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Ortho C–H arylation of arenes at room temperature using visible light ruthenium C–H activation†

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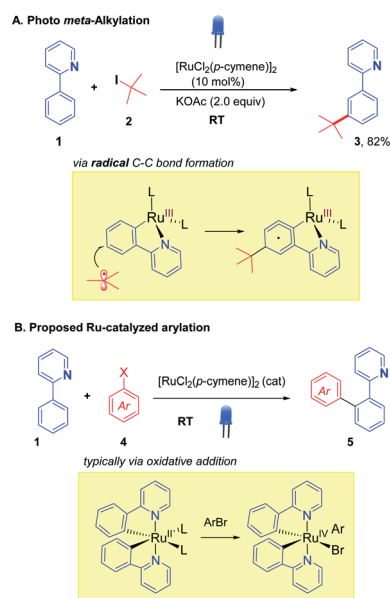
A ruthenium-catalyzed *ortho* C–H arylation process is described using visible light. Using the readily available catalyst $[\text{RuCl}_2(p\text{-cymene})]_2$, visible light irradiation was found to enable arylation of 2-arylpyridines at room temperature for a range of aryl bromides and iodides.

Introduction

The integration of visible light photoredox catalysis with transition metal C–H activation catalysis creates new pathways for bond formation, that frequently operate under mild conditions. The two catalysis regimes can be meshed *via* two separate catalyst entities, with two corresponding catalysis cycles;¹ or alternatively, a single dual-function catalyst system can be used.² We are interested in this latter approach to exploit the facility of some Ru catalysts to absorb visible light, such that their native C–H activation function is enhanced in terms of improved rates, substrate scope, and environmental impact. We, along with the Ackermann group, recently demonstrated this concept for the Ru-catalysed *meta*-alkylation reaction (Scheme 1).³ The *tert*-butylation of 2-phenylpyridine **1**, typically carried out under thermal conditions (*ca.* 100 °C), could proceed at room temperature under blue-light irradiation using the widely employed catalyst $[\text{RuCl}_2(p\text{-cymene})]_2$ to give the alkylated product **3** in good yield.

We were interested in exploring this concept of photo-Ru C–H activation in the arylation regime. Ru-catalysed *ortho*-arylation is a powerful approach to C–C bond formation that has seen extensive development in recent years.⁴ Proceeding *via* Ru(II)/Ru(IV) catalytic cycles, the process has excellent scope for aryl halides (including aryl chlorides), is very tolerant of water and air, and the cost of Ru compares favorably with the far more expensive alternatives of Pd and Rh that are frequently used for *ortho* C–H arylation. High reaction temperatures are standard, however, when using $[\text{RuCl}_2(p\text{-cymene})]_2$ as catalyst.^{5,6} A photo Ru arylation reaction could activate alternative mechanistic paths and offer

the possibility of room temperature reaction.⁷ The two Ru-catalyzed processes, *meta*-alkylation and *ortho*-arylation, operate through very different frameworks in the thermal regime, with the former thought to involve discrete 2° and 3° carbon-centered radicals adding to Ru(III) metallacycles (Scheme 1A),⁸ and the latter involving more typical oxidative additions of aryl halides to a Ru(II) center.⁹ The role of photoexcitation on a putative arylation process was thus interesting to examine in light of this dichotomy; as the photoreductive formation of highly reactive aryl radicals in analogy to Ru-*meta* alkylation chemistry was unlikely to be a significant factor.



Scheme 1 Ruthenium photocatalysis for *meta*-alkylation (A) and proposed *ortho*-arylation (B).

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Results and discussion

Photoarylation of 2-arylazines with aryl halides

We began by examining the archetypal arylation system of 2-phenylpyridine **1a** with bromoanisole **4a** (Table 1). Using $[\text{RuCl}_2(p\text{-cymene})]_2$ as catalyst in the presence of KOAc, under blue LED irradiation, we were pleased to observe successful arylation at room temperature to give a good 70% combined conversion to mono and di-*ortho*-arylated products **5a** and **5aa**. As is typical for Ru *ortho*-arylations of 2-phenyl pyridine, the monoarylated product is a superior substrate than the starting material, giving the diarylated material as the major product.

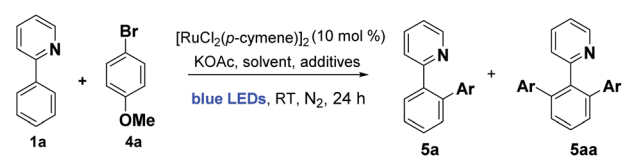
The reaction worked well in ethereal solvents (entries 1–4), and a screen of carboxylate and amino acid additives did not yield substantial improvements, although the acetylisoleucine derivative gave slightly improved yields and was retained for substrate screening (entry 7). Common solvents such as MeOH, DCM, MeCN, or DMF were not effective (entry 8), nor were the simple Ru salts shown in entries (10–12). Control experiments established that both light and catalyst were essential for reaction at room temp (entries 13–15), and as with our previous Ru *meta* systems,¹⁰ the reaction was found to be air sensitive and require inert atmospheres to proceed.

With these conditions in hand, we established the scope of the reaction with respect to the C–H component using *p*-bromoanisole as the arylating agent. Alkyl, alkoxy, carboxy, and

phenyl substitution was tolerated in the 4-position of the arene, favoring the disubstituted product (**5aa–5ff**). Substitution in the 3-position with MeO, Me, Cl, and fused ring of the naphthyl group acted as a steric control element, suppressing the second *ortho* ruthenation step and yielding mono-arylated products exclusively (**5g–5j**). Some alterations to the directing group were possible, with alkylated pyridines being effective in the reaction, along with bicyclic quinoline and isoquinoline directing groups (**5kk–5o**) and the pyrazine **5pp**. Finally, changing the arene C–H to the 5-membered heteroarene thiophene C–H was partially successful in the photoarylation, affording the novel pyridyl thiophene **5q** but in diminished yield (Scheme 2).

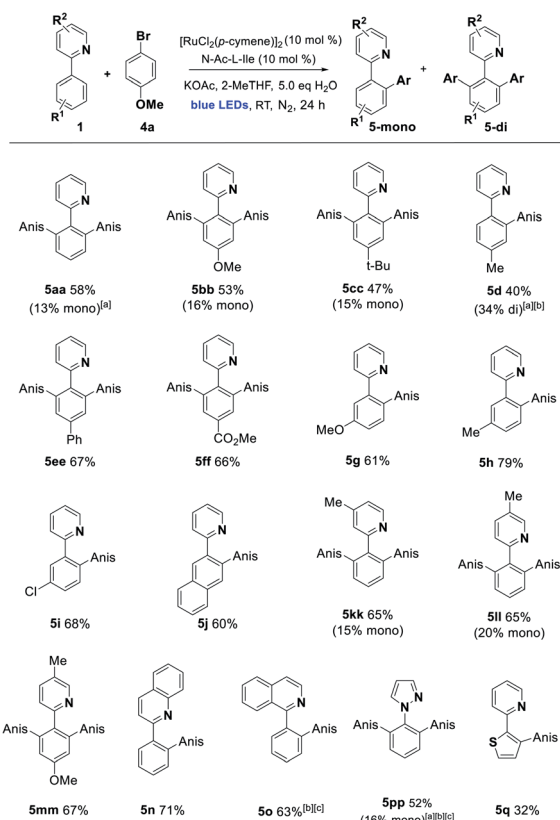
We then turned our attention to the aryl halide coupling partner, and were pleased to find broad substrate scope across a variety of aryl bromides and iodides (Scheme 3). We used 3-methyl-2-phenylpyridine (**1b**) as the substrate in the majority of cases, to simplify the reaction pathway for monoarylation. We observed good efficiencies for 4-alkyl and moderate efficiencies for 4-phenyl aryl halides (**6a–6cc**), along with the 2-thienyliodide substrate (**6dd**). Halogens were well tolerated (**6e–6gg**), and electron poor (4-keto and 4-carboxy ester groups) along with electron rich (4-methoxy) aryl halides reacted smoothly in each case. *Ortho*-substituted aryl halides were not generally effective in this protocol, although 1-bromo-2-methoxybenzene did react successfully to give **6k** in 50% yield. This *ortho* substitution pattern is known to favour an oxidative dimerization pathway for aryl halide substrates.¹¹

Table 1 Development of Ru photoarylation^a



Entry	Catalyst	Additives	Solvent	Yield ^b [%]
1	$[\text{RuCl}_2(p\text{-cymene})]_2$	MesCO ₂ H	1,4-Dioxane	(70)
2	$[\text{RuCl}_2(p\text{-cymene})]_2$	MesCO ₂ H	DME	60
3	$[\text{RuCl}_2(p\text{-cymene})]_2$	MesCO ₂ H	THF	65
4	$[\text{RuCl}_2(p\text{-cymene})]_2$	MesCO ₂ H	2-MeTHF	(72)
5	$[\text{RuCl}_2(p\text{-cymene})]_2$	N-Ac-L-isoleu	2-MeTHF	(74)
6	$[\text{RuCl}_2(p\text{-cymene})]_2$	N-Ac-L-isoleu	2-MeTHF	(78)
7	$[\text{RuCl}_2(p\text{-cymene})]_2$	N-Ac-L-isoleu/H ₂ O	2-MeTHF	(80)
8	$[\text{RuCl}_2(p\text{-cymene})]_2$	None/H ₂ O	2-MeTHF	(80)
9	$[\text{RuCl}_2(p\text{-cymene})]_2$	N-Ac-L-isoleu	MeOH, MeCN, DCM, or DMF	Trace
10	RuCl ₃ ·H ₂ O	None	2-MeTHF	0
11	Ru(PPh ₃) ₄ Cl ₂	N-Ac-L-isoleu/H ₂ O	2-MeTHF	0
12	Ru(bpy) ₃ Cl ₂	None	2-MeTHF	0
13	$[\text{RuCl}_2(p\text{-cymene})]_2$ (5 mol%)	N-Ac-L-isoleu/H ₂ O	2-MeTHF	(72)
14	No catalyst	N-Ac-L-isoleu	2-MeTHF	0
15	$[\text{RuCl}_2(p\text{-cymene})]_2$ dark	N-Ac-L-isoleu/H ₂ O	2-MeTHF	0
16	$[\text{RuCl}_2(p\text{-cymene})]_2$ with air	N-Ac-L-isoleu/H ₂ O	2-MeTHF	0

^a Reaction conditions: **1a** (0.3 mmol), **4a** (0.6 mmol), [Ru] catalyst (10 mol%), additive (10 mol%), base 2.0 equiv., solvent (1 mL). The mixture was irradiated with blue LEDs (40–90 W power) for 24 h under N₂ atmosphere. ^b Yields in brackets refer to combined ¹H NMR yield using 1,3,5-trimethylbenzene (mesitylene) as the internal standard, unbracketed yields are isolated. THF = tetrahydrofuran, 2-MeTHF = 2-methyl tetrahydrofuran, DME = 1,2-dimethoxyethane, DMF = dimethyl formamide, DCM = dichloromethane.

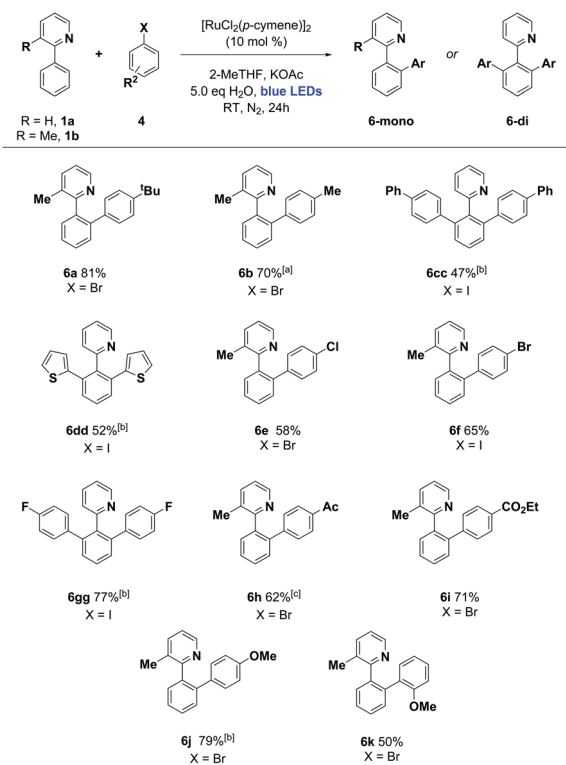


Scheme 2 Photoarylation of 2-arylzines with *p*-bromoanisole (Anis = 4-BrC₆H₄). Unless otherwise noted, reaction conditions were as follows: **1** (1.0 eq., 0.3 mmol), **4a** (2.0 eq., 0.6 mmol), [Ru] catalyst (10 mol%), additive (10 mol%), base (2.0 eq.), solvent (1 mL), H₂O (5 eq.). The mixture was irradiated with blue LEDs (40–90 W power) for 24 h under N₂ (1 atm). The yields refer to isolated yields after purification by column chromatography on silica gel (major product illustrated). ^aReaction performed using 0.250 mmol of **1** (1.0 eq.) and 0.375 mmol of **4a** (1.5 eq.). ^bReaction performed without the addition of N-Ac-L-Ile. ^cReaction run for 40 h.

Mechanistic studies

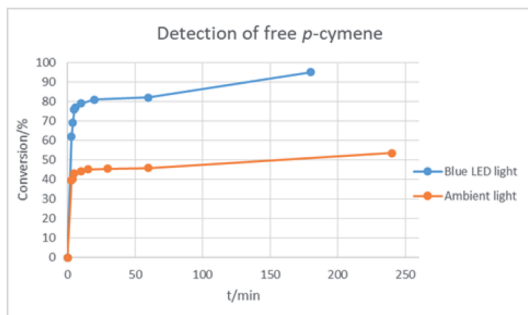
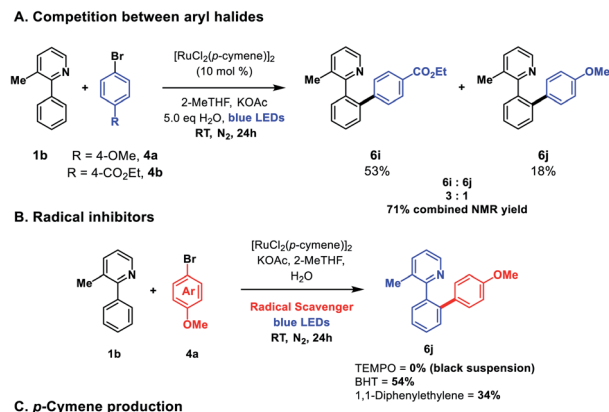
The exclusive formation of *ortho*-arylated products, allied with the high reduction potential of aryl halides (*ca.* –2.5 eV)¹² would likely preclude any discrete aryl radical generation through SET from a Ru(II) catalytic species in the reaction. This was supported with radical quenching experiments, where the reaction proceeded to reasonable conversion in the presence of both BHT and 1,1-diphenylethene (DHP), although TEMPO was observed to completely inhibit the reaction forming an insoluble black suspension. A competition experiment between the electron-rich bromoanisole **4a** and electron-poor bromobenzoate afforded a 3 : 1 ratio of products in favour of the benzoate **6i**, in line with what is commonly observed in high-temperature Ru *ortho*-arylation through an oxidative addition mechanism.¹³

Recent investigations from Larrosa and co-workers into the mechanism of Ru(II)-*ortho* arylation have identified the inhibitory role of the cymene ligand in [RuCl₂(*p*-cymene)]₂ catalysis.^{6,14} While this ligand affords an air-stable, easy to use catalyst, it

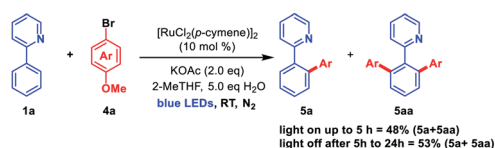


Scheme 3 Photoarylation of 2-arylpriidines with various aryl halides. Unless otherwise noted, reaction conditions were as follows: **1** (1.0 eq., 0.25–0.30 mmol), **4** (1.5 eq., 0.375–0.45 mmol), [Ru] catalyst (10 mol%), base (2.0 eq.), solvent (1 mL), H₂O (5 eq.). The mixture was irradiated with blue LEDs (40–90 W power) for 24 h in N₂ (1 atm). The yields refer to isolated yields after purification by column chromatography on silica gel. ^aReaction run for 72 h. ^bReaction performed using 0.3 mmol of **1** (1.0 eq.) and 0.6 mmol of **4** (2.0 eq.) in the presence of N-Ac-L-Ile (10 mol%). ^cReaction run for 40 h.

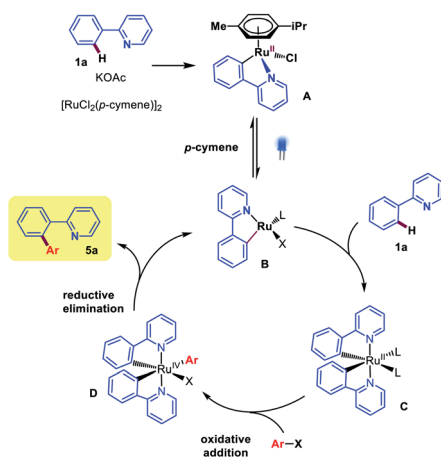
retards activity in catalytic cycles, and must de-complex to enable the formation of the active bis-cycloruthenated complex **C** (Scheme 4E). We analysed the free cymene formed in the reaction under room temperature blue light irradiation against an ambient light control. Decomplexation was observed in both cases, but with a clear rate increase under blue LED irradiation (Scheme 4C). Photo-decomplexation of η⁶-arenes such as cymene is well known, and has been used as a triggering mechanism for both chemical and biological activity in Ru(II) complexes.¹⁵ However, a light/dark experiment (Scheme 4D) demonstrated that continuous irradiation was necessary for complete conversion. This suggests that either reversible cymene re-complexation can inhibit the reaction, or there is an additional role for visible light in the catalytic cycle (*e.g.* photoexcitation of complexes **C** or **D** to facilitate either oxidative addition or reductive elimination, respectively). Stern–Volmer experiments with stoichiometric pre-catalyst **A** and aryl halides did not show clear evidence of photoluminescence quenching, but we cannot rule out an additional role for visible light in subsequent steps in the catalytic cycle at this time.



D. Light on / off



E. Proposed pathway



Scheme 4 (A) Inter-molecular competition experiment between aryl halides. (B) Reaction in the presence of radical inhibitors. (C) Detection of free *p*-cymene. Conversion refers to amount of *p*-cymene produced. (D) Light on/off experiment. (E) Proposed pathway. BHT = butylated hydroxytoluene.

Conclusions

We have established a room temperature, ruthenium catalysed *ortho*-arylation reaction that proceeds at room temperature under the agency of visible light irradiation. The reaction

encompasses a wide selection of aryl halides, producing C–H arylated products that are typically accessed at temperatures in excess of 100 °C. Initial observations point to a photo-decomplexation of the cymene ligand from the ruthenium pre-catalyst as playing a key role in the catalytic cycle. Future work will extend the photoarylation to new C–H substrate classes, and further delineate the role of visible light in the mechanism.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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