2020**, *22*, 4537, <https://doi.org/10.1021/acs.orglett.0c01559>.
- [36] S. Sar, R. Das, D. Barman, P. Latua, S. Guha, L. Gremaud, S. Sen, *Org. Biomol. Chem.* **2021**, *19*, 7627, <https://doi.org/10.1039/D1OB01219C>.
- [37] P. K. Dutta, J. Chauhan, M. K. Ravva, S. Sen, *Org. Lett.* **2019**, *21*, 2025, <https://doi.org/10.1021/acs.orglett.9b00150>.
- [38] A. H. Sandtorv, *Adv. Synth. Catal.* **2015**, *357*, 2403, <https://doi.org/10.1002/adsc.201500374>.
- [39] L. Shi, X. Zhong, H. She, Z. Lei, F. Li, *Chem. Commun.* **2015**, *51*, 7136, <https://doi.org/10.1039/C5CC00249D>.
- [40] Ł. W. Ciszewski, J. Durka, D. Gryko, *Org. Lett.* **2019**, *21*, 7028, <https://doi.org/10.1021/acs.orglett.9b02612>.

- [41] S. Jana, F. Li, C. Empel, D. Verspeek, P. Aseeva, R. M. Koenigs, *Chem. - Eur. J.* **2020**, *26*, 2586, <https://doi.org/10.1002/chem.201904994>.
- [42] M. L. Stivanin, A. A. G. Fernandes, A. F. da Silva, C. Y. Okada Jr, I. D. Jurberg, *Adv. Synth. Catal.* **2020**, *362*, 1106, <https://doi.org/10.1002/adsc.201901343>.
- [43] S. R. Hansen, J. E. Spangler, J. H. Hansen, H. M. L. Davies, *Org. Lett.* **2012**, *14*, 4626, <https://doi.org/10.1021/ol3020754>.
- [44] C. Empel, F. W. Patureau, R. M. Koenigs, *J. Org. Chem.* **2019**, *84*, 11316, <https://doi.org/10.1021/acs.joc.9b01753>.
- [45] C. Y. Okada, C. Y. dos Santos, I. D. Jurberg, *Tetrahedron* **2020**, *76*, 131316, <https://doi.org/10.1016/j.tet.2020.131316>.
- [46] Ł. W. Ciszewski, K. Rybicka-Jasińska, D. Gryko, *Org. Biomol. Chem.* **2019**, *17*, 432, <https://doi.org/10.1039/C8OB02703J>.
- [47] X. Zhang, C. Du, H. Zhang, X.-C. Li, Y.-L. Wang, J.-L. Niu, M.-P. Song, *Synthesis* **2019**, *51*, 889, <https://doi.org/10.1055/s-0037-1610668>.
- [48] I. D. Jurberg, H. M. L. Davies, *Chem. Sci.* **2018**, *9*, 5112, <https://doi.org/10.1039/C8SC01165F>.
- [49] Z. Yang, M. L. Stivanin, I. D. Jurberg, R. M. Koenigs, *Chem. Soc. Rev.* **2020**, *49*, 6833, <https://doi.org/10.1039/D0CS00224K>.
- [50] Y. Matsuda, M. Kitajima, H. Takayama, *Org. Lett.* **2008**, *10*, 125, <https://doi.org/10.1021/ol702637r>.
- [51] N. Takahashi, T. Ito, Y. Matsuda, N. Kogure, M. Kitajima, H. Takayama, *Chem. Commun.* **2010**, *46*, 2501, <https://doi.org/10.1039/b923918a>.
- [52] X.-L. Lian, J. Meng, Z.-Y. Han, *Org. Lett.* **2016**, *18*, 4270, <https://doi.org/10.1021/acs.orglett.6b02019>.
- [53] T. Newhouse, C. A. Lewis, K. J. Eastman, P. S. Baran, *J. Am. Chem. Soc.* **2010**, *132*, 7119, <https://doi.org/10.1021/ja1009458>.
- [54] T. Newhouse, P. S. Baran, *J. Am. Chem. Soc.* **2008**, *130*, 10886, <https://doi.org/10.1021/ja8042307>.
- [55] D. F. Ewing Correlation Analysis in Chemistry: Recent Advances. In Chapman, N. B., Shorter, J., Eds.; Plenum Press: New York, NY, USA, **1978**.
- [56] L. P. Hammett, *Chem. Rev.* **1935**, *17*, 125, <https://doi.org/10.1021/cr60056a010>.
- [57] D. Iguchi, D. Ravelli, R. Erra-Balsells, S. M. Bonesi, *Molecules* **2020**, *25*, <https://doi.org/10.3390/molecules25092061>.
- [58] C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165, <https://doi.org/10.1021/cr00002a004>.
- [59] C. Batsila, E. P. Gogonas, G. Kostakis, L. P. Hadjiarapoglou, *Org. Lett.* **2003**, *5*, 1511, <https://doi.org/10.1021/ol0343008>.
- [60] C.-M. Chu, W.-J. Huang, J.-T. Liu, C.-F. Yao, *Tetrahedron Lett.* **2007**, *48*, 6881, <https://doi.org/10.1016/j.tetlet.2007.07.178>.