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Photo-Nickel Dual Catalytic Benzoylation of Aryl Bromides†

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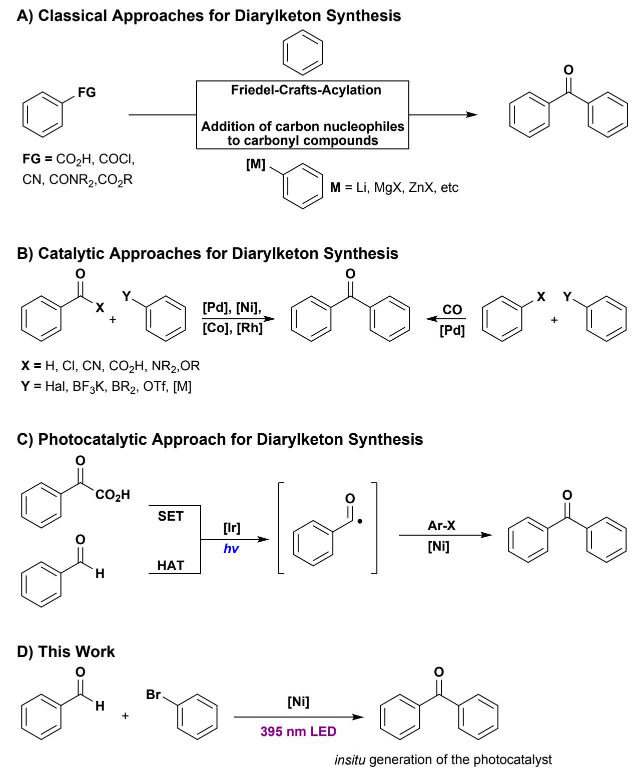
The dual catalytic arylation of aromatic aldehydes by aryl bromides using irradiation and a nickel catalyst is reported. The reaction product serves as photocatalyst and hydrogen atom transfer agent of this transformation.

Photo redox catalysis has emerged into a powerful tool for C–H activation.[1-4] Particularly, merging photo- and nickel-catalysis enabled the functionalization of a wide range of C–H bonds.[5-9] As the field of photocatalysis develops, expensive iridium catalysts are successively replaced by novel organic dyes.[10, 11] At the same time, long known photocatalysts such as benzophenones regain interests due to their ability to act as efficient triplet sensitizer or photoinduced hydrogen atom transfer catalysts.[10,12, 13]

In his recent work on dual catalytic *sp³* C–H functionalization, *Martin* demonstrated the efficiency of a carefully designed benzophenone in dual catalytic transformations.[14] A similar approach was later independently reported by *Hashmi*[15] and *Rueping,*[16] employing benzaldehyde and benzophenones, respectively, as combined HAT-photocatalyst and sensitizer for nickel catalysed *sp³* C–H arylations. Besides their utility in recent synthetic applications as well as classical photochemistry, diaryl ketones are an ubiquitous motive in pharmaceuticals, making their synthesis an attractive target of ongoing research.[17]

As non-catalytic approaches such as the Friedel-Craft acylation often lack regioselectivity and the addition of organometallic reagents to carbonyls either require prefunctionalization or reoxidation (Scheme 1a), catalytic methods have been continuously developed over the years.[18, 19] Both different acyl surrogates and aldehydes have been employed together with transition metals such as palladium[20-29] rhodium[30, 31] nickel[32-35] and cobalt[36] to furnish benzophenones. The use of CO as carbonyl source is likewise well established (scheme 1b).[37, 38]

Recent developments in photoredox catalysis allow to access the acyl radical in a mild and selective manner (Scheme 1c). However, photochemical methods for the synthesis of ketones by C–H activation focused mostly on the coupling of aliphatic aldehydes.[9]



Scheme 1 (a) Classical and (b) catalytic methods for the synthesis of diaryl ketones as well as novel dual catalytic approaches (c and d).

To extend the catalytic approach to aromatic aldehydes, we envisioned a nickel-based dual-catalytic methodology, which exploits the ability of diaryl ketones to act as sensitizer and HAT-catalysts.

We started our investigation with the coupling of 4-chlorobenzaldehyde (**1a**) with 4-bromo-benzonitrile (**2a**). Gratifyingly, the respective ketone **3a** was observed under various conditions, revealing acetone as the optimal solvent, (4,4'-dimethyl-2,2'-bipyridyl)nickel(II) bromide as the most efficient precatalyst and sodium carbonate as best base during the initial screening (Table 1).

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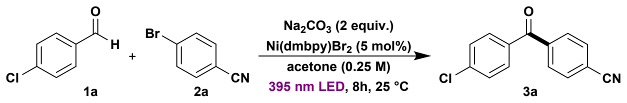
Table 1 Optimization and control reactions [a]

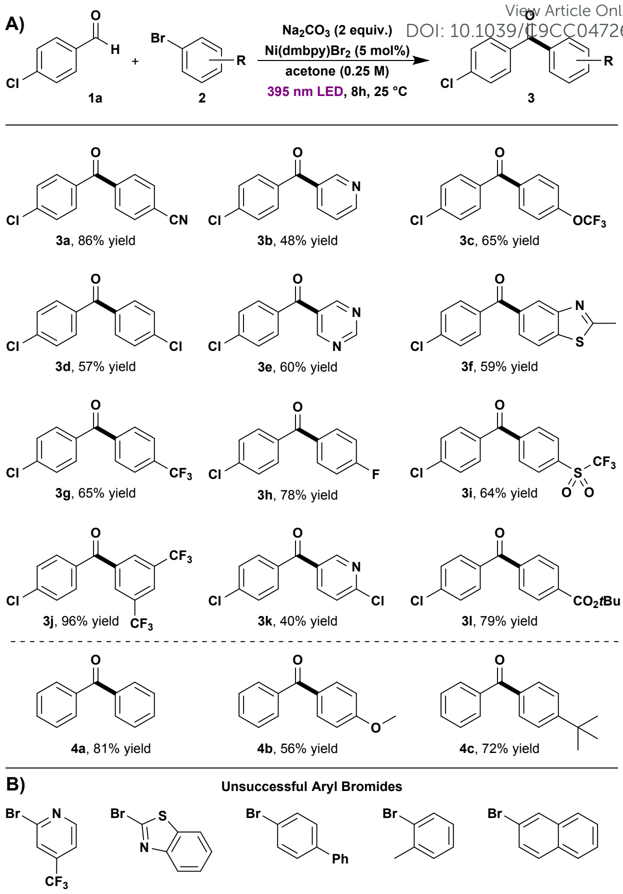


Entry	Deviation from standard condition	Yield[b] [%]
1	None	93% (86%)[c]
2	Ni(dtbbpy)Br_2	40%
3	DMSO	0%
4	MeCN	50%
5	PhH	8%
6	Cs_2CO_3	61%
7	K_2CO_3	71%
8	K_2HPO_4	2%
9	no base	8%
10	$NiBr_2$ as catalyst	0%
11	4,4'-dimethyl-2,2'-bipyridne as catalyst	0%
12	no catalyst	0%
13	in the dark	0%
14	55°C in the dark	0%
15	455 nm	0%

[a] Unless otherwise noted, the reactions were carried out with 4-bromobenzonitrile (0.5 mmol), 4-chlorobenzaldehyde (0.75 mmol), Na_2CO_3 (1.0 mmol) and Ni(dmbpy)Br_2 (0.025 mmol) in dry acetone (0.25 M) under irradiation with UV-LEDs (395 nm) and under N_2-atmosphere for 8 h at 25 °C. [b] Yield determined by calibrated GC-FID analysis with 1,3,5-trimethoxybenzene as internal standard. [c] Isolated yield after purification by column chromatography in parentheses.

After performing the control experiments and confirming the essential contribution of all reaction components to the product formation, we explored the scope of this transformation.

The reaction of electron deficient substrates gave cyano-, ester-, sulfonyl- and trifluoromethyl-substituted benzophenons (**3a**, **3g**, **3i**, **3j**, **3l**) in good to excellent yields. Dihalogenated ketons (**3d**, **3h**) were obtained in moderate to good yields. The reaction is not limited to phenyl bromides. For example, benzothiazoyl ketone **3f** was obtained in 59% yield (Scheme 2). Heteroaryl ketones (**3b**, **3e**, **3k**) were formed from bromopyridines and -pyrimidine in moderate yield. However, neither 2-bromo-4-(trifluoromethyl)pyridine nor 2-bromo-benzothiazole furnished significant amounts of product. The same was observed for 4-bromobiphenyl, 2-bromotoluene and 9-bromophenanthrene.[39] Using benzaldehyde as coupling partner allowed benzoylation of bromobenzene and electron rich aryl bromides in moderate to good yields (**4a**-**c**).



Scheme 2 (a) Aryl bromide scope. All reactions were carried out with aryl bromide (0.5 mmol), 4-chlorobenzaldehyde or benzaldehyde (0.75 mmol), Na_2CO_3 (1.0 mmol) and Ni(dmbpy)Br_2 (0.025 mmol) in dry acetone (0.25 M) under irradiation with UV-LEDs (395 nm) and under N_2-atmosphere for 8 h at 25 °C. Isolated yield after purification by column chromatography. (b) Unsuccessful aryl bromides under standard conditions.

After establishing the aryl bromide scope, we investigated the aldehyde scope, using 4-bromobenzonitrile as the coupling partner (Scheme 3).

Benzaldehyde reacted smoothly under the developed reaction conditions and afforded **5a** in very good yield. Fluorinated benzaldehydes formed the respective ketones in good to excellent yields (**5e**, **5i**-**k**). Both very electron poor benzophenons (**5b**-**e**, **5k**) as well as "*push-pull*" systems (**5f**-**i**), bearing an electron donating on one side, and one electron withdrawing substituent on the other, were synthesized in good to excellent yields (**5f**-**i**). Whilst benzoyl-protected hydroxybenzaldehyde was transformed into ketone **5l** in good yield, neither 4-hydroxybenzaldehyde nor 4-amino-benzaldehyde reacted to the ketone.[40]

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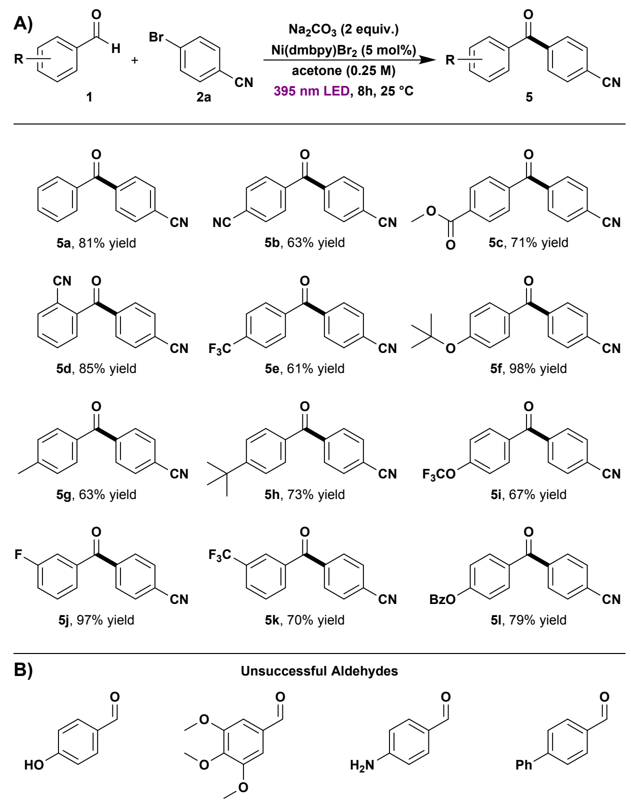
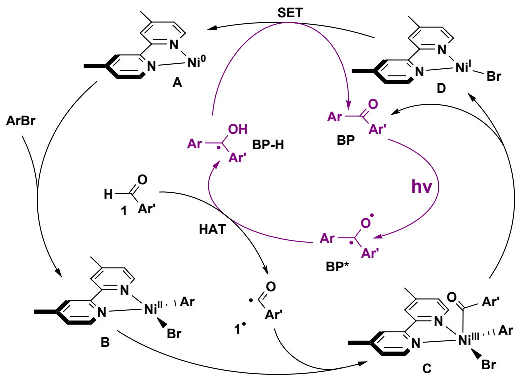


Scheme 3 (a) Aldehyde scope. All reactions were carried out with 4-bromobenzonitrile (0.5 mmol), aldehyde (0.75 mmol), Na_2CO_3 (1.0 mmol) and $Ni(dmbpy)Br_2$ (0.025 mmol) in dry acetone (0.25 M) under irradiation with UV-LEDs (395 nm) and under N_2-atmosphere for 8 h at 25 °C. Isolated yield after purification by column chromatography. (b) Unsuccessful aldehydes under standard conditions

The mechanism of different nickel-based metalla-photocatalyzed reactions have been investigated in computations and experimental studies.[14, 40, 41] Different modes of C-H activation are discussed, including σ-bond metathesis by a sensitized nickel(II)-aryl bromide complex (complex **B,** Scheme 4) and HAT by bromine radicals that form upon homolytic fragmentation of the same excited complex. The use of benzophenones (**BP***) as photocatalyst, however, opens a new potential reaction pathway, as triplet excited **BP*** can serve as sensitizer to facilitate energy transfer based pathways, but additionally can act as HAT catalyst itself.[42, 43] A plausible mechanism based on the latter property is shown below.



Scheme 4 Plausible mechanism.

The photocatalytic cycle starts with benzophenone **BP** absorbing a photon to reach its triplet-state **BP*** and hence enabling it to abstract a hydrogen atom from aldehyde **1** to form both the acyl radical **1**$^{\cdot}$ and radical **BP-H**. The oxidative addition of the nickel(0)-complex **A** into the aryl bromide bond furnishes nickel(II) species **B**, which serves as radical-trap for acyl radical **1**$^{\cdot}$. The formed nickel(III) species **C** is believed to undergo reductive elimination to benzophenone **BP** and complex **D**. Single electron transfer (SET) from **BP-H** to the nickel(I) bromide **D** is closing the catalytic cycle, furnishing both nickel(0) complex **A** and the ground state benzophenone **BP**.

However, the formation of the first photocatalytically active species remains elusive. Attempted photoreduction of the precatalyst with a mixture of benzaldehyde and sodium carbonate allows the observation of an apparently air sensitive species formed after already a few minutes of irradiation (see supporting information). GC-MS analysis of the mixture revealed traces of different products known to form upon photolysis of benzaldehyde such as benzene, benzil and its decarbonylation product benzophenone, of which we consider the latter ones together with the aldehyde capable to initiate the reaction.[44]

In conclusion, we have developed a photochemical nickel-catalyzed benzoylation of aryl bromides with a variety of aldehydes. The reaction does not need the initial addition of a photocatalyst, since the products of the reaction serve as photocatalysts after the reaction was initiated by photolysis of the respective benzaldehyde. Financial support from the German Science Foundation (DFG; KO 1537/18-1) is acknowledged. Shun Wang, Qing-Yuan Meng and Indrajit Gosh are acknowledged for helpful discussions. We thank Julia Zach for her technical support and Ranit Lahmy for her help on the manuscript.

Conflicts of interest

There is no conflict to declare.

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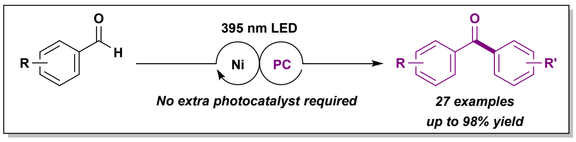

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