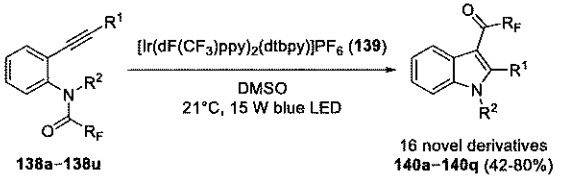
ABSTRACT

Nitrogen heterocycles are a highly important class of compounds widely used in materials science, agrochemistry, and medicinal chemistry.[1] Consequently, developing novel, straightforward synthetic approaches for their synthesis is an important topic in modern organic chemistry.[1,2,3] Of special interest are the syntheses of indole-containing systems,[4,5] as indole is one of the most widely distributed heterocycles in nature.[5,6]

This work investigated a novel photochemical cyclization to form indole derivatives from *o*-alkynylated F-tagged aniline derivatives. The tolerance of the cyclization to different alkynyl- and *N*-substituents was tested with the synthesis of a small library of F-tagged indoles (Scheme 1). The compatibility of the photocyclization with different acyl groups and substituents on the benzene moiety of the indole core was tested, and wide applicability to synthesize differently functionalized indole systems bearing various substituents in the positions *N*-1, *C*-2, *C*-3, *C*-5 and *C*-6 was shown. All cyclization products were synthesized in a batch-photoreactor, specifically designed and developed for the project presented herein. A straightforward and efficient four-step methodology for the synthesis of desired indole derivatives with high yields for single steps and the whole sequence was developed by optimizing the order of reaction steps from 2-iodoaniline to cyclization precursors and combining this sequence with the highly selective photochemical cyclization. Further derivatization of the final cyclization products by the cleavage of the perfluorinated chain yielded a library of novel indole-3-carboxylic acid and indole-3-carboxylic acid ester derivatives.



Scheme 1. Herein described photochemical cyclization of *o*-alkynylated F-tagged aniline derivatives to indoles *via* 1,3-acyl shift.

Variing the conditions of single steps showed that all three steps of the reaction route to the cyclization precursors can be performed using the same solvent and base, providing the possibility to conduct this sequence as a continuous-flow without the need for in-line solvent switch or base exchange and without compromises with respect to the selectivity and yields of single steps. Experiments have shown that the acylation with the perfluorinated acyl chloride could be performed under flow conditions with high selectivity and a residence time less than one minute. Initial difficulties with performing SONOGAHIRA cross coupling in flow due to solubility problems were solved by employing alternative palladium catalyst and copper coil as reactor. The photochemical cyclization was performed in a novel, by the project partner designed and constructed, photo-microreactor. It was shown that the time needed to achieve complete conversion of the cyclization product could be reduced to four hours in comparison to 24 hours when the reaction is performed in the batch-reactor. The visible-light-induced cyclization was also systematically studied in a kinetic study in an in-house assemled capillary photo-microreactor. Kinetic parameters, *i.e.*, reaction order and apparent rate constant, were determined and numerically validated.

1 INTRODUCTION

1.1 Indoles

1.1.1 Structure and synthesis

1*H*-Benzo[*b*]pyrrole, referred to as indole, is a planar bicyclic heterocycle consisting of a pyrrole ring fused through its 2 and 3 positions to a benzene ring (Figure 1).[7,8]

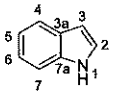


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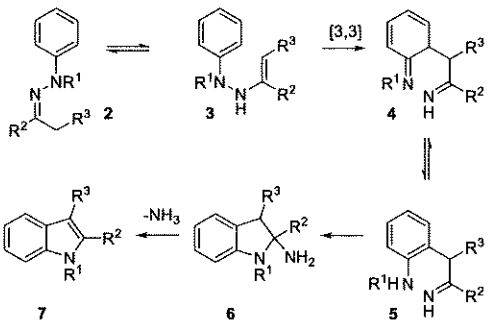
Figure 1. Structure of indole, a heterocycle consisting of a pyrrole ring fused to a benzene ring.

Since its discovery in 1883 by EMIL FISCHER, the FISCHER INDOLE SYNTHESIS (Scheme 2) has been the most commonly employed method for the preparation of indole. It proceeds through an initial acid-catalyzed tautomerization of *N*-arylhydrazone **2** to the ene-hydrazine **3**, which undergoes a [3,3]-sigmatropic rearrangement, providing the bis-imine intermediate **4**. Subsequent re-aromatization of the aniline ring, followed by an intramolecular nucleophilic attack, produces aminal **6**, which yields indole **7** after the elimination of ammonia.[9] Other classical procedures include the BISCHLER-MÖHLAU SYNTHESIS from α-bromoacetophenones with an excess of aniline, the BATCHO–LEIMGRUBER SYNTHESIS from *o*-nitrotoluenes and dimethylformamide acetals, the GASSMANN SYNTHESIS from *N*-haloanilines, the MADELUNG-HOULIHAN CYCLIZATION of *o*-alkyl-*N*-acylanilines, and the REISSERT SYNTHESIS by reductive cyclization of *o*-nitrobenzyl carbonyl compounds.[10]



Scheme 2. Mechanism of the FISCHER-INDOLE SYNTHESIS, the most common method for the preparation of indole. Acid-catalyzed tautomerization of *N*-arylhydrazone **2** to the ene-hydrazine **3**, followed by a [3,3]-sigmatropic rearrangement, provide intermediate **4**. Subsequent re-aromatization of the aniline ring and intramolecular nucleophilic attack provide aminal **6**, which yields the indole **7** after elimination of ammonia.

1.1.2 Reactivity of indole

Due to the presence of the pyrrole ring in its structure, indole is weakly basic and readily reacts with strong acids. Having 10 π-electrons (eight from double bonds and two from the lone pair of electrons on the nitrogen atom), it is an aromatic compound[7,8] which shows enhanced reactivity for electrophilic substitution reactions compared to benzene. Although its higher reactivity can allow reactions that are unfeasible for benzene and similar arenes, a careful assessment of reaction conditions and parameters is needed to avoid polysubstituted and other undesired products.[11]

1.1.2.1 Substitutions on the pyrrole ring

The FRIEDEL-CRAFTS ALKYLATION is the archetypical acid-catalyzed C-C bond-forming reaction to introduce side-chains onto an aromatic compound *via* electrophilic substitution.[5] Based on molecular orbital calculations, the 3-position of the indole scaffold has the highest electron density and is the most reactive site for FRIEDEL-CRAFTS-type reactions, 10^{13} times more reactive than benzene positions.[5,11] The emergence of C-H activation strategies *via* transition metal complexes in the last years has expanded the scope of possible reactions for

selective *C*-3 and *C*-2 functionalization.[12] Unsaturated compounds, such as activated alkenes, imines, and carbonyl compounds, have been identified as suitable electrophilic reagents for FRIEDEL-CRAFTS ACYLATION under organocatalysis.[5] Another possible strategy for attaching substituents on the pyrrole ring is the so-called umpolung (polarity inversion) of indole by placing an electron-withdrawing group (EWG) in the *C*-2 (Figure 2, a) or *C*-3 (Figure 2, b) position, which makes the neighboring position electrophilic and allows nucleophilic substitution reactions.[13]

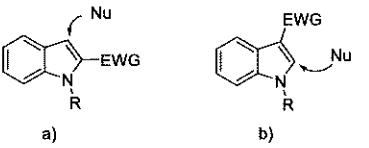


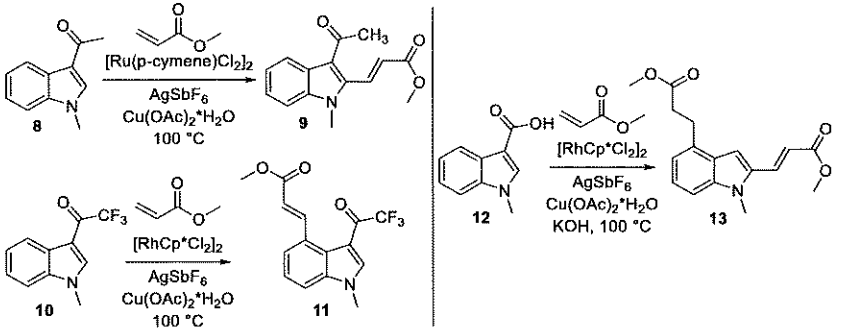
Figure 2. The umpolung, a strategy of attaching substituents on the pyrolle ring of the indole by placing an electron-withdrawing group (EWG) in the position *C*-2 (a) or *C*-3 (b), making the neighboring position electrophilic and allowing nucleophilic substitution reactions.

Selective electrophilic substitution at the *C*-2 position can occur if the pyrrole core is electronically isolated, *i.e.* when 4,7-dihydroinoles are employed.[5] Furthermore, this position can be selectively functionalized *via* transition metal catalysis using precursors bearing directing *N*-substituents.[12] Due to a slight acidity of the N-H bond, indole can undergo *N*-substitution reactions under basic conditions, but only after the N-H proton is removed, *i.e.*, in the presence of strong bases, to generate a strong, charged nucleophile.[5]

1.1.2.2 Substitutions on the benzene ring

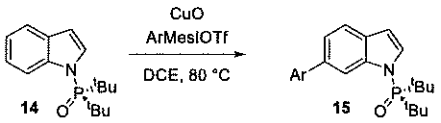
The *C*-4 position of indole can be accessed almost exclusively by blocking off the *C*-3 position, making it the next most electron-rich carbon center of the indole scaffold.[14] Nevertheless, this is often competitive with *C*-2 substitution, depending on the substituent that blocks off *C*-3 (Scheme 3). For example, Prabhu *et al.* have shown that using stronger directing groups ($COCH_3$) in the *C*-3 position results in *C*-2 selectivity (Scheme 3, top left), while weaker directing groups such as CHO or $COCF_3$ result in a selective formation of *C*-4

substituted products (Scheme 3, bottom left).[15] On the other hand, Zhang *et al.* have shown that carboxylic acid directing groups enable C-2 and C-3 disubstitution, followed by *in situ* decarboxylation to afford a C-3 unsubstituted indole (Scheme 3, right).[16]



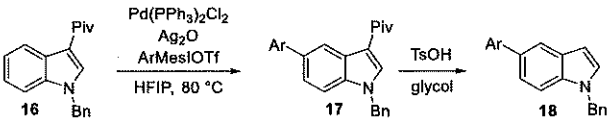
Scheme 3. Influence of the *C*-3 substituent on *C*-4/*C*-2 functionalization of indole. Stronger directing groups like $COCH_3$ result in *C*-2 selectivity (top left), weaker directing groups like CHO or $COCF_3$ lead to *C*-4 selectivity (bottom left), while carboxylic acid directing group allows *C*-2 and *C*-3 disubstitution, which can be followed by decarboxylation to afford a *C*-3 unsubstituted indole (right).

C-7 functionalization is possible with the prior attachment of a sterically demanding directing group to the *N*-1 position,[17] although in many cases, competitive *C*-2[18] or *C*-3[19] functionalization was observed. Smith *et al.* have shown that substitution at the *C*-7 position can also be accomplished by using *C*-2 substituted indoles as precursors, where N-H is proposed to act as a directing group.[20] One of the first among the limited number of examples for *C*-6 functionalization (Scheme 4) was provided by Shi *et al.*, who reported absolute meta-selective *C*-H functionalization of *N*-phosphonate substituted indoles with different coupling partners under copper catalysis.[21] Other examples mostly involve *C*-2 and *C*-3[22] or *N*-1 and *C*-3[23] pre-functionalized substrates.



Scheme 4. Direct and site-selective *C*-6 arylation of a *N*-di-*tert*-butyl phosphonate indole employing diaryliodonium triflate salts under Cu-catalysis.

Although *C*-5 substituted indoles are often found, very few reports show conditions preferentially resulting in *C*-5 functionalization.[14] At the same time, the only example of selective and direct *C*-5 functionalization (Scheme 5) was also reported by Shi *et al.*, who used pivaloyl *C*-3 substituted substrate to access 5-substituted indoles under palladium catalysis. The pivaloyl substituent can subsequently be cleaved off, providing *C*-3 unsubstituted products.[24]



Scheme 5. Selective *C*-5 functionalization of indole, achieved by using pivaloyl *C*-3 protected starting material **16**. The pivaloyl substituent can be cleaved off from the compound **17** to afford the *C*-3 unsubstituted indole **18**.

Although elegant methods for indole derivatization have been developed, site-selective C-H functionalization of the benzene unit is still challenging[14] as pre-functionalized and carefully designed precursors have to be employed to perform such transformations.

1.1.3 Naturally occurring indoles

Indole is one of the most abundant heterocycles in nature[5,6] and part of numerous biomolecules and alkaloids,[7] involved in key biological processes.[25] Among the most important naturally occurring indoles is tryptophan (**19**) – an essential amino acid, constituent of most proteins and a biosynthetic precursor for various secondary metabolites. Bacteria degrade tryptophan to tryptamine, the core structure of some condensed ring alkaloids. Serotonin (**20**) is a vasoconstrictor hormone that also acts as a neurotransmitter in the central nervous

system of animals.[7,26] The structurally similar hormone melatonin (**21**) is thought to control the circadian rhythm of physiological functions.[25,26] Other examples of indole-containing natural compounds include indole-3-acetic acid, a plant growth-regulating hormone,[25] brassinin, produced by plants as a defense mechanism against microorganism, and bufotenine and psilocybin found in mushrooms which are known for their psychotropic effects.[26]

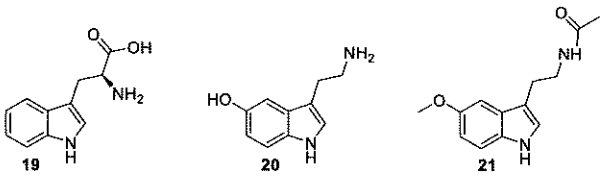


Figure 3. Selected examples of naturally occurring indole compounds. Tryptophan (**19**) is an essential amino acid involved in the biosynthesis of various secondary metabolites, serotonin (**20**) is a neurotransmitter in the central nervous system of animals, and melatonin (**21**) is a hormone thought to control the circadian rhythm of physiological functions.

Besides being involved in bioprocesses as constituents of important biomolecules, many naturally occurring indole derivatives show diverse biological activities,[27] including antibacterial, antifungal, antiviral, anti-inflammatory, antihistamine, antioxidant, anti-diabetic, and antineoplastic.[27] For example, indole-3-carbinol (I3C) and its metabolites are found at relatively high levels in cruciferous vegetables such as broccoli, brussels sprouts, cabbage, and kale.[25,26] They are well-explored for the prevention of a few types of cancer, including colorectal cancer, breast cancer, and lymphoma, while Evodiamine is one of the main constituents of *Evodiae fructus*, a multipurpose herb traditionally used in China for the treatment of headaches, abdominal pain, vomiting, and diarrhea.[26] Among clinically used naturally occurring indoles, the most common ones are dimeric vinca alkaloids Vincristine **22** and Vinblastine isolated from *Catharanthus roseus* (Figure 4), which have been widely employed in the treatment of various cancers including Hodgkin's disease, non-Hodgkin's lymphoma, Kaposi's sarcoma, breast, and testicular cancer.[25–27] Reserpine and Ajmalicine are indole alkaloids used to treat high blood pressure.[7]

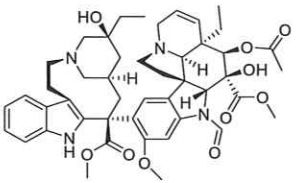


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Figure 4. Dimeric vinca alkaloid Vincristine (**22**) (left), an indole based drug isolated from *Catharanthus roseus* (right), widely employed in the treatment of various cancers including Hodgkin's disease, non-Hodgkin's lymphoma, Kaposi's sarcoma, breast, and testicular cancer. Picture on the right accessed from https://en.wikipedia.org/wiki/Catharanthus_roseus on 11.03.2024. Copyright CC BY-SA 4.0

1.1.4 Indole-based drugs

As it has been shown that indole is a biologically relevant pharmacophore capable of mimicking natural processes and binding reversibly to different targets, indole derivatives are referred to as 'privileged scaffolds' in medicinal chemistry and represent one of the most important compound classes in drug discovery.[6,7,25] The indole moiety is present in several approved synthetic drugs (Figure 5) or promising drug candidates currently undergoing clinical trials[25] for the treatment of various diseases including depression, fungal and viral infections, inflammation, and particularly cancer.[2] Further examples include Indomethacin, a synthetic derivative of indole-3-acetic acid used as a non-steroidal, anti-inflammatory drug to reduce fever, pain, stiffness, and swelling; Yohimbine for the treatment of sexual dysfunction; Panobinostat for the treatment of multiple myeloma, the anti-HIV agent Atevirdine and many more as shown in Table 1.[26] Consequently, synthesizing novel indole derivatives with diverse substitution patterns is highly encouraged.[6] Among differently substituted scaffolds, 2- and 3-functionalized indoles appear most promising as novel compounds with potential biological activity.[7]

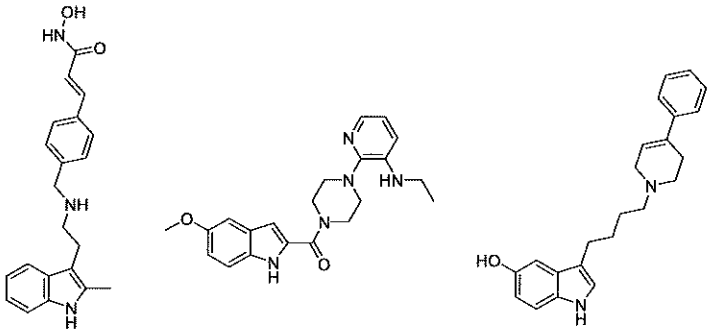


Figure 5. Selected examples of indole-containing drugs. Pan-HDAC inhibitor Panobinostat (**23**) for the treatment of multiple myeloma, non-nucleoside reverse transcriptase inhibitor Atevirdine (**24**) for the treatment of HIV, and dopamine agonist Roxindole (**25**) for the treatment of Schizophrenia.

Table 1. Indole-containing FDA-approved drugs and their applications.

Drug	Application	Drug	Application	Drug	Application
Vinorelbine	Anticancer	Oglufanide	Immunomodulatory	Roxindole	Schizophrenia
Vindesin	Anticancer	Vincamine	Vasodilator	Delavirdine	Anti-HIV
Mitraphylline	Anticancer	Perindopril	Antihypertensive	Arbidol	Antivirus
Cediranib	Anticancer	Binedaline	Antidepressant	Zafirlukast	Anti-Asthmatic
Apaziquone	Anticancer	Amedalin	Antidepressant	Bucinodol	β-blocker
Tropisetron	Antiemetic	Oxypertine	Antipsychotic	Pericine	Opioid agonist
Dolasetron	Antiemetic	Stramesine	Antidepressant	Bufotenidine	Toxin

1.1.5 3-Acylindoles

3-Acylindoles are ubiquitous in natural products, agrochemicals, and pharmaceuticals,[28] often expressing benefits such as anti-inflammatory, analgesic, immunomodulatory, antiemetic, antiviral, antineoplastic, and hypocholesterolemic activity.[29] For example, many cannabimimetic compounds in the designer drug classes FUBINACA, PINACA, and ADBICA are 3-acylindoles (Figure 6).[30]

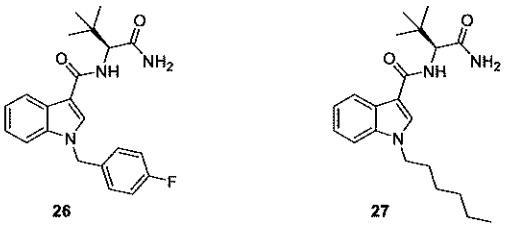


Figure 6. Synthetic indole-based cannabinoid designer drugs ADB-FUBICA (**26**) and AD-BICA (**27**).

3-Acylindoles are also versatile precursors for the synthesis of alkaloids and other related heterocycles[31–33] as well as valuable building blocks for the synthesis of a wide range of other indole derivatives, as the carbonyl group can readily undergo a variety of transformations[34–36] such as reductions and C-C or C-N coupling reactions.[35] Among other *C*-3 substituted indoles, indole-3-carboxylic acids, the corresponding esters, indole-3-carboxaldehydes, and indole-3-nitriles are considered very important and have a significant use as pharmaceuticals or lead structures in the development of novel, potential biologically active compounds. For example, 5-HT_3-receptor antagonists Tropisetron (**28**) and Dolasetron (**29**), used to treat nausea and vomiting caused by chemotherapy, and antiviral Arbidol (**30**) (Figure 7) are based on the indole-3-carboxylic acid ester structure.[37]

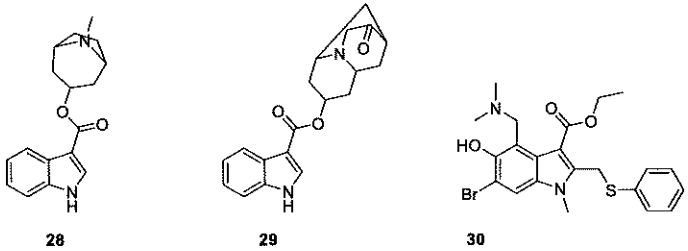
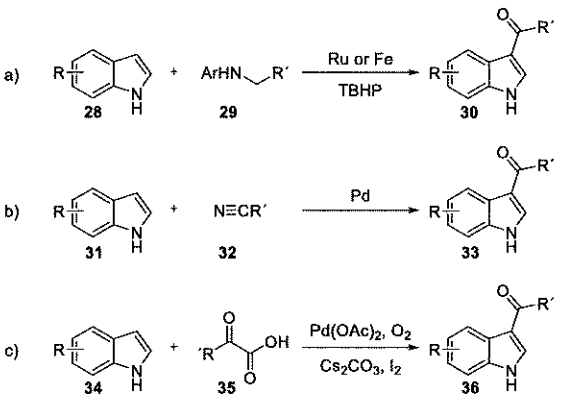


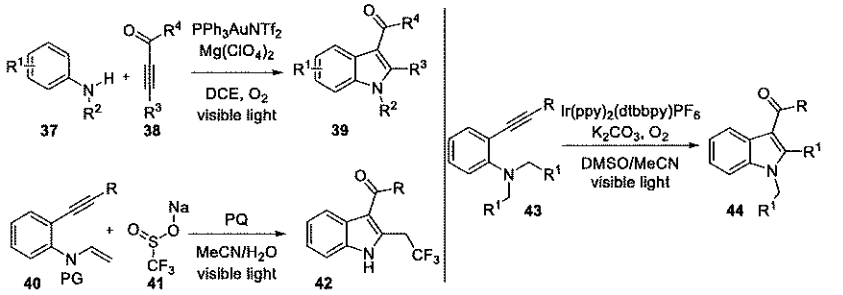
Figure 7. Examples of indole-3-carboxylic acid ester-based drugs. Tropisetron (**28**) and Dolasetron (**29**) are used to treat nausea and vomiting caused by chemotherapy, while Arbidol (**30**) is an antiviral drug.

1.1.5.1 Synthesis of 3-acylindoles

Classical methods for the preparation of 3-acylindoles, including FRIEDEL-CRAFTS ACYLATION, VILSMEIER-HAACK REACTION, and GRIGNARD REACTIONS,[31,33–36] generally often come with limitations such as harsh reaction conditions, side reactions, and production of a big amount of waste.[32] For example, the most frequently used Friedel-Crafts acylation usually requires stoichiometric amounts of Lewis acid, typically $AlCl_3$, and strict exclusion of moisture.[31,33,36] Due to the acidic conditions, it suffers from side reactions involving *N*-1 acylation, *N*-1/*C*-3 diacylation, and polymerization. *N*-Protected or electron-deactivated indoles can address these issues, involving either troublesome *N*-protection and deprotection or limitation of the substrate scope.[33] Although it has been shown that the use of $SnCl_4$,[38] $AlEt_2Cl$[39], or $ZrCl_4$[40] as Lewis acid minimizes side reactions and extends the substrate scope to free indoles, the procedures are still environmentally unfriendly due to the use of stoichiometric amounts of Lewis acid and the formation of large quantities of the respective metal salts.[33] More recent reports for 3-acylindole syntheses using preformed indoles include acylation of free indoles *via* ruthenium- or iron-catalyzed oxidative coupling with anilines (Scheme 6, a)[41] palladium-catalyzed addition of indoles to nitriles (Scheme 6, b),[33,42] palladium-catalyzed decarboxylative cross-coupling reactions using simple, readily available and stable carboxylic acids as coupling partners (Scheme 6, c)[35] and many more.[43] In contrast, approaches for their assembly from readily-available non-indole starting materials using a simple and expedient procedure are still limited,[44] with only a few reports involving photochemically driven processes (Scheme 7). These include directly coupling anilines with alkynes[45] or LANGLOIS' REAGENT[46] under visible-light irradiation and visible-light-induced cyclizations of 2-alkynylated aniline derivatives.[47] For example, Zhang *et al.*[48] developed a visible-light photoredox synthesis of 3-acylindoles *via* intramolecular oxidative cyclization of *o*-alkynylated *N,N*-dialkylamines under iridium catalysis, proceeding under mild conditions using air as oxidant and with only water being formed as a side product.



Scheme 6. Selected examples for 3-acylation of indole. a) Ruthenium- or iron-catalyzed oxidative coupling of indole with anilines, b) palladium-catalyzed addition of indoles to nitriles and c) palladium catalyzed decarboxylative cross-coupling with carboxylic acids.



Scheme 7. Selected examples for the photochemical synthesis of 3-acylindoles. Direct coupling of aniline **37** with alkyne **38** affords the *N*-1 and *C*-2 substituted 3-acylindole **39** (top left), coupling of aniline **40** with the LANGLOIS' REAGENT (**41**) yields the C-2 substituted 3-acylindole **42**, while intramolecular cyclization of **43** yields the 3-acylindole **44**.

Although many interesting, atom-economical, and mild synthetic approaches towards 3-acylindoles have been developed recently, specific substitution patterns are often difficult to obtain by the reported reactions. Furthermore, the availability of starting materials and tolerance towards different functional groups can also be limiting factors.[6] Consequently, developing new, more efficient

methods for synthesizing 3-acylindoles from simple and readily available starting materials is highly encouraged.[29,31,32,34–36]

1.2 Photochemistry

One of the most important and intricate processes in nature is the conversion of solar to chemical energy *via* photosynthesis. In the CALVIN-BENSON cycle, chlorophyll from plants harvests light energy and activates complex chemical reactions which produce oxygen and allow the synthesis of organic compounds that provide energy.[49] Inspired by this process, CIAMICIAN proposed using light to mediate chemical reactions in 1912, and since then, many pharmaceuticals, fine chemicals, and advanced materials have been synthesized by utilizing photochemistry.[49,50] Nevertheless, classical photochemistry required special equipment and involved unselective reactions that were difficult to predict and control due to the employment of high-energy UV-light to excite substrates or reagents.[51] In recent years, visible-light photochemistry has come to the forefront of organic chemistry as a powerful strategy for activating small molecules,[52,53] enabling the development of efficient and selective transformations that are not possible to perform otherwise.[54] The utilization of visible light as energy input allows selective excitation of the specifically designed photocatalyst,[54] typically a metal complex[55] or organic dye[56] (Figure 8), which can induce the substrate to participate in unique, site-specific reactions.[57] This prevents the uncontrolled formation of active intermediates that could lead to unwanted side reactions[54] and allows selective functionalization of organic compounds under mild conditions.[51] Photocatalytic protocols have been reported for many important transformations, such as cross-coupling reactions, α-amino functionalizations, cycloadditions, fluorinations, *etc.*[53]