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COMMUNICATION

Synthesis of Unsymmetrical Ketones by Applying Visible-Light Benzophenone/Nickel Dual Catalysis for Direct Benzylic Acylation

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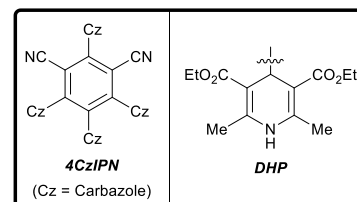
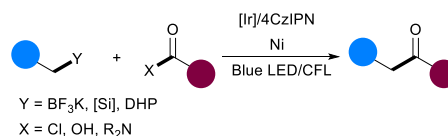
Herein, we report a dual catalytic system for the direct benzylic C-H acylation reaction furnishing a variety of unsymmetrical ketones. A benzophenone-derived photosensitizer combined with a nickel catalyst has been established as the catalytic system. Both acid chlorides and anhydrides are able to acylate the benzylic position of toluene and other methylbenzenes. The method offers a valuable alternative to late transition metal catalyzed C-H acylation reactions.

Ketones are one of the most important and most abundant classes of compounds in organic chemistry.¹ Molecules with the ketone moiety are often encountered in several fields of research – from organic synthesis to materials and drug discovery. Synthesis of unsymmetrical ketones has persistently been at the focal point of many investigations.² However, the traditional carbon-carbon bond formation strategies, adapted for ketone synthesis, may suffer from low functional group tolerance,³ produce substantial transition-metal waste,^{4,3h} involve toxic carbon monoxide gas⁵ and demand high temperatures⁶. Among them, the Weinreb ketone synthesis is a mild and widely applied method.^{3e-g}

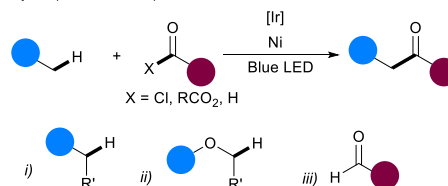
In recent years, dual photoredox/transition-metal catalysis has been used as a mild and robust method for C-C bond formation,⁷ with some reactions yielding ketones as product (Scheme 1).⁸ We desired to achieve the synthesis of valuable unsymmetrical ketones through dual catalysed acylation of C(sp³)-H bonds.⁹ Very recently, substituted benzophenones have been introduced as an elegant multi-tasking photosensitizer for visible-light/nickel catalysed C(sp³)-H bond functionalization via C-C bond formation.¹⁰ In these reports, the photo-excited triplet state of benzophenone facilitates the H-atom abstraction from a labile C-H bond and causes the

generation of an alkyl radical. The radical subsequently enters the nickel catalytic cycle to furnish the desired coupling product. We therefore wondered if benzophenones can be successfully applied as photocatalyst for the ketone synthesis, as it would result in a significant improvement over other dual catalysed acylation reactions avoiding more expensive iridium photocatalysts, or the pre-synthesis of more complex radical precursors.^{8,9}

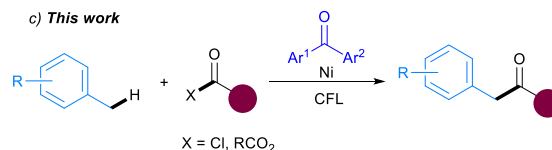
a) Molander, Fensterbank



b) i) Doyle, ii) Shibasaki, iii) Murakami



c) This work



Scheme 1 Dual photoredox/nickel strategies for unsymmetrical ketone synthesis.

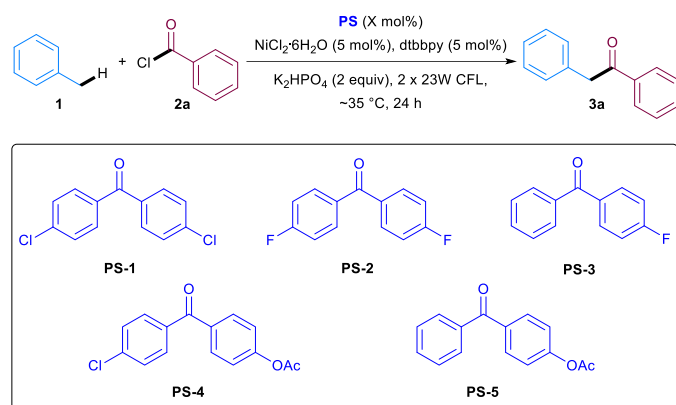
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The acylating agents reported for dual catalysed acylations to date are acids, acid chlorides, anhydrides and amides. For initial trials, we selected benzoyl chloride for the benzylic acylation of toluene. The first reaction, in presence of 4,4'-dichlorobenzophenone (25 mol%), nickel (II) chloride hexahydrate (5 mol%) and 4,4'-di-*tert*-butyl-2,2'-dipyridyl (dtbbpy) (5 mol%), gave the desired 1,2-diphenylethan-1-one (**3a**) in 86% NMR yield after 24 hours – under basic conditions (K_2HPO_4 , 2 equiv) and irradiation of two 23W CFL lamps (Table 1, entry 1). The ambient temperature was maintained around 35 °C by placing a cooling fan on top of the reaction set-up. However, isolation of **3a** proved to be difficult due to the similar polarity of the product and the photocatalyst (**PS-1**).

Table 1 Optimization of the dual catalysed acylation reaction.^a



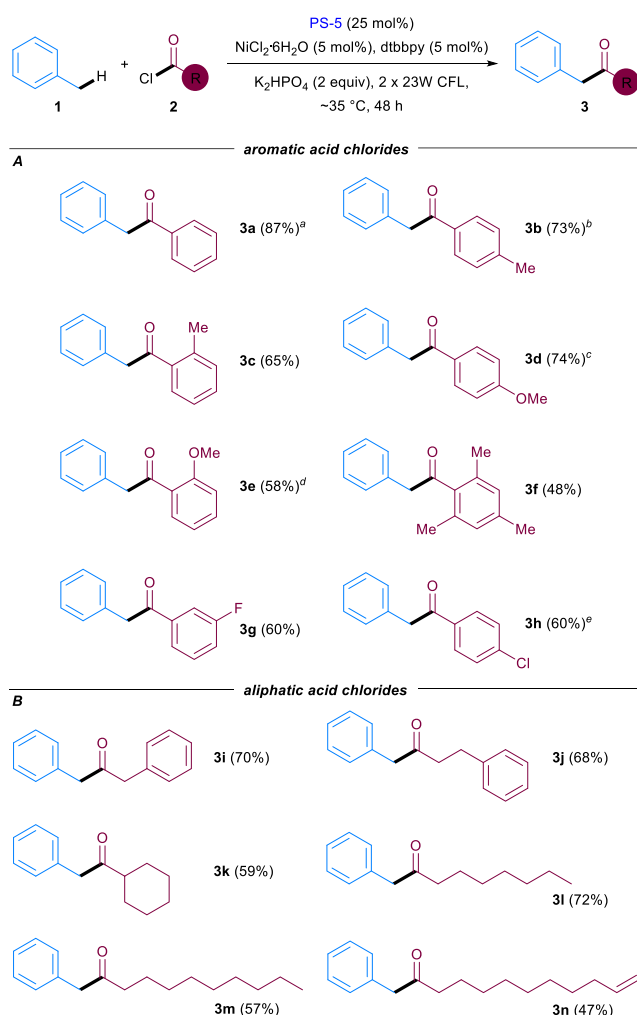
entry	PS	X	Yield (%) ^b
1	PS-1	25	86 (80)
2	PS-1	10	57
3	PS-2	25	79
4	PS-3	10	66
5	PS-4	10	77
6	PS-5	10	71
7	PS-5	25	78
8	PS-5	25	93 ^c

a. The reaction mixture in toluene (6 mL) was irradiated with two 23W-CFL lamps from two sides for 24 h under argon; **b.** Calculated, with CH_2Br_2 (14 μ L, 0.2 mmol) as internal standard, from 1H NMR spectra; **c.** Isolated yield after 48 h reaction time.

Lowering the amount of **PS-1** did result in lower yields (entry 2). Therefore, we set out to find a suitable photosensitizer which would result in undiminished yield and offer better separation from the product. Replacing the chlorine atoms of **PS-1** with fluorines did not provide a better solution (entry 3). Next, we tested a set of three structurally different photosensitizers and **PS-4** and **PS-5** bearing acetate functionality which furnished better yields than the mono-fluorinated benzophenone, **PS-3** (entries 4-6). Both **PS-4** and **PS-5** showed significant separation from the product to simplify the isolation. We chose **PS-5** for further optimization as it is less expensive and devoid of any halogen atoms - ruling out possible side-reaction caused by the nickel catalyst. To our delight, increasing the loading of **PS-5** to

25 mol% and the reaction time, allowed us to isolate **3a** in 93% yield (entries 7-8). Control experiments proved the indispensability of the nickel catalyst, ligand, photosensitizer as well as irradiation for a successful reaction (see SI). Omitting the base led to lower turnovers (32% NMR yield) and therefore, remained as a crucial component of the reaction conditions.

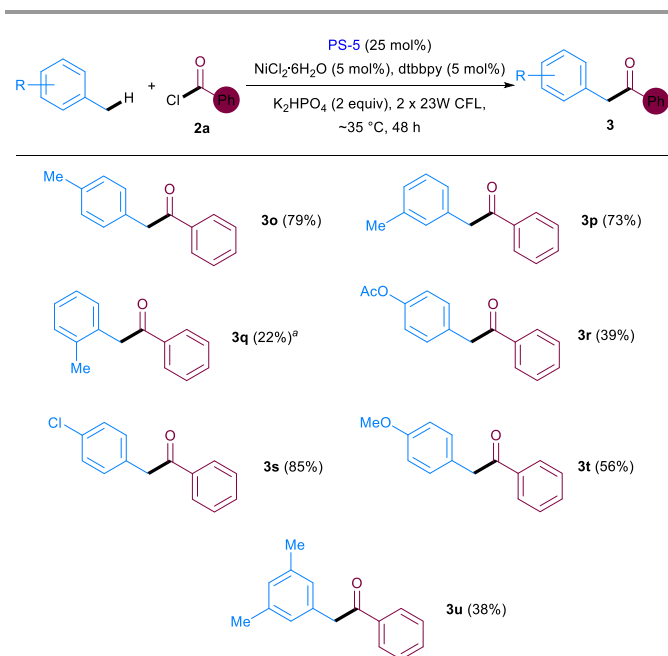
First, we decided to explore the scope of substituted benzoyl chlorides under the optimized conditions by reacting them with toluene (Scheme 2A). The simple methyl group was tolerated both in the *para* (**3b**; 73%) and the *ortho* (**3c**; 65%) position with good yields. Replacing the methyl group with more electron-donating methoxy did not significantly alter the productivity, as **3d** and **3e** were obtained in 74% and 58% yields, respectively. It is worth noting that due to an increased polarity in the methoxy-substituted products, we used **PS-1** and **PS-2** for these two examples, as required for the separation process. In the next trial, mesityl chloride furnished ketone **3f** in reduced yield of 48%, presumably as a result of steric hindrance. **3g** was isolated in 60% yield when 3-fluorobenzoyl chloride was reacted with toluene.



Scheme 2 Scope of acid chlorides. **Reaction conditions:** **2** (0.2 mmol), **1** (equiv), **PS-5** (25 mol%), $NiCl_2 \cdot 6H_2O$ (5 mol%), dtbbpy (5 mol%) and K_2HPO_4 (2 equiv.) was stirred in toluene (**1**) (6 mL) and irradiated with two 23W CFL lamps for 48 h under argon; yields after purification. **a.** Reaction conducted in 1.0 mmol scale; **b.** 10 mol% of **PS-5** was used; **c.** 25 mol% of **PS-1** was used; **d.** 25 mol% of **PS-2** was used.; **e.** Reaction run for 24 h.

Pleasingly, electron-deficient substrate **2h** bearing a chlorine atom provided the coupling product in 60% yield, as well. In this chemoselective reaction, the chlorine on the phenyl ring remained intact.

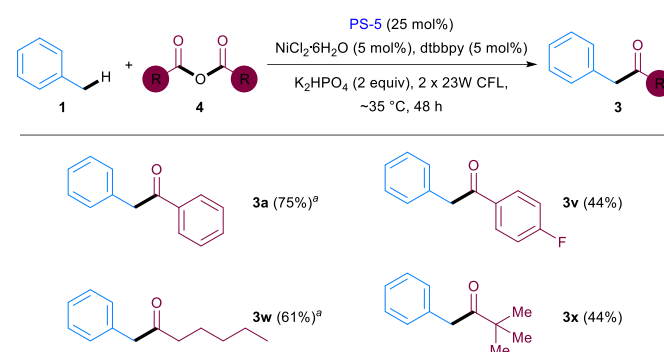
Next, we advanced to try aliphatic acid chlorides as substrates (Scheme 2B). 2-Phenylacetyl chloride produced dibenzyl ketone (**3i**) in 70% yield. Hydrocinnamoyl chloride also showed similar efficiency as it gave the desired product **3j** in 68% yield. We tested the cyclohexanecarboxylic acid chloride as well and ketone **3k** was isolated in moderate yield of 59%. Encouraged by the initial success with aliphatic substrates, we conducted the reaction with a few long-chain acid chlorides. To our delight, octanoyl and decanoyl chloride successfully furnished the corresponding long-chain ketones in 72% (**3l**) and 57% (**3m**) yield. Additionally, a C-11 linear acid chloride with a terminal olefin was converted to **3n** in moderate yield (47%). We could also conduct the reaction in higher scale of 1.0 mmol and **3a** was obtained in 87% yield (Scheme 2A).



We next tested other toluene derivatives in reactions with benzoyl chloride (Scheme 3). *Para* and *meta*-xylene gave rise to the corresponding 1,2-diaryl ethanones in good yield (79% and 73%, respectively). However, *ortho*-xylene was not a good substrate for our reaction (**3q**, 22% NMR yield). *Para*-tolyl acetate showed slightly better reactivity (**3r**, 39%). 4-Chlorotoluene could also be used as a H-bond donating substrate as the Ar-Cl bond did not interfere in the nickel catalytic cycle. This chemoselective reaction produced the ketone **3s** in excellent yield of 85%. Apart from this, 4-methylanisole and mesitylene furnished the desired products with moderate efficiency [**3t** (56%) and **3u** (38%)]. We also tried

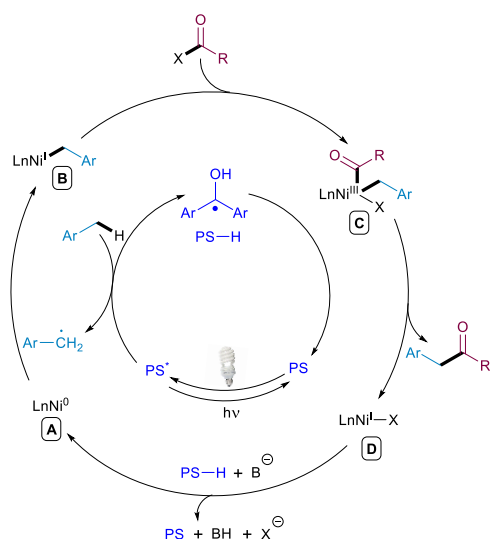
to apply secondary benzylic radicals in our reaction. When the reaction was conducted in ethylbenzene, we failed to observe the desired product in the crude NMR spectra. Instead, we observed products arising from side-reactions of the secondary radical. 2,3-Diphenyl butane and acetophenone were observed as side-products (Scheme S1, SI). When methyl benzyl ether was tested as radical precursor, it led to a messy reaction mixture. However, 1,2-dimethoxy-1,2-diphenylethane was still observed among other unidentified side-products in GC-MS and crude NMR.

Anhydrides were also tested as acylating agents (Scheme 4). Unsubstituted benzoic anhydride was converted to **3a** in 75% yield, comparatively showing that benzoyl chloride is a better acylating agent for this method. The corresponding anhydride



of 4-fluorobenzoic acid gave **3v** in 44% yield. When caproic anhydride was subjected to the optimized conditions, 1-phenylheptan-2-one (**3w**) was isolated in 61% yield. Finally, we observed formation of **3x** in moderate efficiency following the reaction with pivalic anhydride.

Based on the data presented and the previously reported benzylic arylations, the following mechanism can be proposed (Scheme 5). Upon irradiation of CFL lamps, the benzophenone is excited to its triplet state, PS*, which acts as a diradical and initiates the reaction via HAT at the benzylic position. PS* is converted to a tertiary radical PS-H. The benzyl radical, formed in this process, is intercepted by an in situ-generated Ni(0) complex **A** to furnish **B**, which is a Ni(I) species. **B** performs an oxidative addition step onto the (CO)-X bond of the acyl substrate and is converted to complex **C**, where the nickel centre is in Ni^{III} oxidation state. Subsequently, **C** undergoes facile reductive elimination to form the desired ketone along with generating another Ni(I) species **D**. Finally, **D** is reduced via base-assisted electron transfer from PS-H to regenerate **A** and thereby, closing the catalytic cycle. Regarding the lack of success with α -substituted toluene derivatives - we presume that since a secondary benzylic radical is more stabilized, its trapping by the nickel is slower and reversible. Thus, it leads to inefficient turnover and formation of side-product via radical-radical recombination.



Scheme 5 Plausible mechanism.

To summarize, we developed a mild method for synthesis of unsymmetrical ketones via acylation of benzylic C-H bond. The method uses the combination of a photoactive benzophenone derivative and a nickel complex, in a dual catalytic reaction. 4-benzoylphenyl acetate was chosen as the photocatalyst after careful optimization. A broad range of aromatic and aliphatic acid chlorides could be successfully employed for the acylation of toluene. Additionally, anhydrides worked well as acylating agent under our conditions. Apart from toluene, other substituted methylbenzenes also underwent acylation at the benzylic position providing a valuable and efficient alternative to classical ketone synthesis using acylations.

Conflicts of interest

There are no conflicts to declare.

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