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meta-Selective C-H Activation of Arenes at Room Temperature Using Visible Light: Dual-Function Ruthenium Catalysis

Arunachalam Sagadevan and Michael F. Greaney*

Abstract: Ruthenium-catalyzed *meta* C-H activation of arenes at room temperature is reported, under blue light irradiation. A variety of heteroarenes are compatible with this photochemical process, which leads to the corresponding *meta* C-C coupling products in good to very good yield. Initial mechanistic studies suggest a single-electron transfer (SET) process occurs between photoexcited Ru^{II}-cyclometalated complex and alkyl halides that enable *meta* C-H functionalization reaction via carbon-centered radicals.

Photoredox catalysis (PRC) using visible light is now established as a powerful synthetic method with tremendous scope for application in biology chemistry, material sciences and drug discovery.^[1] Photoredox catalysts, frequently Ir or Ru coordination complexes, undergo photoexcitation with visible light and can then oxidize or reduce organic substrates through outer sphere single electron transfer. The resultant catalytic cycles offer low-energy pathways for reaction, creating far more sustainable and mild reaction conditions than classic processes involving, for example, UV photochemical equipment or stoichiometric metal reagents. An exciting recent development exploits the versatile nature of PRC to set up dual catalysis systems, where the photocatalyst generates radical species that are captured by a second metal catalyst (Scheme 1A), enabling new reactivity and bond formation.^[2,3] Here, as in conventional PRC, the photoredox catalyst is operating with the single function of outer-sphere SET. An alternative approach to dual catalytic chemistry would be to exploit the inner coordination sphere of photoredox catalysts, to capture a second catalytic activity from the same metal center. The common photoredox metals Ru and Ir have rich C-H activation chemistry, for example, which in principle could be integrated with photoredox activity to create powerful dual-function catalysts. This dual function concept, though less developed than outer sphere PRC, has recently been exemplified in some impressive transformations.^[4-5] Fu, Peters and co-workers have demonstrated *in situ* assembly of copper catalysts that effect alkylation of N, O, and S nucleophiles under visible light irradiation (Scheme 1B).^[6] Meggers and co-workers showed that chiral-at-metal Ir photocatalysts can act as chiral Lewis acids, binding (and activating) acyl imidazoles (Scheme 1B).^[7] Simultaneously, photoexcitation of the Ir complex enables SET reduction of an electrophile to a carbon-centered radical which undergoes stereoselective addition.

We were interested in developing a dual-functional PRC system in the area of Ru-catalyzed *meta* C-H activation.^[8] Ru catalysis offers a very direct approach to the *meta*-functionalization of arenes containing azine directing groups, *via* the preference of the intermediate ruthenacycle to undergo radical addition *para* to

the C-Ru bond. These reactions, introduced in the catalytic regime by the Frost and Ackermann groups,^[9a,b] have been exemplified for a small but growing number of transformations (e.g. sulfonylation, alkylation, halogenation, nitration, carboxylation), and usually function under thermal conditions at elevated temperatures ($T > 100\text{ }^{\circ}\text{C}$).^[9] We hypothesized that the ruthenacycle formed *in situ* could act as a putative photoredox catalyst, enabling SET to an alkyl halide coupling-partner, whilst simultaneously directing *meta* C-H activation under far milder conditions with no requirement for exogenous photosensitizers. Further, this dual function approach would introduce a control element to the key SET event of Ru-*meta* chemistry that is frequently implied in mechanistic rationale but currently not well understood.

A: Dual Catalysis: Two metals, two functions

B: Dual-Function Catalysis: One metal, two functions

C: Current work: Dual-Function Ru Catalysis

Scheme 1. Dual catalysis and Dual-function catalysts

We began our investigations using 2-phenyl-pyridine (**1a**) and *t*-butyl-iodide (**2a**) under blue light irradiation and examined various conditions in respect of catalyst, additives, solvents, and bases. We were pleased to find that a combination of $[\text{RuCl}_2(\text{p-cymene})_2]$, MeSCo_2H and KOAc in dioxane solvent furnished **3a** in 65% yield after 24 hr irradiation under visible light, at room temperature (Table 1, entry 1). Continuing optimization studies established that AdCO_2H in 2-Me-THF as solvent gave a slightly improved yield (entry 2), which could be further improved to 78% with the addition of 5.0 equiv of water to the reaction mixture

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(entry 3). The carboxylate additive was not essential in this system, with the yield actually improving to 82% in its absence (entry 4). Switching solvents to MeCN and DMF shut down the reaction (entry 6), whilst alternative Ru-catalysts used in *meta*-C-H activation were also ineffective (entry 7). A series of controls were then carried out, which established that the exclusion of light, base, and [Ru]-catalyst all resulted in no reaction (entries 9-11). The reaction was also found to be air sensitive – when performed under air or O₂ atmosphere the reaction mixture turned black and no reaction was observed (entry 12).

Table 1. Optimization of reaction conditions.^[a]

entry	variation from initial conditions	yield (%) ^[b]
1	none	65
2	1-AdCO ₂ H, 2-MeTHF	68
3	1-AdCO ₂ H, 2-MeTHF, H ₂ O (5.0 equiv)	78
4	no additives, 2-MeTHF, H₂O	82
5	1-AdCO ₂ H, THF, H ₂ O	70
6	MeCN or DMF as solvent	0
7	RuCl ₃ , Ru(PPh ₃) ₄ Cl ₂ , or Ru(bpy) ₃ Cl ₂ instead of [RuCl ₂ (p-cymene)] ₂	0
8	[RuCl ₂ (p-cymene)] ₂ (5 mol%)	70
9	reaction in the dark	0
10	no catalyst	n.r
11	no base	0
12	in the presence of air	0

[a] Initial conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), [RuCl₂(p-cymene)]₂ (10 mol%), MesCO₂H (10 mol%), KOAc 2.0 equiv, dioxane (1 mL). The mixture was irradiated with blue LEDs (40-90W power) for 24 h under N₂ (1 atm.), 5 - 7 cm distance with cooling fan: Internal reaction temperature 28-30 °C for 2-MeTHF. [b] Yield of the isolated product.

With optimal reaction conditions established (Table 1, entry 4), we set out to explore the scope of this reaction with various 2-phenylpyridines (Table 2). Substitution at the 4-position was tolerated for a wide range of functional groups (**3b** – **3h**), with electron neutral / donating groups generally facilitating the transformation and affording the *meta* C-H functionalization products in high yield (**3b** – **3d**). The reaction was also effective on a 5 mmol scale (67% yield of **3a**). Substitution at the *meta* position of phenylpyridines was more restricted, being adjacent to the site of C-H ruthenation, but could be achieved with small groups such as OMe (**3i**) and F (**3j**). *ortho*-Substitution was not generally tolerated (*vide infra*), in line with literature observations on steric encumbrance at this position shutting down the Ru C-H activation pathway. The additional substitution was feasible on the pyridyl ring, including chloro and methoxy groups to provide sites for further functionalization. Pleasingly, the *meta*-alkylation proceeded in high yield for alternative aza-heterocycles such as isoquinoline (**3q** and **3r**), pyrimidine (**3s**), pyrazole (**3u**) and purine (**3v**). The pyridine **3t** is an example of *ortho*-substitution being feasible on the phenyl ring in *meta*-functionalization, with

the small fluorine atom being accommodated in the absence of an *ortho*-C-H bond on the adjacent pyridine ring.

Table 2. Substrate scope of arenes.^[a]

[a] Standard condition. Isolated yield after purification by column chromatography. [b] The reaction was performed on a 5 mmol scale.

We then turned our attention to the alkyl halide coupling partner, and were pleased to find broad substrate scope across a variety of unactivated tertiary and secondary alkyl iodides (Table 3), with good yields isolated of *meta* products **4b** – **4f**. Unactivated alkyl bromides were slow to react, generally giving lower yields after prolonged irradiation, but activation of the bromide with a neighboring carbonyl group, for example, gave effective reaction (**4h**).

The reaction could also be used to install piperidinyl and cyclobutyl motifs (**4g** and **4h**). When we turned to primary alkyl iodides we observed a switch in selectivity to the *ortho*-position. This is in line with previous studies which have identified *ortho*-alkylation as the dominant mode in thermal Ru C-H activation of 2-arylpyridines with alkyl radical precursors of low steric demand.^[9e, 10] Here, we were pleased to observe the photochemical activation effectively deliver *ortho*-alkylated products in reasonable yield (**4k** – **4q**), with the activated benzyl bromide affording excellent yields of the doubly benzylated product.

To gain mechanistic insights, various control experiments were carried out (Scheme 2, Eq. 1-4). First, the pre-synthesized cycloruthenated complex **A** was used directly in the reaction and found to be a competent catalyst, affording **3b** in high yield upon visible light irradiation (Eq. 1). Further, the pre-synthesized cycloruthenated complex was used as a stoichiometric starting material and underwent smooth reaction with *t*-butyl iodide in the presence of KOAc to give **3b** in 94% yield after 8 hr irradiation (see Eq. 2). These control studies suggest that an *in-situ* generated cycloruthenated complex is the key photocatalyst.

Table 3. Substrate scope of alkyl halides.^[a]

[a] Standard condition. Isolated yield after purification by column chromatography on silica gel.

Notably, all controls were ineffective under dark conditions, producing 0% of **3b** (internal reaction temperature 28–30 °C). When the reaction of **1a** with **2b** was carried out in the presence of TEMPO (1.0 equiv), the formation of meta C-H activation product (**4b**) was completely inhibited (see Eq. 3), in line with the radical nature of the transformation. The use of *cis*-**2r** gave a 70% yield of **4r** as a 1:1 mixture of diastereoisomers, lending additional support to the radical nature of the *meta*-alkylation.

To further probe the reaction mechanism, we measured UV-Vis absorption spectra of the Ru catalyst, carboxylate components, and starting material in Me-THF (SI Figure S1). The excitation and emission profile of in situ generated complex **A** are shown in Figure 1. Broad absorbance was observed in the region 400 – 500 nm, indicative of photochemical activity under blue light irradiation. Fluorescence quenching experiments of cycloruthenated complex **A** with *t*-butyl iodide (**2a**) demonstrated a progressive quenching profile in line with the envisaged SET event to generate the *t*-butyl radical (Figure 2). An energy transfer mechanism cannot be ruled out at this stage, but we note that cyclometalated Ru(II) complexes are more strongly reducing than the archetypal $Ru(bpy)_3^{2+}$ photocatalyst ($E_{1/2} III^*/II = -0.81 \text{ V vs SCE}$), with values of E_{red} from -1.3 to -1.9 V (vs SCE) being reported.^[11]

Scheme 2. Mechanistic investigations **Figure 1:** Excitation and emission spectra of in-situ Ru-Complex (**A**) in 2Me-THF. **Figure 2:** Photoluminescence spectra of 5.0 mM Ru-Complex (**A**) (in-situ generated from a reaction mixture) in the absence (black colour line) and the presence of sequential concentration of **2a** (*t*-butyl iodide) in 2Me-THF solvent (bottom).

Based on the above results and literature observations on Ru-*meta* chemistry,^[9,12] a possible mechanism is shown in Scheme

3. Blue-light irradiation of in-situ formed Ru^{II}-cyclometalated complex **B** generates a long-lived excited state of Ru^{II}-complex **C**, which can undergo SET to the alkyl halide (X = Br or I) and to form a C-centered radical and Ru(III)-cyclometalated complex **D**. In the next step, the nucleophilic carbon-centered alkyl radical then undergoes a radical attack on para-position to electrophilic Ru(III)-cyclometalated complex **D** to afford the complex **E**. Recent computational work from Ackermann and co-workers has implicated Ru(III) as having substantially higher selectivity in this step than Ru(II), in line with the proposed electron transfer step from Ru(II) to alkyl halide.^[13] A final LMCT step is then required to regenerate the Ru(II) complex **F** which can lose a proton to rearomatize and deliver the desired *meta*-C-H activation product (**3a**) through protonolysis.

Scheme 3. Proposed reaction mechanism.

In summary, we have developed a ruthenium-catalyzed *meta*-alkylation process mediated by visible light. The reaction proceeds at room temperature, utilizing a ruthenium dual-functional catalyst to mediate both C-H activation and photoredox generation of the reactive alkyl radical coupling partner. The resulting process is mild, compatible with a wide variety of heteroarenes as well as coupling partner aliphatic halides, and leads to the corresponding *meta* C-C coupling products in good to very good yield. Further studies to exploit this dual-functional catalysis are underway in our laboratory.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: photochemistry, ruthenium, *meta* C-H activation, dual catalysis

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COMMUNICATION

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