Photoredox Catalyzed Dehydrogenative Csp^3-Csp^2 Cross-Coupling of Alkylarenes to Aldehydes in Flow

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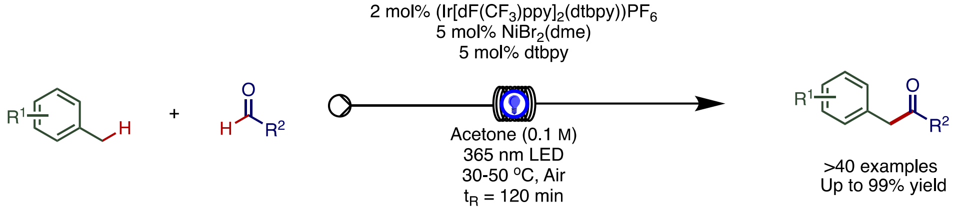
Supporting Information Placeholder



- Improved conditions and preparation
- Multi-gram scale up
- API late-stage functionalisation
- Photocatalyst recycling

ABSTRACT: Executing photoredox reactions in flow offers solutions to frequently encountered issues regarding reproducibility, reaction time and scale-up. Here we report the transfer of a photoredox catalyzed benzylic coupling of alkylarenes to aldehydes to a flow chemistry setting leading to improvements in terms of higher concentration, shorter residence times, better yields, ease of catalyst preparation and enhanced substrate scope. Its applicability has been demonstrated by a multi-gram scale reaction using high-power LEDs, the late-stage functionalization of selected APIs and also a photocatalyst recycling method.

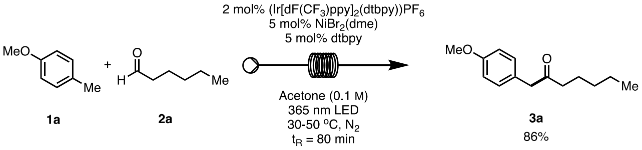
Constructing new Csp^2-Csp^3 bonds constitutes a significant process in the molecular assembly and late-stage functionalization of biologically relevant molecules. Consequently, the development of straightforward methods to quickly forge these bonds has been a focus of attention for synthetic chemists in recent years. Noteworthy in this context, photoredox catalysis has arisen as a valuable tool that enables the construction of complex molecular architectures in a modular manner under mild conditions via the intermediacy of highly reactive species generated by various light sources.[1]

This strategy has enabled the direct activation of unfunctionalized C–H bonds for cross coupling using a synergistic combination of photoredox and transition metal catalysis.[2] The opportunities to explore cross dehydrogenative coupling reactions using this strategy are particularly attractive since no pre-functionalization is required in either coupling partner, resulting in high atom economies and access to a large array of late-stage functionalization opportunities, employing cheap and abundant chemical feedstocks.[3]

Recently, Murakami *et al.* reported a dehydrogenative photocatalytic $C(sp^2)$–$C(sp^3)$ coupling reaction between alkylarenes and aldehydes in the presence of an iridium photocatalyst and a nickel co-catalyst. This method facilitates the introduction of acyl groups to aromatic side-chains to afford α-aryl ketones[4]; versatile building blocks and key intermediates towards the preparation of many active pharmaceutical ingredients (APIs) such as amphetamines and opiates.[5] Despite the potential utility of this and related transformations, there are significant challenges hampering the widespread adoption of photochemical reactions more generally in chemical synthesis, particularly in terms of scalability.[6] Although photochemical reactions are attractive in terms of product outcome, their efficiency is dependent on the incident photon flux on the reaction mixture. This adds to existing concerns relating to poorer reproducibility, difficulties of optimization, photo-degradation and unwanted side reactions.[7] Scale-up issues associated with irradiating reactions are governed by the Beer-Lambert-Bouguer law, which describes exponentially decreasing photon-flux penetration through solutions of high molar absorptive molecules, such as photocatalysts.[6] Consequently, visible light-mediated reactions only take place on the periphery regions of a batch reaction vessel.[8]

To address these issues, many researchers have shown that transferring photochemical reactions to a continuous flow regime using high-power LEDs can improve reproducibility, scalability, reaction outcome and reaction times.[9] Many of these benefits arise from superior heat distribution, mixing and photon-flux as a result of the small cross section of tubing found in flow reactor platforms.

Scheme 1. Initial conditions found.

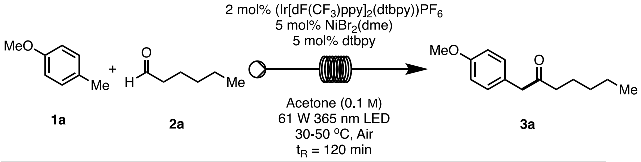


Inspired by the opportunity to further develop the reaction discovered by Murakami through exploiting the potential benefits of flow chemistry, we set out to investigate conditions applicable for scale-up of this dehydrogenative C(sp^2)–C(sp^3) cross coupling reaction.

Establishing 4-methylanisole (**1a**) and hexanal (**2a**) as model substrates, we found initial conditions to execute the reaction (Scheme 1). We then commenced a reaction optimization campaign using a commercial flow reactor. The results are summarized in **Table 1**.

We found that while the photocatalyst was essential (entry 2), to obtain a high yield of product, small quantities of product were observed in the absence of ligand or nickel co-catalyst, provided a bromide source such as tetra-butylammonium bromide (TBAB) was added to the reaction mixture (entries 3 and 4). The presence of Br$^-$ is important as Br• is likely the radical abstractor for this reaction.[4] Using nickel chloride as an alternative catalyst also gave reasonable conversion to the product (entry 5), although the addition of TBAB increased the conversion considerably (entry 6) and is in line with their respective oxidation potentials.[10] We were also pleased to find that the reaction could be carried out under aerobic conditions with no significant depreciation in product yield (entry 7). Stock solutions of the iridium photocatalyst, nickel co-catalyst and ligand could be prepared and stored under air for 2 months then used directly with no observed deleterious effects on the reaction. Optimization of the flow reactor parameters showed that only 120 min residence time was required for full conversion of the aldehyde component (entry 8) and a 365 nm LED light source was preferred over 420 nm LEDs (entry 9). Finally, acetone was also preferable to previously used ethyl acetate (entry 10)[4] and the concentration was found to be optimal at 0.1 M (entry 11).

Table 1. Reaction optimization[a].

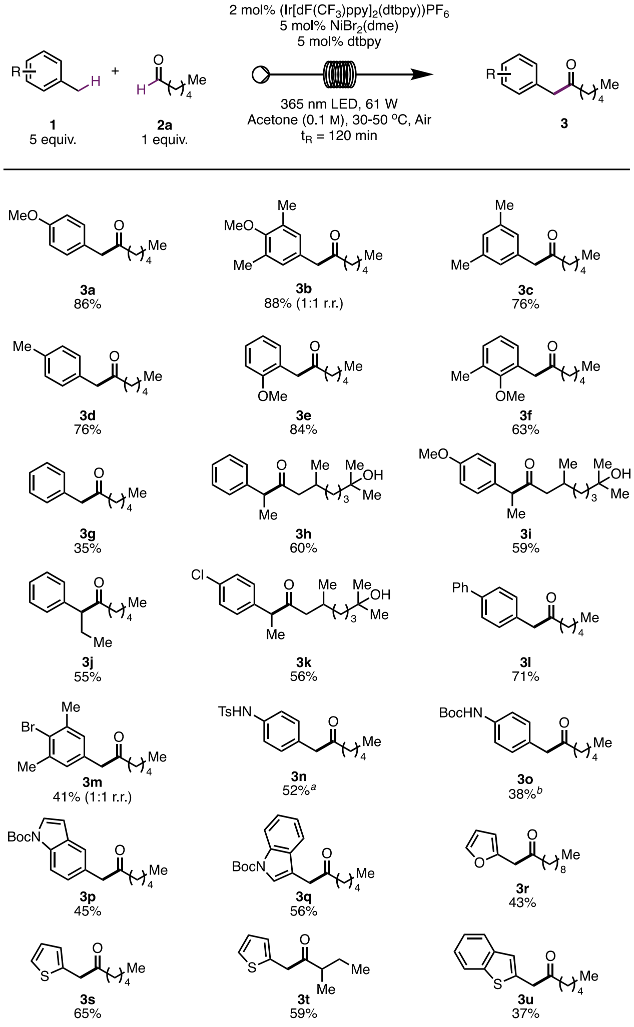


entry	deviation from standard conditions	yield[a] (%)
1	none	96 (86)[b]
2	No photocatalyst	0[c]
3	No ligand added	59[c]
4	No $NiBr_2$(dme) and ligand (0.5 equiv. TBAB added)	17[c]
5	$NiCl_2$(dme) instead of $NiBr_2$(dme)	55
6	$NiCl_2$(dme) instead of $NiBr_2$(dme) (0.5 equiv TBAB added)	71
7	Under N_2, reaction mixture degassed	91
8	t_R = 80 min	77[c]
9	t_R = 80 min, 45 W 420 nm LED	28[c]
10	EtOAc solvent	77
11	0.2 M	66

Reaction conditions: 0.2 mmol, 1.0 equiv of hexanal, 5.0 equiv of 4-methyl anisole, 2 mol % of (Ir[dF(CF_3)ppy]$_2$(dtbpy))PF_6, 5 mol % $NiBr_2$(dme), 5 mol % dtbpy, 2 mL of acetone. [a]NMR conversion to the product with 1,3,5-trimethoxybenzene as an internal standard. [b]Isolated yield. [c]Unreacted hexanal detected by ^{1}H NMR.

Upon defining a suitable set of conditions, a range of alkylarenes were then evaluated (**Tables 2** and **3**). Electron rich methylarenes (**1a-f**) were found to work well and were acylated in good to excellent yields. While the absence of an electron-donating group, such as in toluene, led to decreased yield (**3g**), the presence of secondary benzylic sites appeared to be beneficial (**3h-k**) enabling good reactivity with electron deficient aromatic rings (**3k**). An extended aromatic system was also tolerated (**3l**). Aryl halides were also amenable to this transformation (**3m**), providing a handle for further functionalization via orthogonal cross-coupling chemistry. Pleasingly, protected aniline derivatives were also reasonable substrates, giving **3n** and **3o** in 52% and 38%, respectively. Finally, we examined a range of heterocyclic methylarenes and found that indoles, furans and thiophenes and were competent substrates in this reaction (**3p-x**), however, basic N-heterocyclic substrates such as methyl-pyridines or methyl-imidazole failed to deliver the expected ketones (see ESI).

Table 2. Alkylarene scope.

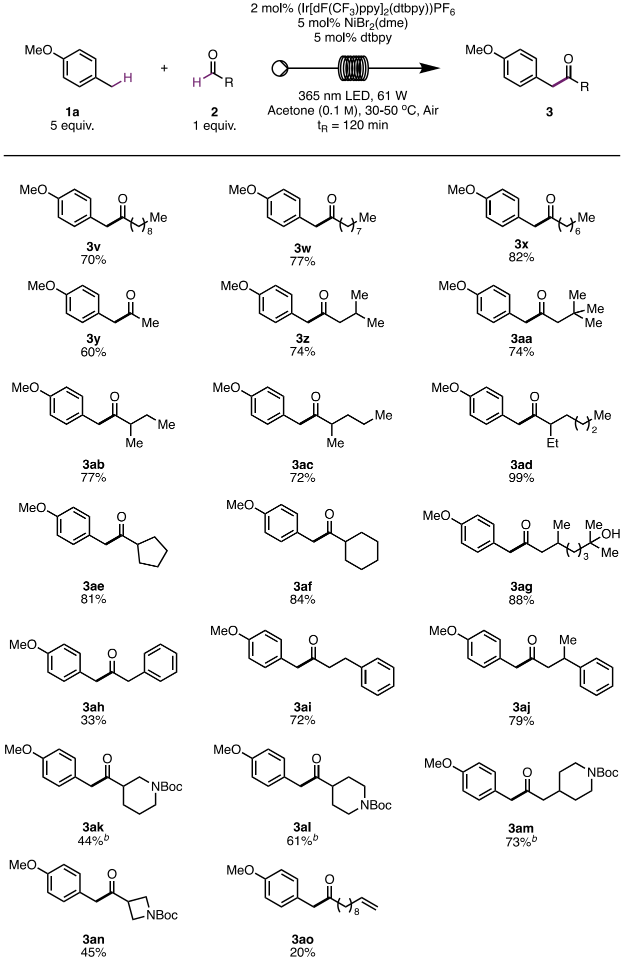


3a 86%
3b 88% (1:1 r.r.)
3c 76%
3d 76%
3e 84%
3f 63%
3g 35%
3h 60%
3i 59%
3j 55%
3k 56%
3l 71%
3m 41% (1:1 r.r.)
3n 52%[a]
3o 38%[b]
3p 45%
3q 56%
3r 43%
3s 65%
3t 59%
3u 37%

Reaction conditions: **1** (2.0 mmol), aldehyde (0.4 mmol), (Ir[dF(CF$_3$)ppy]$_2$(dtbpy))PF$_6$ (2 mol%), NiBr$_2$(dme) (5 mol %), dtbpy (5 mol%) and acetone (4.0 mL). [a] t$_R$ = 180 min; [b] t$_R$ = 300 min.

Next, we turned our attention to the aldehyde component in this coupling reaction. A variety of aliphatic aldehydes with a range of chain lengths, as well as substrates bearing α-alkyl groups, were found to give good to excellent yields of the corresponding products (**3v-af**). Alcohols and aromatic rings were well tolerated (**3ag-aj**), although significant decomposition via aldehyde decarbonylation was observed with phenylacetaldehyde (**3ah**) (see ESI). Aldehydes bearing Boc-protected amines also delivered the desired ketone products in moderate to good yields (**3ak-an**), while a substrate containing a terminal alkene was less well suited (**3ao**), exhibiting product photodegradation.

Table 3. Aldehyde scope.

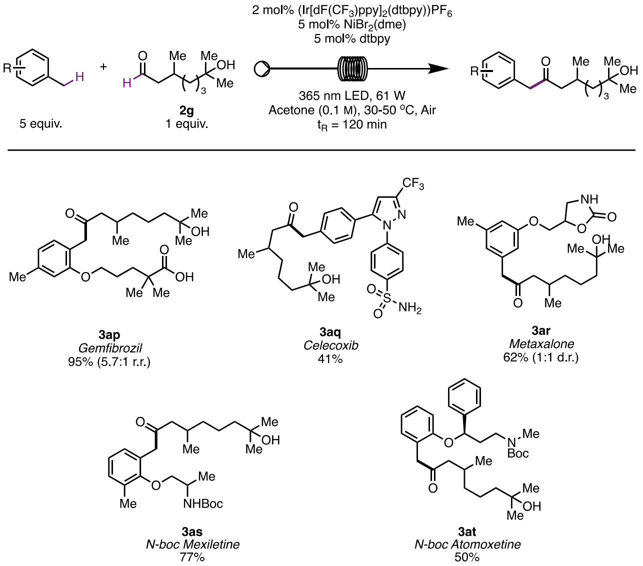


3v 70%
3w 77%
3x 82%
3y 60%
3z 74%
3aa 74%
3ab 77%
3ac 72%
3ad 99%
3ae 81%
3af 84%
3ag 88%
3ah 33%
3ai 72%
3aj 79%
3ak 44%[b]
3al 61%[b]
3am 73%[b]
3an 45%
3ao 20%

Reaction conditions: **1** (2.0 mmol), aldehyde (0.4 mmol), (Ir[dF(CF$_3$)ppy]$_2$(dtbpy))PF$_6$ (2 mol%), NiBr$_2$(dme) (5 mol %), dtbpy (5 mol %) and acetone (4.0 mL). [a] t$_R$ = 180 min.

Key to our interests in this reaction was the potential applicability towards late-stage functionalization of APIs in flow. Methyl-substituted aromatic rings are frequently found amongst APIs, agrochemicals and natural products and are, therefore, highly desirable targets for selective modification. The opportunity to acylate APIs directly to α-aryl ketones is particularly attractive due to the versatility of ketones to be transformed to a plethora of other desirable functional groups, therefore opening up a wider range of chemical space to be explored for biological activity. We were pleased to find therefore that a selection of molecules could be derivatized in moderate to excellent yields (**Table 4**). Gemfibrozil was acylated in 95% yield, with 5.7:1 regioselectivity for the *ortho*-methyl group over the *meta*-methyl position (**3ap**). Anti-inflammatory drug celecoxib gave ketone **3aq** in 41% yield, demonstrating the ability to incorporate N-containing aromatic heterocycles in the substrate scope, provided they are deactivated as bases. Muscle relaxant metaxalone was acylated in 62% yield and isolated as 1:1 mixture of diastereoisomers (**3ar**). N-Boc protected Mexiletine was functionalized to give ketone **3as** in 77% yield. N-Boc protected Atomoxetine was also derivatized in 50% yield (**3at**).

Table 4. Late-stage functionalization of APIs and analogues.



3ap *Gemfibrozil* 95% (5.7:1 r.r.)

3aq *Celecoxib* 41%

3ar *Metaxalone* 62% (1:1 d.r.)

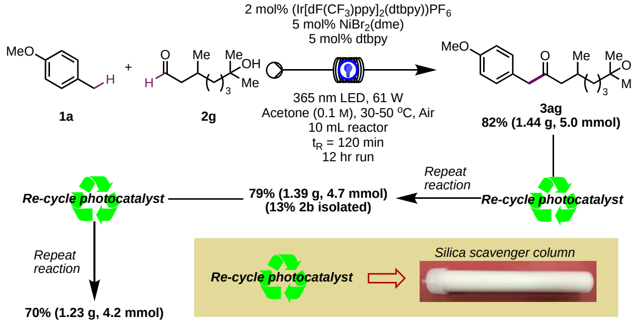
3as *N-boc Mexiletine* 77%

3at *N-boc Atomoxetine* 50%

Reaction conditions: **1** (2.0 mmol), 7-hydroxycitronellal (0.4 mmol), (Ir[dF(CF$_3$)ppy]$_2$(dtbpy))PF$_6$ (2 mol%), NiBr$_2$(dme) (5 mol %), dtbpy (5 mol %) and acetone (4.0 mL).

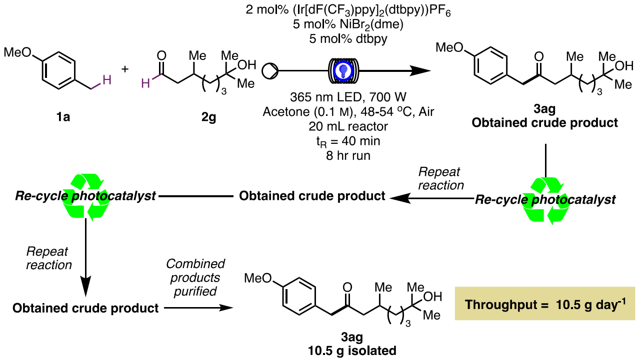
Solutions to scalability issues faced with photochemical reactions, such as the above process, have been investigated previously by the group and so we set out to address this aspect of the procedure.[9f,11] Firstly, using the original reactor with a 61 W 365 nm LED as the light source (**Figure 1**) and 7-hydroxycitronellal (**2g)** selected as the aldehyde component for this scaled reaction, 5.0 mmol of ketone **3ag** was synthesized continuously in 82% yield at a throughput of 2.56 g day^{-1}. However, in order to increase the value of the new procedure, we felt it important to recover the expensive photocatalyst from the reaction with the aim of recycling it. We were able to show that the photocatalyst and co-catalyst were readily removed from the reaction mixture by simply passing the product solution through a silica gel plug acting as a scavenger. Elution with the reaction solvent (acetone) removed all organic components of the product mixture while subsequent washing with methanol selectively eluted the photocatalyst (90% recovery), which could then be successfully re-used (x2) with only slightly diminished conversion to the final product (**Figure 1**).

Figure 1. Scale-up and catalyst recycling.



Encouraged by this result, we then set about scaling up the reaction further using a higher power flow photoreactor (**Figure 2**). This set-up utilized a 20 mL reactor coil (ID = 1.0 mm) and a more powerful LED (365 nm LEDs, 700 W) system. Initial experiments with this platform revealed the optimum throughput was obtained with a 40 minutes residence time (see ESI). With our aim to perform a multi-gram scale reaction over 24 hours, optimized for throughput rather than yield, we acknowledged that a continuous reaction for this length of time would require 1.62 g of the [Ir] photocatalyst. With this in mind, we employed our photocatalyst recycling strategy to reduce the amount required and the scale-up was carried out in 3 consecutive continuous 8-hour-average segments. After each run, the photocatalyst was recovered and then re-used immediately in the subsequent reaction (Figure 2). The combined crude products yielded 10.5 g of ketone **3ag** after purification in 50% overall yield. Crucially, a total of only 640 mg of [Ir] photocatalyst was required as a result of the recycling methodology.

Figure 2. PhotoSyn reactor scale-up



In summary, we have enhanced the dehydrogenative cross-coupling reaction between aromatic alkyl side-chains and aldehydes in terms of shorter reaction times, improved yields, in situ reagent preparation and catalyst preparation and higher reaction concentrations using flow chemistry techniques as an enabling tool. Furthermore, we have shown the reaction is amenable towards the late-stage functionalization of a range of APIs. Finally, we have demonstrated that this transformation can be executed continuously on a multi-gram scale using high-power LEDs, whilst also recovering and re-using the iridium photocatalyst.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Details of experimental procedure, compound characterization data and NMR spectra (PDF).

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest(s) other than DCB is an employee and stockholder of Pfizer Inc.

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