Letter

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Merger of Visible Light Photoredox Catalysis and C–H Activation for the Room Temperature C-2 Acylation of Indoles in Batch and Flow

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ABSTRACT: A mild and versatile protocol for the C−H acylation of indoles *via* dual photoredox/transition-metal catalysis was established in batch and flow. The C−H bond functionalization occurred selectively at the C-2 position of *N*-pyrimidylindoles. This room temperature protocol tolerated a wide range of functional groups and allowed for the synthesis of a diverse set of acylated indoles. Various aromatic as well as aliphatic aldehydes (both primary and secondary) reacted successfully. Interestingly, significant acceleration (20 h to 2 h) and higher yields were obtained under micro flow conditions.

KEYWORDS: C−H acylation, Photocatalysis, dual catalysis, Palladium catalysis, indoles, flow chemistry.

With the genesis of transition metal-catalyzed C–H activation strategies,[1,2] direct Csp^2–H bond acylation has witnessed a substantial growth over the past decade.[3,4] Despite extensive progress in the field, the low reactivity and limited selectivity continue to be the two main bottlenecks in this field. Therefore, the development of mild and widely applicable C–H acylation methodologies are of relevant importance.[3c]

Recently, visible light photoredox catalysis has played a tremendous role for the translation of single electron transfer processes into mild catalytic cycles. Its popularity stems from the access to unique synthetic pathways which have previously been elusive.[5] More specifically, the power of single-electron transfer processes enabled by photoredox catalysis has provided new opportunities for transition metal catalyzed cross-coupling reactions.[6,7] In addition, these dual catalytic strategies allow to carry out the reaction at room temperature.

(Hetero)arylketones are important structural components present in various natural products, pharmaceuticals and organic materials (Figure 1).[8] Palladium-catalyzed, ligand-directed C–H acylations of (hetero)arenes with aldehydes, alcohols or toluene as acyl surrogates have been described over the past decade as a powerful and versatile tool in organic chemistry.[9] In these examples, the Pd^{II} and Pd^{IV} catalytic cycle appears to be the major pathway and utilizes stoichiometric amounts of oxidants in combination with elevated reaction temperatures to enable the desired transformation.

More recently, single electron transfer pathways have been investigated to generate acyl radicals under mild reaction conditions.[10] Hereto, α-ketoacids have been explored as acyl radical precursors to enable the room temperature acylation of aryl rings *via* a dual photoredox/palladium catalytic strategy.[11]

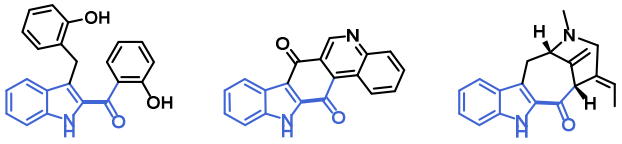
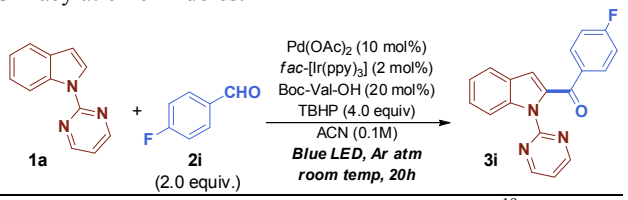


Figure 1: Natural products containing 2-acylindole framework.

However, to the best of our knowledge, aldehydes, while being the most abundant acyl surrogates, have never been investigated for the C–H acylation of (hetero)arenes *via* dual photoredox/palladium catalysis at room temperature. This prompted us to develop a novel methodology with aldehydes as acyl surrogates for the direct C-2 acylation of indoles at ambient temperature by merging visible light photoredox catalysis and C–H activation.

We commenced our investigations with the C–H acylation of *N*-pyrimidylindole (**1a**) using 4-methylbenzaldehyde (**2b**) as a coupling partner under standard batch conditions (See Supporting Information, Table S1). In the presence of $Pd(OAc)_2$ (10 mol%), $Ru(bpy)_2Cl_2$ (2 mol%), PivOH (50 mol%) and TBHP (4 equiv.) in acetonitrile (ACN, 0.1 M) under argon, and exposed to a 24W CFL light source, we were pleased to find selectively the C-2 acylated product **3b** with a 75% ^{1}H-NMR yield after 20 h. Prolonged reaction times resulted in a further increase in yield up to 84% after 36 h. Further optimization was carried out employing 4-fluorobenzaldehyde (**2i**) in combination with a more efficient 3.12W blue LED (λ_{max} = 465 nm) light source (Table 1). When screening different photocatalysts, *fac*-$[Ir(ppy)_3]$ was found to be superior

Table 1: Optimization of reaction conditions in batch for the C-2 acylation of indoles.[a]



Entry	Changes to standard conditions	^{19}F-NMR Yield (%)
1	none	73 (72)
2	$Ru(bpy)_3Cl_2$, 36 h	70 (66)
3	fac-[Ir(dF-ppy)$_3$]	26
4	fac-[Ir(ppy)$_2$(dtbpy)]PF_6	45
5	[Ir(dF-CF_3- ppy)$_2$(dtbpy)]PF_6	41
6	[Mes-Acr]ClO_4	38
7	no ligand	65
8	PivOH	73
9	Ac-Ile-OH	71
10	Ac-Val-OH	68
11	Boc-Ile-OH	70

[a]Reaction conditions: 0.5 mmol of *N*-pyrimidylindole, 10 mol% $Pd(OAc)_2$, 2 mol% *fac*-[Ir(ppy)$_3$], 20 mol% Boc-Val-OH, 2.0 equiv. of 4-fluorobenzaldehyde and 4.0 equiv. TBHP in ACN (0.1 M) for 20 h, blue LED light, isolated yield in parentheses.

(Table 1, Entries 1-5). The use of an organic dye, such as 9-mesityl-10-methylacridinium perchlorate ([Mes-Acr]ClO_4), resulted in a modest yield of 38% (Table 1, Entry 6). Furthermore, replacing PivOH with mono-protected amino acids (MPAA) as ligands[12] resulted in an improved reactivity and avoided the observed induction period (Table 1, Entries 8-11 and Figure 2). Optimal reactivity was observed using Boc-protected L-valine: a yield of 73% was obtained within 20 h under blue light irradiation (Figure 2).

One of the major limitations of photochemical transformations in batch is the so-called light attenuation effect through absorbing media as dictated by the Bouguer-Lambert-Beer law. This becomes especially apparent when the reaction is scaled by increasing the reactor dimensions. However, such limitations can easily be overcome by using continuous-flow capillaries.[13] These reactors allow for homogeneous irradiation of the reaction mixture and thus leads to a reduction in reaction time, a lower catalyst loading and an optimal scalability.[14,15] Bearing this in mind, we developed a photomicroreactor assembly consisting of a 3D printed holder containing a 3 mL perfluoroalkoxy alkane capillary reactor (PFA, I.D. 750 µm, see ESI Picture S1) in order to investigate our C-2 acylation protocol in micro flow.[16] Translating the optimal batch reaction conditions to flow yielded 34% of the desired product **3i** within 2 h residence time (see ESI, Table S2, entry 5). Additional flow optimization showed that the iridium loading could be decreased four times (0.5 mol%) while the concentration could be doubled (0.2 M) without any loss of reactivity. Furthermore, with 4 equiv. of **2i** and 6 equiv. of TBHP, an improved isolated yield of 89% was obtained for **3i** (see Table 2). This dramatic improvement in the reaction rate (20 h *vs* 2 h) and yield

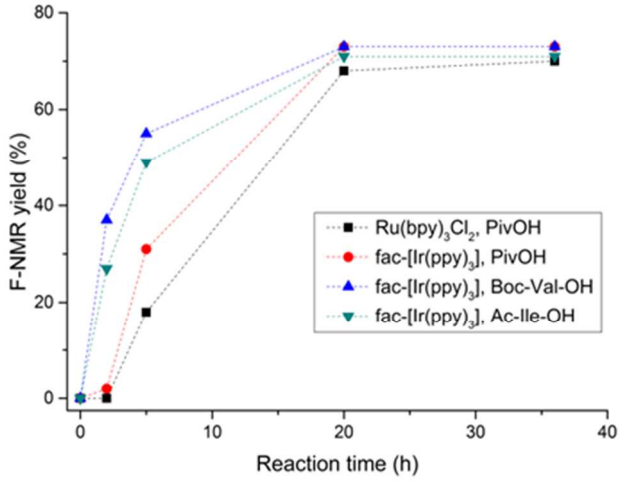


Figure 2: Yield *vs* time plot for the direct C-2 acylation of *N*-pyrimidylindole (**1a**) with 4-fluorobenzaldehyde (**2i**).

(72% *vs* 89%) can be attributed to the homogeneous irradiation of the reaction mixture.

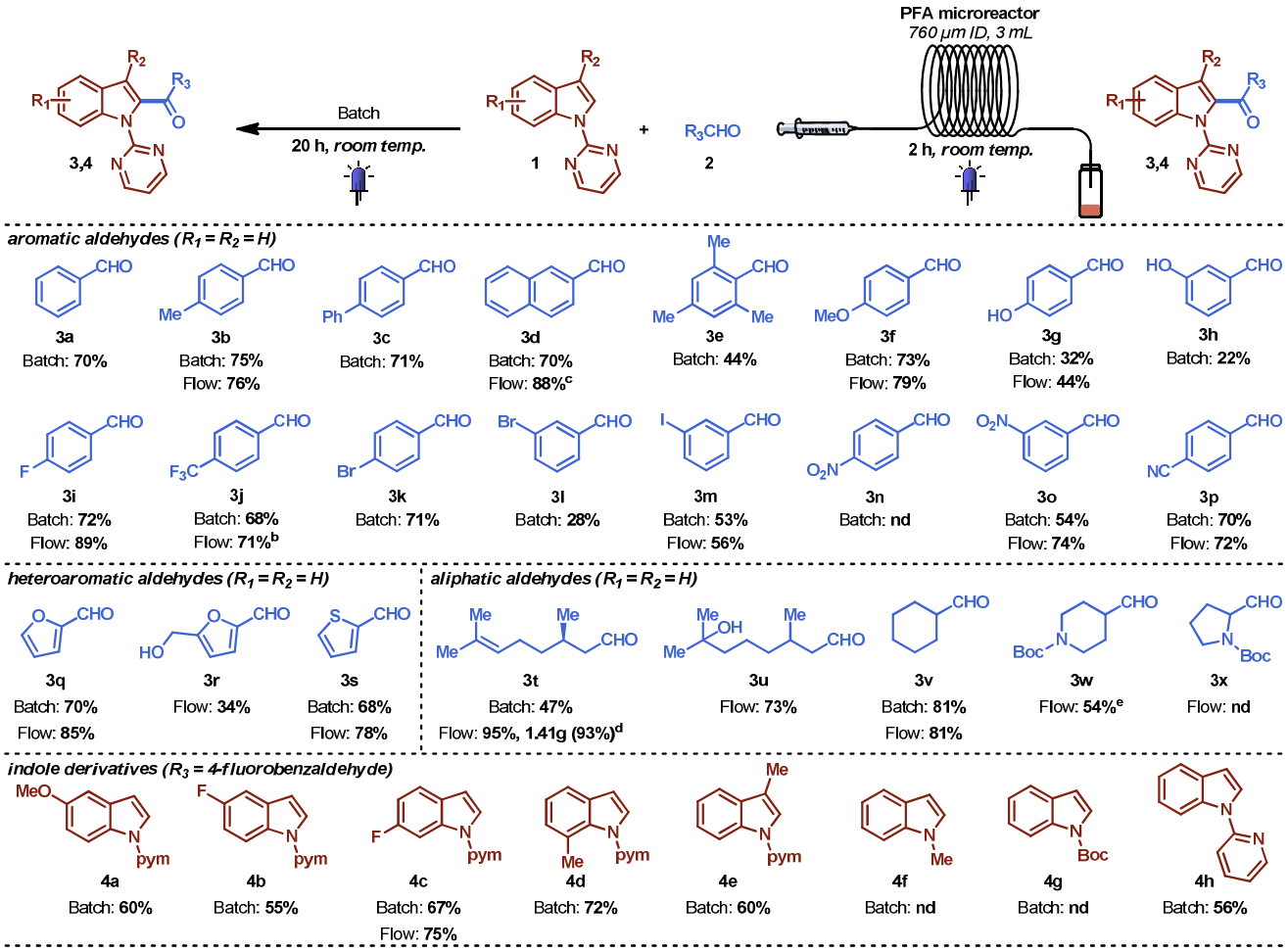
With optimized reaction conditions in hand, we evaluated the scope of the reaction (Table 2). The acylation reaction tolerated a wide variety of substituents on the benzaldehyde coupling partner. Indole acylation with benzaldehyde (**3a**) and aldehydes bearing alkyl/aryl substituents (**3b**, **3c**, **3d**), were well tolerated and high yielding (70-88% yield). When using the sterically demanding mesitaldehyde (**3e**), a moderate yield of 44% was obtained. Bearing an electron donating substituent (4-OMe), substrate **3f** afforded excellent isolated yields of 73% and 79% in batch and flow respectively. Moreover, it was demonstrated that benzaldehydes bearing a free hydroxyl group (**3g**, **3h**) showed some reactivity (22-44%). Aldehydes containing electron withdrawing groups such as 4-F (**3i**), 4-CF_3 (**3j**), 4-Br (**3k**), 3-NO_2 (**3o**) and 4-CN (**3p**) all gave the desired product in good yield (54-89%). However, 3-bromobenzaldehyde (**3l**) gave a lower yield (28%), while 4-nitrobenzaldehyde (**3n)** did not yield any product. Furthermore, 3-iodobenzaldehyde (**3m**) gave a moderate yield (53-56%).

The latter example together with **3g** and **3h** (free hydroxyl functionality) showcase the mild character of our room temperature protocol, since such functional group tolerability is unprecedented for the high temperature C–H acylation protocols of (hetero)arenes. Moreover, functional handles such as iodine provide opportunities for further decoration of the molecule (*e.g., via* cross-coupling).

Subsequently, relevant heterocyclic aldehydes were explored as potential acyl source. Reactions with furfural (**3q**) and thenaldehyde (**3s**) were both high yielding in batch as well as in flow (68-85%). Interestingly, 5-hydroxymethylfurfural (**3r**), a versatile platform chemical,[17] showed some reactivity albeit with a lower isolated yield (34%).

Next, we explored the potential of aliphatic aldehydes to engage in the direct C-2 acylation protocol. Primary aliphatic aldehydes such as (-)-citronellal (**3t**) and 7-hydroxycitronellal (**3u**) gave high to excellent yields (up to 95%). Notably, when using cyclohexanecarboxaldehyde (**2v**) as a branched aldehyde, no decarbonylation was observed, despite the fact this side reaction was described in the literature.[18]

Table 2: Batch[a] and Flow[b] scope.



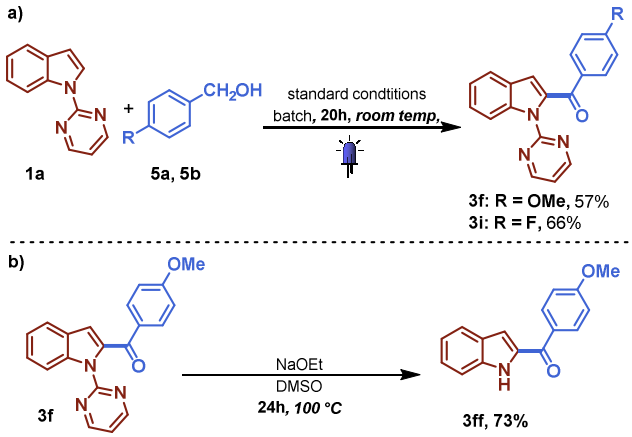
[a]Reaction conditions batch: 1.0 mmol of *N*-pyrimidylindole, 10 mol % $Pd(OAc)_2$, 2 mol % *fac*-$[Ir(ppy)_3]$, 20 mol % Boc-Val-OH, 2.0 equiv. of aldehyde and 4.0 equiv. TBHP in ACN (0.1 M), blue LED light, 20h reaction time; [b]Reaction conditions flow: 1.0 mmol of *N*-pyrimidylindole, 10 mol % $Pd(OAc)_2$, 0.5 mol % *fac*-$[Ir(ppy)_3]$, 20 mol % Boc-Val-OH, 4.0 equiv. of aldehyde and 6.0 equiv. TBHP in ACN (0.2 M), blue LED light, 2h residence time; reported yields are isolated yields; [c]3h residence time, 8.0 equiv. TBHP; [d]4.36 mmol scale. [e]<2.5 equiv. of aldehyde (due to limited solubility), 29% starting material recovered.

Instead, the acyl radical could be successfully trapped, rendering the desired product **3v** in a high yield (81%). *N*-Boc-piperidine-4-carboxaldehyde (**3w**) gave a moderate yield of 54% in flow conditions. The lower yield was mainly due to the limited solubility of the aldehyde in the reaction mixture. However, the use of Boc-prolinal as a coupling partner did not yield any product (**3x**).

In general, it was observed that, in addition to the reduced reaction time and lower catalyst loadings, the obtained isolated yields were higher under micro flow conditions when compared to the batch counterparts. Moreover, in order to demonstrate the practical utility of the developed protocol, a continuous-flow gram-scale experiment with *N*-pyrimidylindole (**1a**) and (-)-citronellal (**2t**) was carried out. With a simple numbered-up scale-up procedure[19] (2 x 3mL photomicroreactors), 1.41g (93%) of isolated product **3t** could be obtained in less than 9 hours of operation time (2h residence time). Finally, the scope of various indole derivatives was evaluated with substituents on the 3, 5, 6 and 7 position (**4a-4e**). Moderate to good yields (55-75%) were obtained for the latter substrates. Moreover, among different *N*-substitution or directing groups evaluated, the *N*-pyrimidyl group proved to be superior (**4f-4h**).

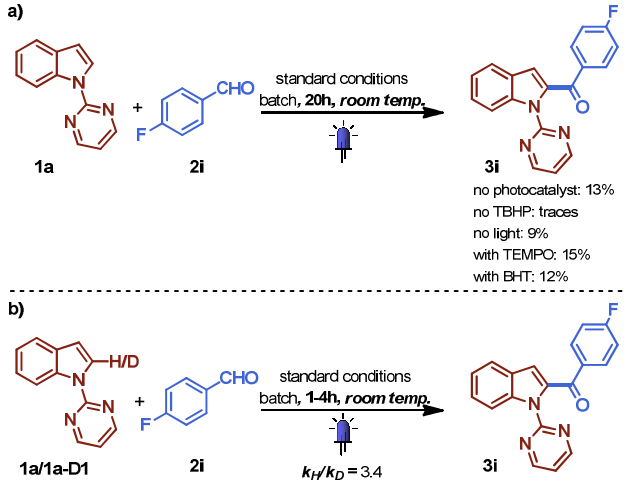
Encouraged by the obtained results, we further investigated the possibility of using benzyl alcohols as acylation reagents. Benzyl alcohols can be readily oxidized into the corresponding benzaldehydes in the presence of the oxidant TBHP.[20] As shown in Scheme 1a, benzyl alcohol with 4-OMe (**5a**) or 4-F (**5b**) as substituent, could be successfully used as acyl surrogates, rendering **3f** and **3i** in 57% and 66% respectively. To further enhance the synthetic utility of this process, facile removal of the *N*-pyrimidyl group was carried out in a traceless fashion using sodium methoxide in DMSO for 24 h at 100 °C, with an overall yield of 73% **3ff** (Scheme 1b).

In order to gain more insight into the reaction mechanism, some control experiments were carried out (Scheme 2). When the reaction was carried out with **1a** and **2i** in absence of photocatalyst, TBHP or light, only traces of acylated product were observed (Scheme 2a). Moreover, upon the addition of radical scavengers, such as 2,2,6,6-tetramethylpiperidyl-1-oxyl (TEMPO) or butylated hydroxytoluene (BHT) to the reaction mixture, suppression of the reaction is taking place, suggesting that a SET-type mechanism is at hand. Moreover, the mass of the trapped acyl radical with TEMPO (Scheme 3, **2i''**) was detected via GC-MS analysis.



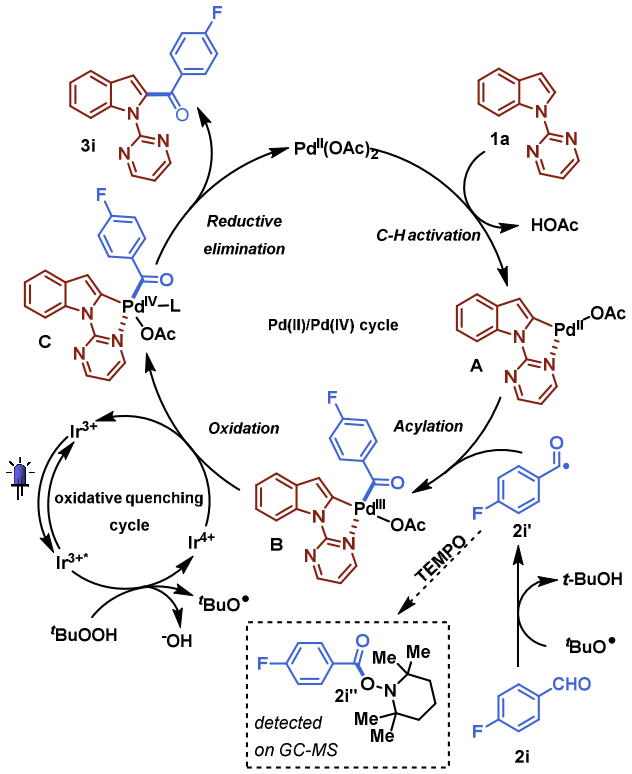
Scheme 1: a) evaluation of benzyl alcohols as acyl surrogates; b) traceless deprotection.

Finally, kinetic isotope experiments (KIE) of **1a** and its deuterated analogue **1a-D1** were performed under optimized conditions revealing a noticeable KIE effect (k_H/k_D = 3.4, Scheme 2b). This indicates that the C–H bond cleavage might be the rate limiting step.[21] Based on our observations and analogous literature precedents,[7,9,11] a plausible reaction mechanism was proposed (Scheme 3). The reaction starts with the formation of a five membered palladacycle **A**. Meanwhile, an acyl radical is generated *via* the photocatalytic process. Herein, the photoexcitation of the photocatalyst produces the excited state (Ir^{3+*}), which is oxidatively quenched by *t*-BuOOH to generate the key radical intermediate *t*-BuO$^{\cdot}$. Next a hydrogen abstraction occurs between the *t*-BuO$^{\cdot}$ radical and 4-fluorobenzaldehyde (**2i**) to afford the acyl radical **2i'**. The acyl radical **2i'** is then trapped by the palladacycle **A** which results in the formation of intermediate **B**. Intermediate **B** can undergo a single electron oxidation to Pd^{IV}, which closes the photocatalytic cycle *via* a back electron donation. Finally, a reductive elimination takes place, releasing the desired product **3i** and regenerating the Pd^{II} catalyst. Further efforts towards a detailed mechanistic understanding of this transformation is currently pursued in our labs.



Scheme 2: a) Control experiments; b) KIE experiments.

In summary, a room temperature C-2 acylation protocol for indoles was developed *via* a productive merger of visible light photoredox catalysis and C–H functionalization. The reaction was conducted both in batch and flow and is compatible with a wide variety of functional groups. The protocol could be ex-



Scheme 3: Proposed Pd(II)/Pd(IV) cycle for the C-2 acylation of indoles.

-tended from aromatic to both primary and secondary aliphatic aldehydes with good to excellent yields. Moreover, continuous-flow chemistry proved its effectiveness by decreasing the reaction time up to 10 times (2h *vs* 20h), the catalyst loading 4 times (0.5 mol % vs 2 mol %), increasing the yields and scaling the reaction conditions. In addition, the scope could be further extended to benzyl alcohols as abundant acyl surrogates. Finally, KIE experiments suggest the C−H activation to be the rate limiting step.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website.
Complete experimental details and characterization data for the synthesized compound (PDF).

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ABBREVIATIONS

nd = not detected; TBHP = tert-butyl hydroperoxide; PFA = perfluoroalkoxy alkane; ACN = acetonitrile.

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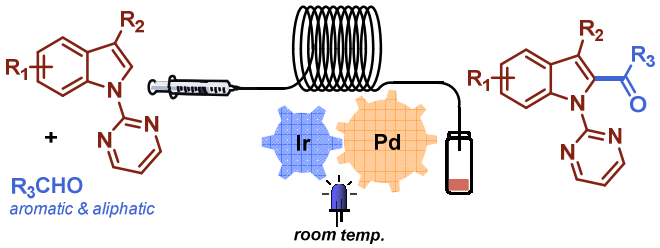
R2
R1
N
N
+
R3CHO
aromatic & aliphatic
Ir
Pd
room temp.
R2
R3
R1
N
O
N
N