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The Dual Role of Benzophenone in Visible-Light/Nickel Photoredox-Catalyzed C−H Arylations: Hydrogen-Atom Transfer and Energy Transfer

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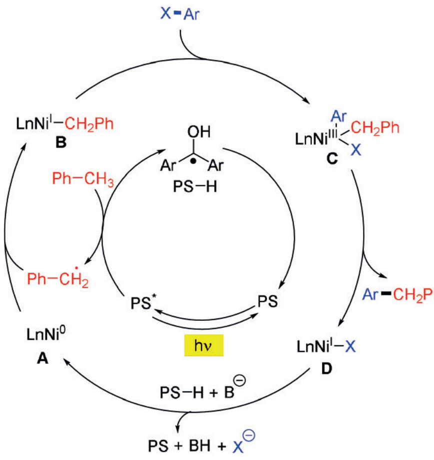
Abstract: *A dual catalytic protocol for the direct arylation of non-activated* $C(sp^3)$*−H bonds has been developed. Upon photochemical excitation, the excited triplet state of a diaryl ketone photosensitizer abstracts a hydrogen atom from an aliphatic C−H bond. This inherent reactivity was exploited for the generation of benzylic radicals which subsequently enter a nickel catalytic cycle, accomplishing the benzylic arylation.*

The direct functionalization of inert C−H bonds facilitates the access to complex molecular structures in organic synthesis. Hence, the direct modification of C−H bonds has been extensively investigated in the last two decades. Whereas transition metal-catalyzed processes, with the assistance of directing groups, have been widely used for the activation of $C(sp^2)$−H bonds,[1] applying this strategy to $C(sp^3)$−H bonds is more challenging.[2] Nevertheless, organic free-radical chemistry has been utilized as an alternative tool for the functionalization of inert aliphatic C−H bonds.[3]

Conventionally, harsh reaction conditions employing strong acids, peroxides or high-energy UV light are necessary for the generation of $C(sp^3)$ radicals. The recent progress in the field of visible light-mediated photoredox-catalyzed reactions allows easier access to $C(sp^3)$-centered radical intermediates and their subsequent functionalization.[4] Furthermore, the combination of photocatalysis and nickel catalysis has emerged as an elegant approach for the direct arylation of unactivated $C(sp^3)$−H bonds.[5] For example, MacMillan and co-workers reported a protocol for the α-arylation of cyclic and acyclic amines, lactams, and ureas.[5a] The groups of Doyle[5b] and Molander[5c] described the α-arylation of ethers. Recently, our group successfully achieved the arylation of allylic $C(sp^3)$−H bonds.[5g]

The H-atom abstraction agent, in these reports, has been a transient radical species generated either through electron transfer or via energy transfer by the photocatalyst. We considered simplifying this step by using the excited state of a photosensitizer itself for the H-atom abstraction. Organic compounds,[4a,6] as well as inorganic complex structures,[4d,5f,7] are known for their ability to abstract H-atoms upon photochemical excitation. Among the organic compounds applied, diaryl ketones have long served this purpose, owing to their accessible triplet excited states. Therefore, we decided to engage this class of compounds in catalytic amounts as organic photosensitizers (PS) for the $C(sp^3)$−H arylation.[8]

Diarylmethane moieties are important structural motifs in bio-active compounds, drug molecules, and organic materials.[9] Hence, methods for their facile synthesis are in great demand. We therefore aimed at developing a general protocol for the benzylic arylation using visible-light catalysis and at the same time expanding the application of diaryl ketones in dual photoredox/transition-metal catalysis.[10,11] Our mechanistic hypothesis is depicted in Scheme 1.



Scheme 1. Mechanistic hypothesis.

The triplet PS*, formed upon photochemical excitation of the ground state PS, initiates the reaction via H-atom abstraction from toluene. The resulting benzyl radical is trapped by an in situ-generated Ni^0 species **A** to form **B**. The Ni^I species **B** oxidatively adds to the haloarene substrate and the resulting Ni^{III} complex **C** subsequently produces the desired coupling product via reductive elimination. This step leads also to the formation of **D** which, upon base-assisted reduction by the reduced PS (PS-H), gives **A**, closing the catalytic cycle (E_{red} $[Ni^I/Ni^0] = -1.10$ V vs. Ag/AgCl in DMF;[12] $E_{1/2}^{red}$ $[PhCOPh] = -2.20$ V vs. $Ag/AgNO_3$ in MeCN[13]). An alternative mechanism in which the oxidative

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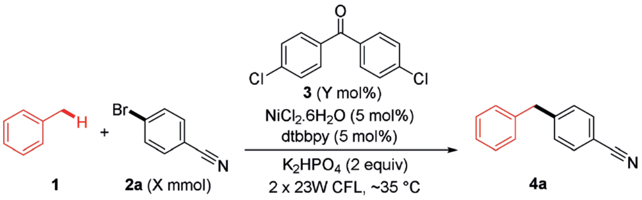
addition of Ni^0 species to the aryl halide precedes the radical trapping step might also be operating.[14]

For the initial experiments, we selected 4,4′-dichlorobenzophenone (**3**) ($E_{1/2}^{red}$ [**3**] = −2.09 V vs. Ag/AgNO$_3$ in MeCN, λ_{max} = 344 nm) (see the Supporting Information) as photosensitizer, as it was recently successfully used by Guin and coworkers, in combination with household CFL lamps, in the C(sp^3)−H alkenylation/alkynylation reaction.[6h] Initially, 4-bromobenzonitrile (**2a**) was irradiated, in the presence of **3** (25 mol %), $NiCl_2{\cdot}6H_2O$ (5 mol %), 4,4′-di-*tert*-butyl-2,2′-dipyridyl (dtbbpy) as ligand (5 mol %), and K_2HPO_4 as base (2 equiv), with two 23 W CFL lamps for 18 hours, in toluene as solvent. The reaction setup was cooled with a fan from the top to keep the reaction temperature constant at approximately 35 °C (see the Supporting Information). Pleasingly, the desired coupling product **4a** was formed in 51 % yield (Table 1, entry 1). The reaction reached full conversion with further dilution of the reaction mixture from 0.35 M to 0.2 M and gave **4a** in 94 % yield after purification (Table 1, entry 2). Furthermore, 20 mol % of **3** was also sufficient to achieve full reaction efficiency (Table 1, entry 3). A further decrease in the amount of photosensitizer led to diminished yields (Table 1, entries 4 and 5).

Table 1: Optimization of the reaction conditions.[a]



Entry	**2a** (X mmol)	**3** (Y mol %)	Conc. [M]	Yield [%][b]
1	0.35	25	0.12	51
2	0.2	25	0.05	94[c]
3	0.2	20	0.05	100
4	0.2	10	0.05	48
5	0.2	5	0.05	37

[a] The reaction mixture in toluene was irradiated with two household CFL lamps from two sides for 18 h under Ar. [b] Calculated, with CH_2Br_2 as internal standard, from NMR spectra. [c] Yield after purification.

Control experiments proved that all reagents, as well as light-irradiation, are indispensable for the reaction to proceed (see the Supporting Information). Furthermore, a wide range of diaryl ketones and similar compounds were evaluated as photosensitizers (see the Supporting Information). Interestingly, among the diaryl ketones tested, **3** turned out to be the most efficient candidate for our reaction (see the Supporting Information).

With the optimized conditions in hand, we proceeded to explore the scope of the reaction. First, the reactivity of different bromoarenes was tested in the reaction with toluene (Figure 1). Aryl bromides bearing electron-withdrawing groups (CF_3, Ac, or CO_2Me) in the *para* position reacted efficiently to give the corresponding desired products **4b**–**4d** in good yields (53–79 %). Notably, chemoselectivity was achieved in the case of 4-chlorobromobenzene as the reaction took place only at the C–Br bond (**4e**, 62 % yield). Fluorine as substituent was tolerated as well and the corresponding product **4f** was isolated in 71 % yield. However, the yield dropped to 41 % when the substituent at the *para* position was changed to a phenyl group (**4g**). To our delight, electron-rich substrates were also suitable for this reaction. 4-Bromotoluene gave the desired product **4h** as an inseparable mixture with trace amount of bibenzyl, which was formed as a result of the homocoupling of the benzyl radicals (Scheme 2b). 1-Bromo-4-(*tert*-butyl)benzene as substrate showed similar reactivity (68 % yield, **4i**). Compound **4j** was obtained in excellent yield (92 %) when 4-bromoanisole reacted with toluene. The reaction between bromobenzene and toluene furnished diphenylmethane (**4k**) in 55 % yield. Pleasingly, increased steric hindrance posed by *meta* and *ortho* substituents did not inhibit the reaction (**4l**–**4n**). To be noted, radical species were never formed at the benzylic position of the bromotoluenes (**2h**, **2l**, and **2n**). This chemoselectivity can be attributed to the statistical leverage of **1** over the limiting reagents.

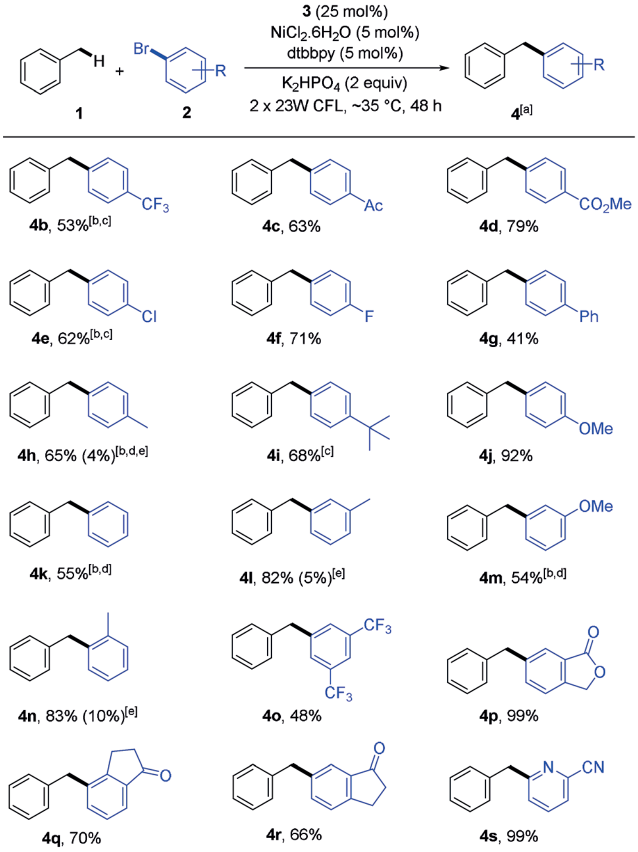
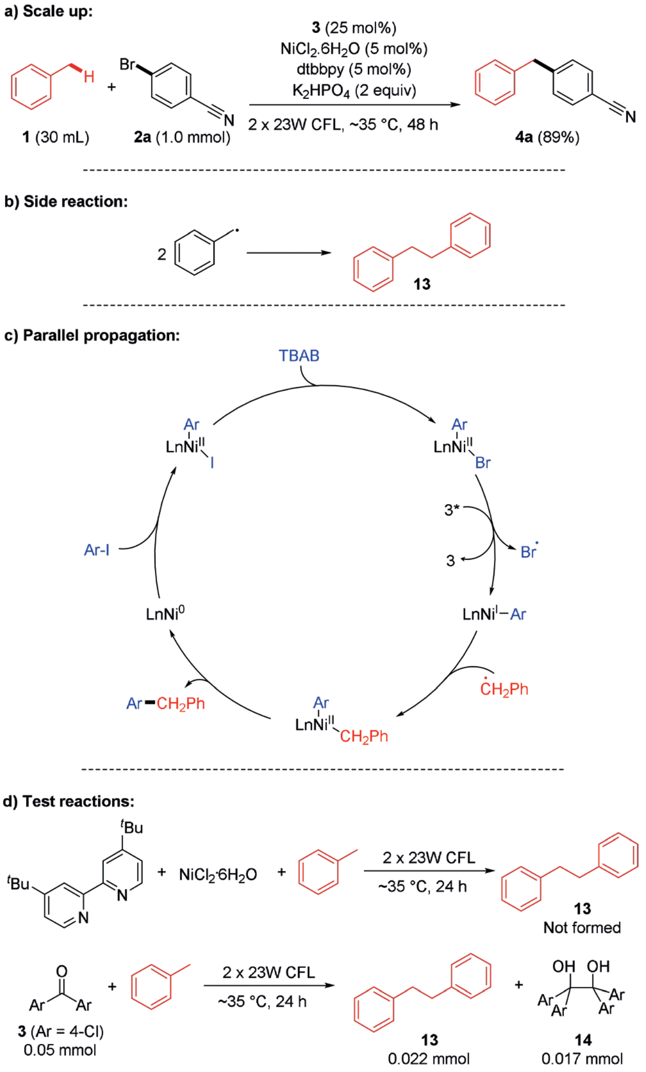


Figure 1. Substrate scope of aryl bromides. [a] Reaction conditions: **2** (0.2 mmol), **3** (0.05 mmol, 0.25 equiv), $NiCl_2{\cdot}6H_2O$ (0.01 mmol, 0.05 equiv), dtbbpy (0.01 mmol, 0.05 equiv), K_2HPO_4 (0.4 mmol, 2.0 equiv), **1** (6 mL), under irradiation with two 23 W CFL lamps, under Ar, 48 h; yields after purification. [b] 4 mL of toluene were used. [c] 18 h. [d] 24 h. [e] Amount of inseparable bibenzyl impurity is given in parenthesis.

Substrates **2p**–**2r** with fused rings were also tolerated and the products **4p**–**4r** were obtained, respectively, in good to excellent yields. Furthermore, a heteroaromatic bromide



Scheme 2. Scale-up and mechanistic insight.

substrate, 2-bromo-6-cyanopyridine **2s**, furnished the product **4s** in almost quantitative yield (99%).

After exploring the scope of the reaction with respect to the structure of the bromo-containing substrates, we turned our attention to the iodo and chloro analogues (Figure 2). Unexpectedly, 4-iodobenzonitrile (**5a**) exhibited much lower reactivity (39% NMR yield) compared to its bromo analogue **2a**. This was surprising because the aryl–I bond should be more reactive towards oxidative addition compared to the aryl–Br bond.[15] This observation led us to consider an underlying parallel propagation mechanism where **3** acts as a triplet sensitizer (Scheme 2c).[16]

Recently, our group and the Molander group proposed an energy-transfer step from the photocatalyst to a Ni^{II} species leading to an excited Ni^{II} species, which undergoes subsequent homolysis to give Ni^{I} and a halide radical.[5c,g] The halide radical can then abstract a H-atom from the H-donor. To find support for this hypothesis, and in pursuit of an improved scope of iodoarenes, the reaction between **5a** and toluene (**1**) was conducted in the presence of 1 equivalent of tetrabutyl ammonium bromide (TBAB) as an additive. In line with our assumption, the yield of **4a** increased to 72%. The same strategy was applied to other iodoarenes **5** and all of them worked quite well, furnishing the desired products in good yields.

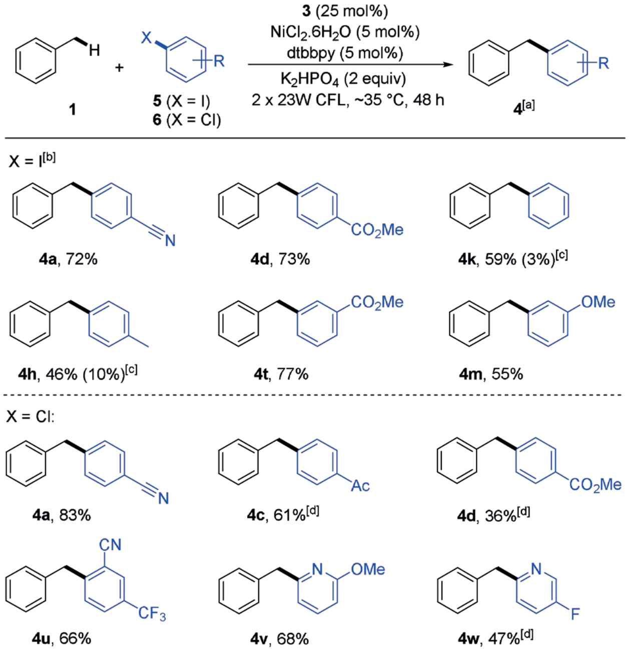


Figure 2. Substrate scope of aryl iodides and chlorides. [a] Reaction conditions: **5**/**6** (0.2 mmol), **3** (0.05 mmol, 0.25 equiv), $NiCl_2{\cdot}6H_2O$ (0.01 mmol, 0.05 equiv), dtbbpy (0.01 mmol, 0.05 equiv), K_2HPO_4 (0.4 mmol, 2.0 equiv), **1** (6 mL), under irradiation with two 23 W CFL lamps, under Ar, 48 h; yields after purification. [b] In the case of aryl iodides, TBAB (0.2 mmol, 1.0 equiv) was added. [c] Amount of inseparable bibenzyl impurity in parenthesis. [d] Calculated, with CH_2Br_2 as internal standard, from NMR spectra.

When 4-chlorobenzonitrile was reacted with toluene for 48 hours, the desired product was isolated in 83% yield. However, substrates bearing acyl and carboxymethyl groups showed moderate reactivity affording the products **4c** and **4d** with 61% and 36% NMR yield. A di-substituted aryl chloride was also tested and gave the corresponding product **4u** in 66% yield. Similar efficiency (68%) was observed when 2-chloro-6-methoxypyridine was reacted with toluene under the standard conditions. Finally, 2-chloro-5-fluoropyridine also reacted in moderate yield. It is worth mentioning that while exploring the chloro-substrate scope, sometimes the photosensitizer **3** was also partially benzylated at the C–Cl bond, leading to a mixture of monobenzyl and dibenzyl benzophenones. A control experiment was conducted replacing **3** with 4-chloro-4′-benzyl benzophenone, which gave a decreased yield of 57% (Supporting Information, Table S1, entry 15). This observation provides a rationale for diminished yields in the case of chloroarenes. Next, other C–H bond-donating coupling partners were explored in reaction with bromo-derivative **2a** (Figure 3). *Para*-xylene reacted smoothly to produce diarylmethane **12a** in 89% yield in 24 hours. *Meta* and *ortho* isomers of xylene gave similar yields as well (82% and 87%, respectively). Following the same trend, mesitylene showed excellent reactivity with 85% yield for product **12d**. Furthermore, **12e** was formed in a good yield (67%) within

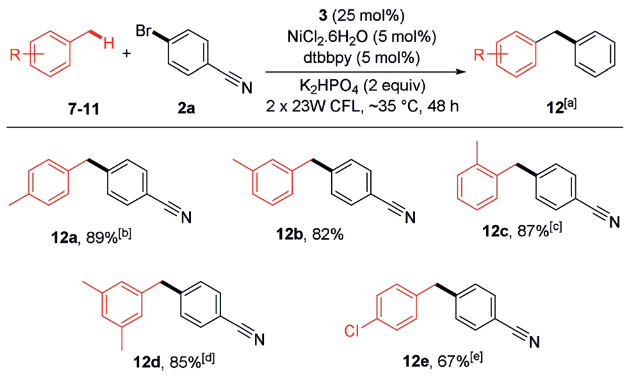


Figure 3. C–H bond-donating coupling partners. [a] Reaction conditions: **2a** (0.2 mmol), **3** (0.05 mmol, 0.25 equiv), $NiCl_2{\cdot}6H_2O$ (0.01 mmol, 0.05 equiv), dtbbpy (0.01 mmol, 0.05 equiv), K_2HPO_4 (0.4 mmol, 2.0 equiv), **7–11** (6 mL) under irradiation with two 23 W CFL lamps, under Ar, 48 h; yields after purification. [b] 24 h. [c] *o*-Xylene (4 mL) was used. [d] Mesitylene (5 mL) and benzene as co-solvent (1 mL) were used. [e] **3** (20 mol%), 4-chlorotoluene (4 mL), 20 h.

20 hours when relatively electron-deficient 4-chlorotoluene was reacted with **2a**.

To examine the scalability of the reaction, the transformation with substrate **2a** was performed on a larger scale (1.0 mmol) with the same reaction setup (Scheme 2a). Pleasingly, the yield of **4a** did not decrease significantly with the scale-up. It is noteworthy that a flow-reactor, which is often used for scaling up photoredox-catalyzed transformations, was not necessary in this case. Finally, further experiments were performed to gain a deeper insight into the mechanism. The involvement of the benzyl radical in the reaction was confirmed by the formation of bibenzyl (**13**) as a side-product. Regarding the generation of the benzyl radicals, this process can be accomplished either by the photocatalyst with the formation of PS-H (Scheme 1), which is subsequently involved in the generation of Ni^0, or by a chlorine radical, which results from the homolysis of the excited state of the ligated $NiCl_2$ complex by the light-source.[17]

To address these questions, an equimolar mixture of $NiCl_2{\cdot}6H_2O$ and dtbbpy (0.05 mmol) in toluene (6 mL) was irradiated for 24 hours (Scheme 2d). Formation of bibenzyl was not detected in the NMR spectra after the reaction. When the same experiment was performed with **3**, 0.022 mmol of bibenzyl (arising from the homocoupling of benzyl radicals) and 0.017 mmol of benzopinacol **14** were detected by NMR spectroscopy after the reaction. Therefore, we conclude that diaryl ketone **3** serves as initiator as well as catalyst for this reaction. This, together with the improved yields for iodoarenes after the addition of TBAB, leads to the conclusion that **3** acts as both hydrogen-atom-transfer agent and energy-transfer agent.

In summary, we developed a protocol for the benzylic arylation of toluene, and derivatives, with aryl halides as arylating agents using a dual metal/ photocatalytic system. Benzophenone was applied as photocatalyst, serving both purposes of hydrogen-atom-transfer and electron-transfer agent. Furthermore, mechanistic experiments indicate that the photocatalyst plays an additional role of energy-transfer agent. The newly designed transformation tolerates a broad range of aryl halides and different arenes containing methyl groups, leading to diarylmethanes in good yields. Notably, the reaction could be scaled up with ease without the need of specialized equipment.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: atom transfer · benzophenone · C–H functionalization · energy transfer · metallaphotoredox

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Communications

Photochemistry

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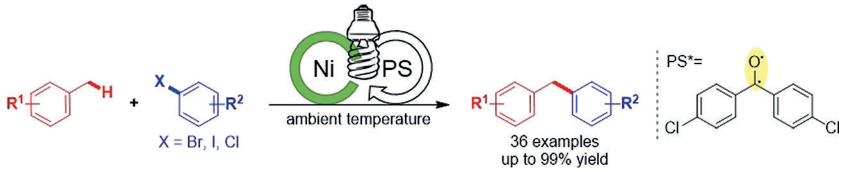
The Dual Role of Benzophenone in Visible-Light/Nickel Photoredox-Catalyzed C—H Arylations: Hydrogen-Atom Transfer and Energy Transfer



Benzophenone resurrected: The inherent reactivity of benzophenone upon photochemical excitation is used for the aliphatic C—H arylation reaction. The conditions are tolerant to a broad range of functional groups. Mechanistic experiments shed light on the dual role of the new photocatalyst of the metallaphotoredox family.