C(sp^3)–C(sp^3) Cross-Coupling of Alkyl Bromides and Ethers Mediated by Metal and Visible Light Photoredox Catalysis

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Abstract: We report a C(sp^3)–C(sp^3) cross-coupling of alkyl bromides and alkyl chlorides with ethers by dual photoredox-nickel catalysis. The catalytic system comprises of the organic photocatalyst 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4-CzIPN) and bench stable nickel (II) acetylacetonate in the presence of visible-light, providing the coupling products in up to 92% yield. Preliminary mechanistic studies suggest two catalytic cycles, as well as the photogeneration of bromine or chlorine radicals from halide atoms that are present in the structures of the coupling partners. The halide radical mediates the hydrogen atom transfer event, avoiding the need of an additional HAT catalyst.

Keywords: cross-coupling; alkyl bromides; dual catalysis; visible-light; nickel; ethers

Transition-metal-catalysed cross-coupling reactions are a key technology that has enabled the formation of carbon-carbon bonds between specific coupling partners.[1] Even though such reactions have provided access to numerous valuable structures, the selective formation of C(sp^3)–C(sp^3) bonds remains challenging. For instance, the Kumada reaction enables the coupling of alkyl Grignard reagents with alkyl, vinyl and aryl halides, however, it is limited to halides and these are unreactive to organomagnesium compounds.[2]

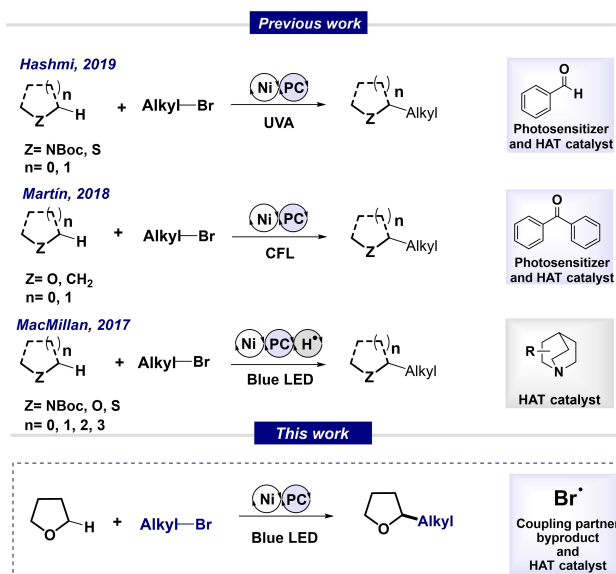The combination of metal and photocatalysis[3,4] allows for C(sp^3)–C(sp^3) bond formation from easily available reagents, that would not be possible through conventional polar chemistry (Scheme 1).[5–9]

Metallaphotoredox systems generally employ nickel complexes as transition metal catalysts, as well as organic or metallic photocatalysts.[5] The electropositive nature of nickel favours oxidative addition of alkyl and aryl halides.[10] Nickel-catalyzed reactions proceed through polar and radical mechanisms, where different nickel oxidation states can be achieved. The addition of a photosensitizer allows for the activation of the other coupling partner through a redox process of a functional group or by direct C–H activation.[5]

For C–H functionalization processes, hydrogen atom transfer (HAT) agents are crucial for generating alkyl radicals.[11]

Triplet state of aryl ketones,[6] as well as excited decatungstate anions ($W_{10}O_{32}^{-4}$),[7] can act as potent HAT catalysts for strong C–H bonds (99 kcal.mol^{-1}). In addition, the quinuclidinium radical cation has been reported as an efficient HAT catalyst for hydridic C–H bonds.[8] Even in the presence of a weaker C–H bond, the electrophilic aminium radical shows selectivity for more polarized bonds independent of bond dissociation energy (BDE) values.

The efficiency of halide radicals as HAT catalysts in dual catalysis has been reported in C(sp^3)–H cross coupling reactions of aryl halides and weak C–H bonds.[9] Photochemical Ni/Ir dual catalysis allows for the coupling of aryl and heteroaryl bromides with aliphatic heterocycles and benzyl compounds. The mechanistic proposal involves the generation of a bromine radical after Ni–Br bond homolysis of the

Scheme 1. Photoredox approaches for coupling of C(sp^3)–H and alkyl bromides.

Table 1. Selected optimization tests and control experiments.

Entry	Deviations[a]	Yield (%)[b]
1	No deviations	66[c]
2	NaBr (10 mol%)	64
3	NaBr (10 mol%)[d]	70
4	Under air	72
5	NiBr₂dtbppy	40
	Optimization of entry 3 (under air)	
6	Ni(acac)₂ (5 mol%)	71
7	NaBr (20 mol%) [d]	84
8	No CF₃CO₂Na	73
9	No dtbbpy	39[c]
10	No Ni(acac)₂	0
11	No Na₂CO₃	Traces
12	No 4-CzIPN	Traces
13	No light	0

[a] Reactions were performed in 0.15 mmol scale and 0.075 M of THF

[b] Yields calculated by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

[c] No full conversion.

[d] 2 mol% of photocatalyst.

excited-state nickel complex, which is activated by an energy-transfer pathway. The photoinduced halogen elimination from a Ni (III) trichloride complex, previously reported by Nocera,[12] was elegantly explored by Doyle's group. They merged the ability of chlorine radicals to activate C(sp^3)–H bonds with the ability use of nickel to perform alkyl cross-couplings.[13] This catalytic concept showed great performance in C(sp^3)–H arylations of cyclic and acyclic ethers. The current advances in metallaphotoredox catalysis in combination with the previous reports in C(sp^3)–H arylation, have inspired us to apply these principles to C(sp^3)–C(sp^3) bond formation. We envisioned that elected alkyl bromides could be the source of the bromine radical which would be able to perform the hydrogen atom transfer of aliphatic ethers. Mediated by the nickel complex, the generated alkyl radical could then be coupled with the alkyl partner in the final step to afford the desired product.

Initially, we conducted the coupling reaction by using a catalytic system composed of the bench stable Ni(acac)₂ (acac = bis(acetylacetonate), dtbbpy ligand (dtbbpy = 4,4'-di-tert-butyl-2,2'-dipyridine) and 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4-CzIPN) photocatalyst. Sodium carbonate was used as a base, while tetrahydrofuran was employed as both solvent and C(sp^3)–H partner (Table 1). Martin and coworkers reported improved yields for C(sp^3)–C(sp^3) coupling reactions when performed in the presence of sodium carbonate and sodium trifluoroacetate.[8a] According to the authors, the trifluoro salt increases the electrophilicity of the alkyl-Ni(II)halide by anion exchange, facilitating the interception of the alkyl radical and preventing ß-hydride elimination or homo-

coupling. The reaction was carried out for 48 hours under a nitrogen atmosphere and blue light irradiation to deliver the desired product in 66% yield. Reaction optimization was continued to evaluate other catalyst sources. Conversion to the desired product was not observed for most of the tested photocatalysts, except for Ir[dF(CF₃)₂(ppy)₂](dtbbpy) that gave the product in 82% yield (see supporting information).

Since iridium-based catalysts are the most expensive photosensitizers employed in photoredox catalysis, we decided to continue the optimization studies with 4-CzIPN. The photocatalyst was successfully utilized in photoredox/Ni dual catalytic C(sp^3)–C(sp^2) cross-coupling reactions and other transformations.[14]

To confirm the role of a bromine radical in the HAT event, sodium bromide was used as an additive (Table 1 – entry 2). We were pleased to find that the presence of the salt increased the efficiency of the reaction (yield and conversion), even when diminished loadings of the photocatalyst were used (Table 1 – entry 3). The effect of oxygen on the reaction was minor, with no significant changes observed between aerobic and anaerobic conditions (Table 1 – entry 4). Other nickel sources, such as NiBr₂dtbbpy (Table 1 – entry 5), were evaluated to exclude the possibility of acetylacetonate (acac) acting as a HAT agent.[15] The product was obtained in 40% yield after 48 hours, indicating that acetylacetonate was not essential for the

HAT process. The amount of nickel catalyst and pyridyl ligand were reduced to 5 mol% without an effect on yield and reaction time (entry 6). In the presence of 20 mol% of sodium bromine, the desired product was obtained in 84% yield. A similar result was obtained when Ir-photocatalyst was utilized (see supporting information). Additional bromine sources were tested, however, in regards to cost and toxicity of the reagents, sodium bromide was considered the optimal choice (entry 7). Control experiments revealed that sodium trifluoroacetate did not impact the yield (Table 1 – entry 8) and that the pyridyl-based ligand had an important effect on the reaction efficiency (Table 1 – entry 9). Additionally, product formation required the combination of nickel catalyst, 4-CzIPN, sodium carbonate and light irradiation, which validated the metal and photocatalytic pathways of this reaction (entries 10–13). After identifying the optimized reaction condition (Table 1 – entry 7), the scope study was initiated (Scheme 2).

We evaluated whether the reaction could be carried out with fewer equivalents of the C(sp^3)–H partner.

Solvent screening revealed that traces of alkyl bromide were detected in acetonitrile, and poor yield was obtained in DMSO (see supporting information).

Diverse alkyl bromides were compatible with THF being the C(sp^3)–H source, as good yields were obtained. Linear and branched alkyl bromides were able to functionalize the cyclic ether and afford the C(sp^3)–C(sp^3) products (**5** and **6**). Halides that contained substituted and unsubstituted benzene rings were also efficient substrates (**3** and **7–10**). In addition, diverse functional groups were tolerated (**4**, **7** and **11–18**), including chlorine atoms and terminal olefins. Benzyl chloride was a suitable alkyl halide for the transformation, affording the coupling products (**9** and **10**). Surprising only traces of product were observed when 2-MeTHF and 1,3-dioxolane were employed (**20** and **21**); the compounds convert only partially and the homocoupling product was found as the main by-product. However, the reaction was effective with oxetane (**22**) and dimethoxyethane (**23**).

The scope of the protocol is limited in the choice of the C–H reaction partner. Six membered cyclic ethers, such as tetrahydropyran and 1,4-dioxane, as well as acyclic ether, such as 1,2-diethyl ether do not react (**24–26**). We rationalize this by differences in the rate of hydrogen atom abstraction that is influenced by ring size and stereoelectronic factors.[16]

In order to demonstrate the robustness of this protocol, we performed the coupling of 4-bromobutyl-benzene and THF in gram-scale, affording 0.91 g of the desired product **3** in 63% yield.

The role of bromine as HAT was further evaluated using alkyl triflate and iodine (Scheme 3).

These electrophiles have a similar reactivity as alkyl bromide to perform the oxidative addition, but do
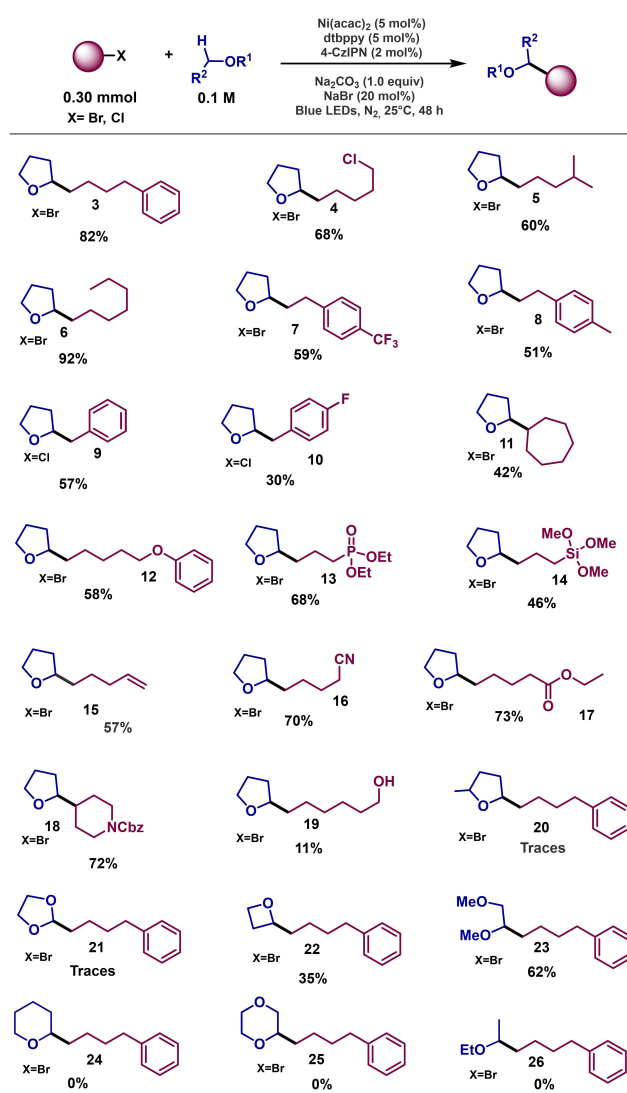

Scheme 2. Scope study. Reactions were performed in 0.30 mmol scale according to entry 7. Isolated yields are reported.

not promote hydrogen atom transfer from THF.[13] In both cases, there was no observed C–H cross-coupled product. To investigate whether 4-CzIPN was acting as an energy transfer photocatalyst,[17] an experiment was carried out under UV irradiation in the absence of the photocatalyst. Under this condition, no product was detected, suggesting that energy transfer may not be an essential step in the reaction mechanism.

A plausible mechanism for the reaction between alkyl halides and ethers is shown in Scheme 4. We postulate that the mechanism proceeds through metallophotoredox cycles, as previously reported for C(sp^3)–C(sp^2) cross coupling.[10–13] The alkyl bromide undergoes oxidative addition on the Ni (0) complex to give a Ni (II)-alkyl halide complex (**II**). Reduction of Ni(II) to Ni(0) may occur through a photocatalytic
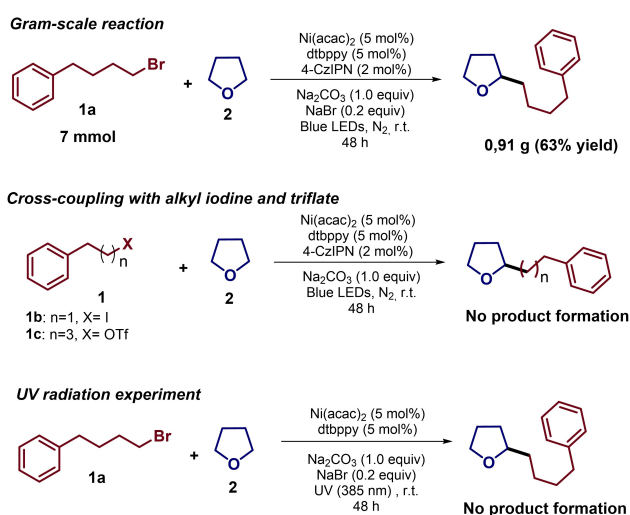
Scheme 3. Experiments used for scale-up and mechanism investigations.
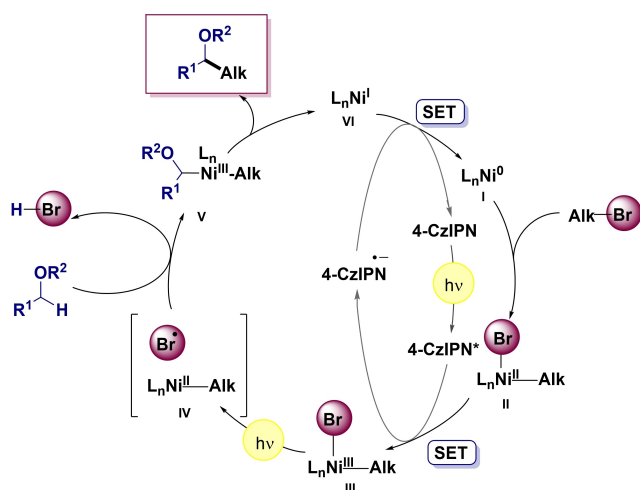
Scheme 4. Proposed mechanism for C(sp^3)–C(sp^3) coupling.

reduction via two single electron transfer events, performed by the photocatalyst. Upon excitation with visible light, the ground state 4-CzIPN is promoted to its highly oxidizing singlet excited state, 4-CzIPN* [$E_{1/2}$ (PC*/PC$^{\bullet}$– = +1.35 V vs SCE) in CH$_3$CN],[18] which undergoes a single electron transfer step with intermediate **II**. This results in the corresponding Ni(III) complex, accompanied by the reduced form of the catalyst. The oxidized Br–Ni(III)-alkyl complex (**III**) could then absorb visible light and undergo photo-elimination, generating the halogen radical (**IV**).[19] The electrophilic bromine radical can act as a HAT agent, abstracting the hydrogen atom from the carbon α to oxygen, and generating a carbon-centered radical. This would then add to the Ni (II) complex (**V**). The reductive elimination would form the cross-coupling product and the Ni (I) complex (**VI**) would be reduced

to Ni (0) [$E_{1/2red}$ (Ni^{II}/Ni^0) = −1.2 V vs SCE in N,N'-dimethylformamide (DMF)] by 4CzIPN$^{\bullet}$– [($E_{1/2}$ (PC/PC$^{\bullet}$–) = −1.24 V vs SCE in CH$_3$CN]. As a result, the photocatalyst would be regenerated to ground-state, closing both catalytic cycles.

The potential occurrence of two excitation steps in the mechanism was supported by a kinetic experiment that used different irradiation intensities. A quadratic dependence of the product yield for full and half-power irradiation (see supporting information) suggested the participation of a second photon in the redox-neutral catalytic cycle.[20] Online UV-Vis measurements showed the presence of a band between 450 nm and 550 nm, which may be assigned to a reaction intermediate that is able to absorb in the visible range.[21]

In conclusion, we have reported a metallophotoredox protocol for selective C(sp^3)–C(sp^3) coupling of alkyl bromides/chlorides and ethers, employing an inexpensive organic photocatalyst. The reaction is related to an earlier report from the MacMillan group, however, proceeds in the absence of an additional HAT catalyst. Experiments suggested the generation of bromine radical from the alkyl bromide, which acts as a HAT catalyst and therefore, generates the alkyl radical from the THF. The reaction conditions allow the application of a range of highly functionalized alkyl bromides with high tolerance. Moreover, the simplicity of this protocol granted it to be implemented under scaling-up.

Experimental Section

For full experimental data see Supporting Information.

General Procedure C(sp^3)-C(sp^3) Cross Coupling of Alkyl Bromides and Ethers

A 5 mL vial equipped with a stir bar was charged with Na$_2$CO$_3$ (32 mg, 0.30 mmol, 1 equiv.), NaBr (6 mg, 0.06 mmol, 0.20 equiv.), 4′-di-tert-butyl-2,2′- bipyridine (4.0 mg, 0.015 mol, 0.05 equiv.), Ni(acac)$_2$ source (3.9 mg, 0.05 equiv.) and 4-CzIPN (4.7 mg, 6 μmol, 0.02 equiv.). To the reaction under N$_2$ atmosphere, was added 3 mL of the specified ether and the alkyl halide (0.30 mmol, 1 equiv.) The resulting mixture was irradiated through the plane bottom side of the snap vial using a 455 (±15) nm LED. The reaction progress was monitored by thin layer chromatography and GC-MS. After 48 h, the reaction mixture was diluted to 10 mL with ethyl acetate, transferred into a separating funnel and extracted with 10 mL of distilled water and 10 mL of brine. The organic layer was dried over Na$_2$SO$_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography using a mixture of petrolether:ethyl acetate as eluents on silica gel.

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Acknowledgements

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[21] During the mechanistic studies, a visible-light active intermediate was observed in a spectroeletrochemistry measurement. In order to confirm the existence of the photoactive intermediate, a photo-electrochemical version of the reaction was performed, however the attempts were not conclusive for the studies.

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