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Visible-Light for Ruthenium-Catalyzed *meta*-C–H Alkylation at Room Temperature

Parthasarathy Gandeepan,[¶] Julian Koeller,[¶] Korkit Korvorapun, Jens Mohr, and Lutz Ackermann*[a]

Abstract: Visible-light-induced ruthenium catalysis enabled remote C–H alkylations with excellent levels of position control under exceedingly mild conditions at room temperature. The metallaphotocatalysis occurred under exogenous-photosensitizer-free conditions with ample substrate scope. The robust nature of the photo-induced mild *meta*-C–H functionalization was reflected by broad functional group tolerance in an operationally-simple manner, setting the stage for challenging secondary and tertiary *meta*-C–H alkylations via ruthenaphotoredox catalysis.

The development of catalytic methods for the position-selective functionalization of C–H bonds represents a key challenge in molecular syntheses.[1] Thus far, chelation assistance by directing groups has been identified as a versatile tool for site-selective C–H metalations.[2] Thereby, proximity-induced C–H activations have set the stage for a plethora of *ortho*-selective C–H functionalizations. In sharp contrast, strategies for the assembly of *meta*-substituted arenes continue to be scarce. To overcome the challenge of *meta*-C–H functionalization, useful approaches have been devised (Figure 1).[3] Hence, exploiting the substrate's inherent substitution pattern has proven useful, but still largely suffers from limited substrate scope.[4] Directing group-based reactions via transient norbornene mediators,[5] hydrogen-bonding ligands,[6] or template-directing groups[7] provided significant recent momentum towards *meta*-decorated arenes. While representing key advances, these methods require multistep syntheses of ligands or templates, and often give mixtures of regioisomeric products that are difficult to separate. As a uniquely versatile alternative, *meta* C–H functionalizations through arene *σ*-activation[8] were realized by chelation-assisted *ortho*-cycloruthenation.[9-13] Despite indisputable progress, the *σ*-activation approach is limited to elevated reaction temperatures that resulted in significantly reduced yields and low functional group tolerance. Conversely, room temperature metal-catalyzed *meta*-C–H functionalization has thus far unfortunately proven elusive.

During the past decade, photo-induced C–H functionalization has emerged as a powerful tool for molecular syntheses,[14] both in terms of classical *ortho*-functionalizations or with electronically-biased heteroarenes.[15] In sharp contrast, within our program on metallaphotoredox-catalyzed C–H functionalization,[16] we have now devised the unprecedented visible-light-induced *meta*-C–H alkylation at room temperature. Notable features of our findings include a) expedient ruthenium-catalyzed *meta*-C–H alkylations, b) visible-light-induced metallaphotocatalysis for remote C–H functionalization, c) exogenous-photosensitizer-free photocatalysis, and d) exceedingly mild reaction conditions at room temperature.

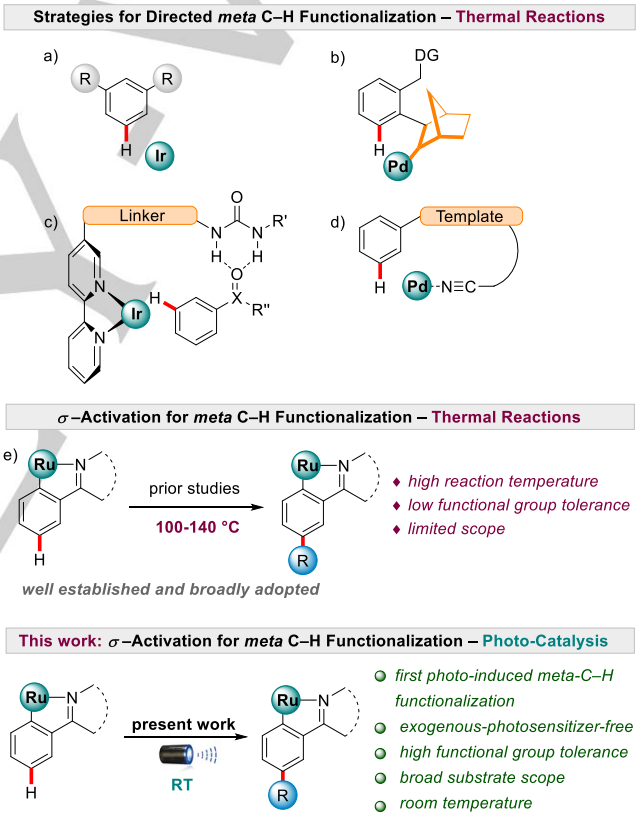

Figure 1. Strategies for *meta*-selective C–H functionalization. a) Control by steric interactions, b) Transient norbornene mediator enabled *meta*-selectivity, c) Hydrogen-bond interactions controlled selectivity, d) Template auxiliaries chelation assistance and e) Catalytic arene *σ*-activation by cycloruthenation.

We initiated our studies by probing reaction conditions for the *meta*-C–H alkylation of arene **1a** with challenging *tert*-butyl bromide (**2a**) (Table 1 and Tables S1-S5 in the Supporting Information). After considerable experimentation, we were pleased to obtain the *meta*-alkylated product **3a** in 80% yield with $[RuCl_2(p\text{-cymene})]_2$ as the catalyst and diphenyl phosphoric acid[17] as the ligand under blue light irradiation at room temperature (Table 1, entry 1). Control experiments verified the

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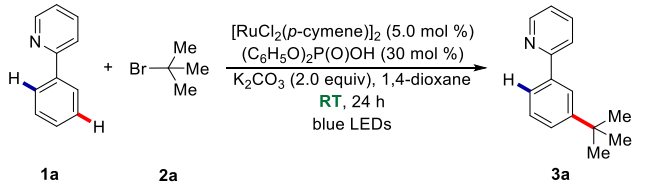
essential role of the ruthenium catalyst (entries 2 and 3), the ligand (entries 4-6), the base (entries 7 and 8), the solvent (entry 9), and light (entry 10). Notably, other commonly used transition metal catalysts for C–H activation, such as $Pd(OAc)_2$, $[Cp^*RhCl_2]_2$, and $[Cp^*IrCl_2]_2$, fell short in giving the desired product **3a** under otherwise identical reaction conditions (entry 11), highlighting the unique features of the ruthenaphotocatalysis for *meta*-C–H functionalization at room temperature. The addition of external photosensitizer, such as $Ir(ppy)_3$, $Ru(bpy)_3Cl_2$, Eosin Y, Rhodamine 6G, Rose Bengal, 9-Mesityl-10-methylacridinium perchlorate, did not significantly affect the efficacy of the ruthenaphotoredox catalysis (Table S4).

Table 1. Optimization of Photo-Induced Ruthenium(II)-Catalyzed *meta*-C–H Alkylation

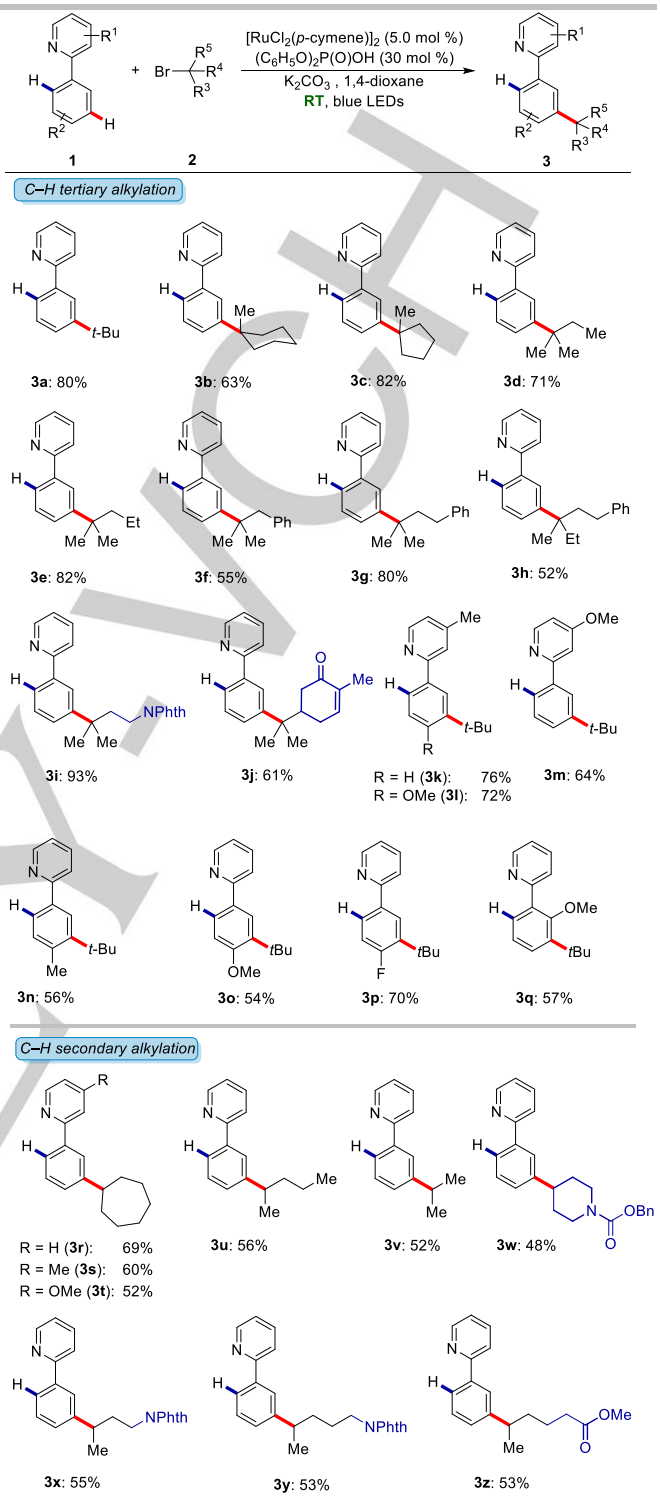


1a 2a 3a

Entry	Deviation from standard condition	Yield [%][a]
1	None	80
2	No [Ru]	0
3	$Ru(bpy)_3Cl_2$, $[Ru(NCtBu)_6][PF_6]_2$ or $[Ru(OAc)_2(p$-cymene)] as the catalyst	0, 0, 35
4	BNDHP instead of $(C_6H_5O)_2P(O)OH$	73
5	PivOH, $MesCO_2H$ or $1\text{-}AdCO_2H$ instead of $(C_6H_5O)_2P(O)OH$	14, 12, 19
6	No $(C_6H_5O)_2P(O)OH$	24
7	No K_2CO_3	0
8	KOAc, NaOAc or K_3PO_4 instead of K_2CO_3	19, 30, 70
9	THF, PhMe, DME, or DMA instead of 1,4-dioxane	61, 0, 70, 79
10	No light	0
11	$Pd(OAc)_2$, $[Cp^*RhCl_2]_2$, and $[Cp^*IrCl_2]_2$ as the catalyst	0
12	oil bath at 80 °C, no light	0

[a] Reaction conditions: **1a** (0.4 mmol), **2a** (1.2 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $(C_6H_5O)_2P(O)OH$ (30 mol %), K_2CO_3 (2.0 equiv), 1,4-dioxane (2.0 mL), blue LEDs, 24 h, 25-30 °C, yield of isolated products. BNDHP = (±)-1,1'-Binaphthyl-2,2'-diyl hydrogenphosphate. DME = 1,2-Dimethoxyethane.

With the optimized reaction conditions established, we investigated the versatility of the photo-*meta*-C–H alkylation of arenes **1** (Scheme 1). We were delighted to observe that a variety of both tertiary and secondary unactivated alkyl bromides **2** were compatible electrophiles to provide the desired products **3** with outstanding performance. Thus, alkyl bromides **2** bearing imides, enones, piperidyl, and ester motifs were fully tolerated by the ruthenaphotoredox *meta*-C–H functionalization.



Scheme 1. Photo-induced *meta*-C–H alkylation at room temperature.

The ruthenium-catalyzed visible-light-induced *meta*-C–H alkylation at ambient temperature was not limited to alkyl bromides **2**. Indeed, the ruthenaphotoredox catalysis proved also applicable to the photo-induced C–H functionalization with synthetically meaningful *α*-bromoesters **4** (Scheme 2). Also, the *meta*-substituted products **5c-e** derived from alkyl bromides containing sugar, menthol, or steroid motifs were selectively converted, which should prove instrumental for applications to

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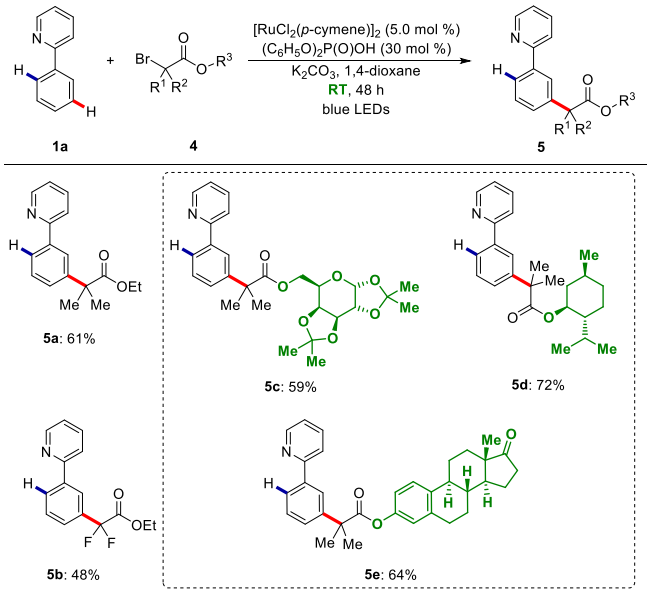
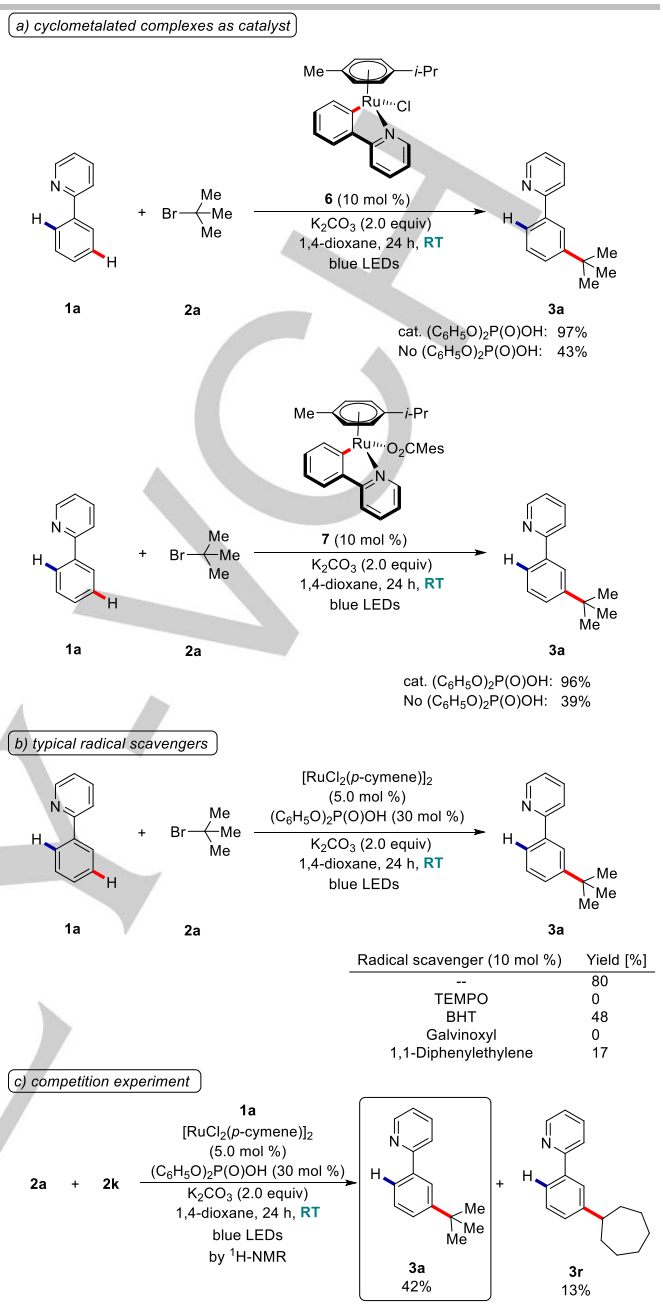
pharmaceutical industries in terms of late-stage diversification under mild conditions.[18,19]



Scheme 2. Photo-induced *meta*-alkylation with *α*-bromoesters **4**.

Given the unique features of the photo-induced ruthenium-catalyzed *meta*-C–H functionalization, we became attracted to elucidating its mode of action (Scheme 3). To this end, the chloro-ruthenacycle[20] **6** was found to be catalytically competent, provided that the ligand $(PhO)_2P(O)OH$ was present (Scheme 3a). Likewise, the well-defined mesityl carboxylate-ruthenacycle[9d, 9n] **7** was effective for the photo-induced remote C–H functionalization, again solely in the presence of $(PhO)_2P(O)OH$. Interestingly, both cyclometalated complexes **6** and **7** gave the product **3a** with almost quantitative isolated yield. Thereafter, we examined a single-electron-transfer (SET)-regime by the use of typical radical scavengers TEMPO, BHT, galvinoxyl, and 1,1-diphenylethylene (Scheme 3b), which significantly suppressed the catalytic efficacy. Finally, competition experiments between secondary and tertiary alkyl bromides **2** revealed the latter to be preferentially converted (Scheme 3c)



Scheme 3. Key mechanistic studies.

In consideration of the mild nature of the photo-induced ruthenium-catalyzed *meta*-C–H alkylation process, we became interested in elucidating the role of visible light. Here, the absorption spectra of ruthenium complexes **6** and **7** highlighted a minor, yet significant light absorption in the relevant blue region (Figure 2a). Furthermore, we performed fluorescent quenching studies towards Stern-Volmer-plot analyses (Pages S-42-S-44 in the Supporting Information), and monitored the conversion profile of the photocatalytic *meta*-alkylation, revealing the remote-C–H alkylation to be completely suppressed in the absence of light (Figure 2b). These findings highlight the importance of visible-light irradiation to the success of *meta* C–H functionalization at room temperature, while showing that constant irradiation is required for effective product formation.[21] Cyclic voltammetric studies

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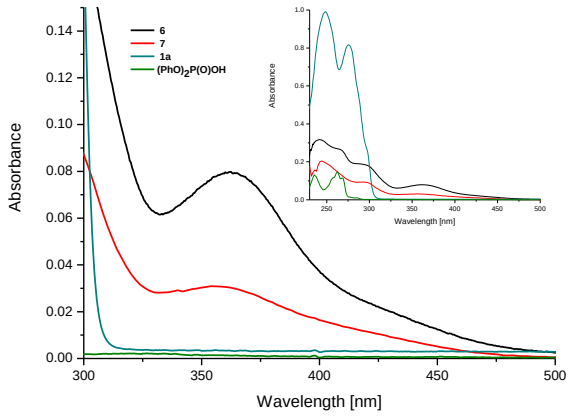
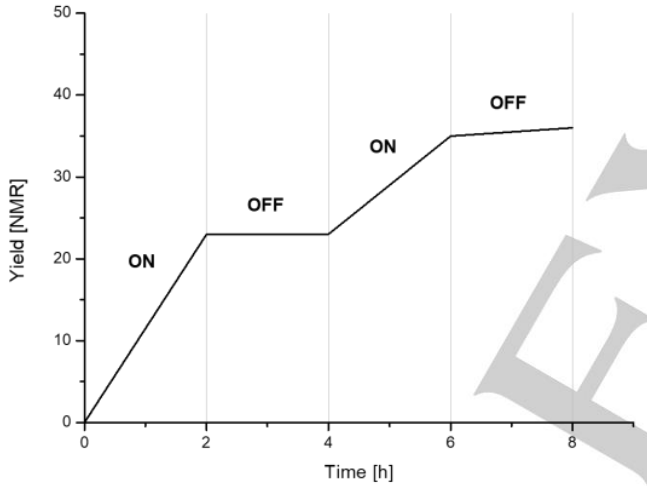
featured a reversible oxidation event with an oxidation peak at 0.98 V in DCE (Figure 2c).

a)



b)



c)

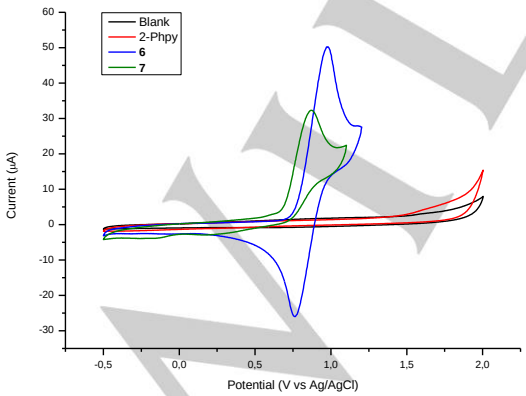
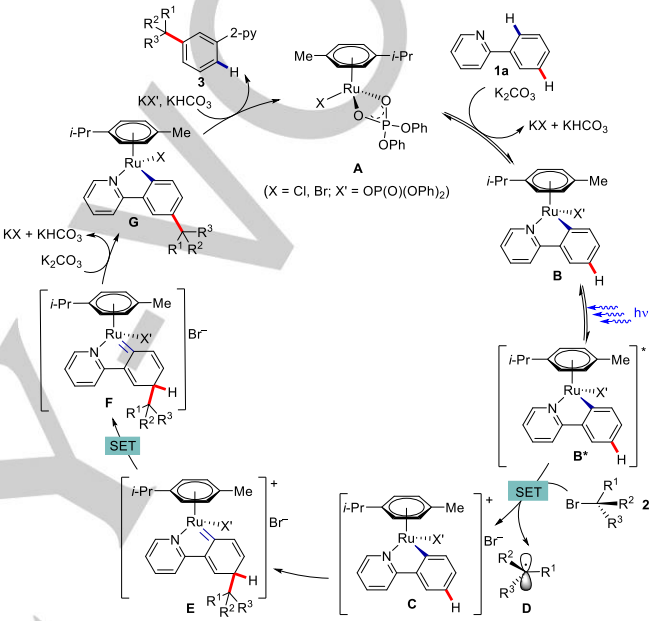


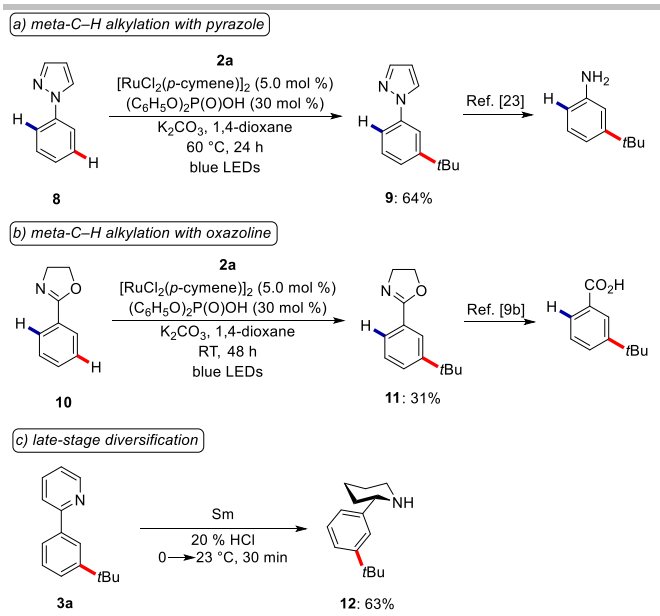
Figure 2. a) Absorption spectra of ruthenacycles **6** and **7**. b) On/off light experiments. c) Cyclic voltammograms at 100 mVs^{-1} in DCE. nBu_4NPF_6 (0.1 M in DCE), concentration of substrate 4 mM. E_{Ox} of **6**: 0.98 V, E_{ox} of **7**: 0.87 V. DCE = 1,2-dichloroethane.

On the basis of our mechanistic findings, we propose a plausible catalytic cycle to commence by phosphate-assisted[22] C–H ruthenation[17] (Scheme 4). The cyclometalated ruthenium complex **B** is then excited by blue-light absorption to give intermediate **B***, which is followed by SET to alkyl halides **2**. Thereby, ruthenium(III) complex **C** and alkyl radical **D** are generated. Next, radical attack on the aromatic moiety at the position *para* to ruthenium forms intermediate **E**, which undergoes intramolecular SET and subsequent rearomatization to provide ruthenacycle **G**. Finally, protodemetalation releases the desired *meta*-alkylated product **3** and regenerates the catalytically competent ruthenium(II) species **A**.



Scheme 4. Plausible catalytic cycle.

Finally, we examined the visible-light-enabled *meta*-C–H alkylation with alternative modifiable heteroarenes (Scheme 5). To our delight, synthetically useful pyrazoles and oxazolines enabled the synthesis of the desired *meta*-functionalized products **9** and **11**, which are readily converted into meaningful amino and carboxylic acid groups.[9b, 23] The power of our visible-light-enabled *meta*-C–H alkylation was further substantiated by the late-stage modification towards the valuable piperidine moiety (Scheme 5c).



Scheme 5. Late-Stage Diversification.

In conclusion, we have devised a novel strategy towards *meta*-decorated arenes by unprecedented visible-light-induced ruthenium-catalyzed remote C–H functionalization. The versatile metallaphotoredox protocol proceeded in the absence of exogenous photosensitizers with outstanding efficacy and functional group tolerance under exceedingly mild conditions at room temperature. The versatile photo-*meta*-C–H functionalization enabled both challenging secondary and tertiary alkylations. Overall, our findings demonstrate, for the first time, the unique potential of merging visible-light photoredox catalysis with ruthenium(II)-mediated *meta*-C–H functionalizations. Further studies are ongoing in our laboratories and will be reported in due course.

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Keywords: C–H activation • *meta* selectivity • photocatalysis • remote C–H functionalization • room temperature • ruthenium

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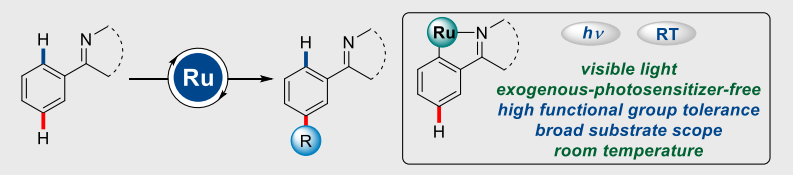

***meta*-light**: Visible-light enabled remote arene diversification under exceedingly mild conditions for expedient *meta*-C–H-functionalization at room temperature.

*Parthasarathy Gandeepan, Julian Koeller, Korkit Korvorapun, Jens Mohr, Lutz Ackermann**

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Visible-Light for Ruthenium-Catalyzed *meta*-C–H Alkylation at Room Temperature