C-H Activation Hot Paper

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Photo-Induced Ruthenium-Catalyzed Double Remote C(sp^2)–H / C(sp^3)–H Functionalizations by Radical Relay

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Abstract: Distal C(sp^2)–H and C(sp^3)–H functionalizations have recently emerged as step-economical tools for molecular synthesis. However, while the C(sp^2)–C(sp^3) construction is of fundamental importance, its formation through double remote C(sp^2)–H/C(sp^3)–H activation has proven elusive. By merging the ruthenium-catalyzed *meta*-C(sp^2)–H functionalization with an aliphatic hydrogen atom transfer (HAT) process, we, herein, describe the catalyzed twofold remote C(sp^2)–H/C(sp^3)–H functionalizations via photo-induced ruthenium-mediated radical relay. Thus, *meta*-C(sp^2)–H arene bonds and remote C(sp^3)–H alkane bonds were activated by a single catalyst in a single operation. This process was accomplished at room temperature by visible light—notably without exogenous photocatalysts. Experimental and computational theory studies uncovered a manifold comprising *ortho*-C–H activation, single-electron-transfer (SET), 1,*n*-HAT (n = 5–7) and σ-activation by means of a single ruthenium(II) catalyst.

Introduction

C–H bonds are the ubiquitous backbone of organic compounds. The direct and site-selective functionalization of C–H bonds to amend molecular complexity are tremendously attractive on grounds of step and atom economy. While the activation of C–H bonds, adjacent to a functional groups, has been common,[1] distal C–H functionalization is significantly more difficult by challenges that include the intrinsic inertness as well as regioselectivity due to subtle differences of bond dissociation energies of multiple C–H bonds. Encouragingly, significant progress has been achieved for remote C–H functionalization in the last decade.[2–12] Elegant approaches, such as the use of transient mediators,[3] templates,[4] non-covalent interactions,[5] ruthenium-catalyzed σ-activation,[6] as well as non-directed[7] and/or metal-free methods,[8] are now available for the remote arene C(sp^2)–H activation (Scheme 1a). Meanwhile, cyclometallation[9] and metal carbene[10] pathways as well as radical strategies involving hydrogen atom transfer (HAT) processes[11,12] are amenable for the remote C(sp^3)–H functionalization (Scheme 1b). However, while the molecules containing C(sp^2)–C(sp^3) bonds are omnipresent in petrochemical, agrochemical, pharmaceutical and food industries, the C(sp^2)–C(sp^3) bond construction through double remote C(sp^2)–H/C(sp^3)–H activation has thus far proven elusive.

From a mechanistic viewpoint of the arene C(sp^2)–H activation, the ruthenium-catalyzed *meta*-C(sp^2)–H functionalization involving a single electron transfer process is unique and unusual as compared to other transition metals, which typically rely on two-electron manifolds (Scheme 1a). In recent years, Ackermann, and Greaney, among others have investigated ruthenium-catalyzed arene *meta*-C–H alkylations.[6] This transformation proceeds via single-electron-transfer (SET) process between

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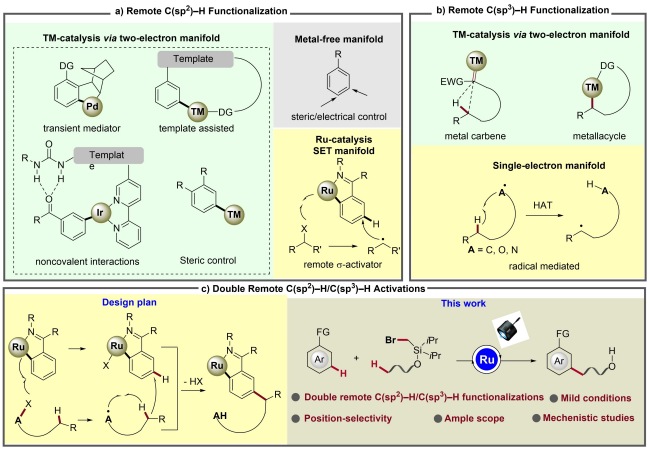


Scheme 1. Design of transition-metal-catalyzed double remote C(sp^2)–H/C(sp^3)–H functionalizations via radical relay.

alkyl halide RX and an in situ generated ruthenacycle(II), generating a ruthenium(III) species and an alkyl radical. Then, the alkyl radical attacks the ruthenacycle(III) at the position *para* to the C–Ru bond, followed by an elimination of HX to deliver the *meta*-alkylated product.

In contrast, benefiting from the rapid development of a mild method for the generation of heteroatom- or carbon-centered radical species,[11–14] the HAT process has emerged as a versatile tool for remote C(sp^3)–H functionalization. This process generally occurs under mild conditions with high efficiency and regioselectivity, exhibiting a selectivity trend of tertiary C–H sites over secondary and primary ones. This is complementary to that observed for transition metal-catalyzed distal C(sp^3)–H activation via metallacycle or carbene-insertion pathway, which largely require high temperatures, directing groups, and featuring preference for primary C–H bonds (Scheme 1b).

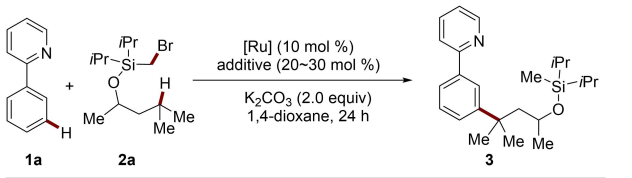
Based on this analysis and within our program on ruthenium-catalyzed remote functionalizations, we questioned whether it would be possible to establish a double remote C(sp^2)–H/C(sp^3)–H activation by the combination of the ruthenium-catalyzed *meta*-C(sp^2)–H functionalization with an aliphatic HAT process (Scheme 1c). We, thus, envisioned that a suitable alkyl radical precursor reacts with ruthenacycle(II) to generate ruthenacycle(III) and a heteroatom or carbon-centered radical species, following by an intramolecular HAT process to produce a new carbon-centered radical species, which subsequently adds to ruthenacycle(III) at the *para*-position of the C–Ru bond to form a doubly remote C(sp^2)–C(sp^3) bond. As a result of our studies, we, herein, report the transition metal-catalyzed double remote C(sp^2)–H/C(sp^3)–H functionalizations via radical relay catalysis by user-friendly [RuX_2(*p*-cymene)]$_2$ (Scheme 1c).[15] The ruthenium-catalysis was accomplished under exceedingly mild visible-light-mediated conditions without an exogenous photocatalysts, featuring high levels of positional selectivity and ample substrate scope.

Results and Discussion

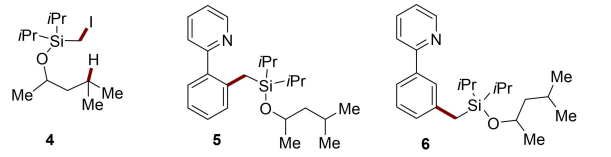
Optimization of the Reaction Conditions

At the outset of our studies, phenylpyridine (**1a**) was employed as the substrate. After preliminary experimentation, alcohol **2a** with an easily installed and removable silylmethyl bromide was selected as the HAT substrate (Table 1). The reaction in 1,4-dioxane with K_2CO_3 as the base and Ru(OAc)$_2$(*p*-cymene) as the catalyst gave a low conversion after 24 h at 80 °C (Entry 1). When PPh_3 was added as a ligand, the desired twofold remote C(sp^2)–H/C(sp^3)–H functionalization product **3** was formed in 28 % yield (Entry 2). However, a non-negligible number of isomeric byproducts were also observed. (*p*-$CF_3C_6H_4$)$_3$P instead of PPh_3 did not afford a satisfactory yield and selectivity (Entry 3). Therefore, we next focused on testing photoconditions at room temperature with [$RuCl_2$(*p*-cymene)]$_2$ as the precatalyst. While $MesCO_2H$ as the additive gave no desired product **3** (Entry 4), (*n*-BuO)$_2PO_2H$ afforded **3** in 34 % isolated yield with high selectivity (Entry 5). Further tests showed that (PhO)$_2$P(O)OH was ideal, giving *meta*-product **3** in 73 % isolated yield (Entry 6).[16] Thereby, only traces of other isomers of less than 5 % were observed. Alternative solvents, such as DCE and DMAc, led to significantly lower efficacies (Entries 7 and 8). The transformation could not occur under base-free conditions or when using KOAc in lieu of K_2CO_3 (Entry 9). An improved yield of 82 % was obtained when adjusting the stoichiometry of substrate **2a** (Entry 10). While [$RuCl_2$(benzene)]$_2$ was also an effective catalyst, other ruthenium complexes, such as Ru(OAc)$_2$(*p*-cymene), $RuCl_3 \cdot 3H_2O$ and $Ru_3(CO)_{12}$, failed to efficiently mediate the double remote functionalization (Entries 11–14). Control experiments verified the essential

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



Entry	Catalyst	Additive	Energy	Yield (%)[b]
1	Ru(OAc)$_2$(*p*-cymene)	/	80 °C	trace
2	Ru(OAc)$_2$(*p*-cymene)	Ph_3P	80 °C	28
3	Ru(OAc)$_2$(*p*-cymene)	(*p*-$CF_3C_6H_4$)$_3$P	80 °C	36
4	[$RuCl_2$(*p*-cymene)]$_2$	$MesCO_2H$	Blue LEDs, RT	trace
5	[$RuCl_2$(*p*-cymene)]$_2$	(*n*-BuO)$_2PO_2H$	Blue LEDs, RT	34
6	[$RuCl_2$(*p*-cymene)]$_2$	(PhO)$_2PO_2H$	Blue LEDs, RT	73
7[c]	[$RuCl_2$(*p*-cymene)]$_2$	(PhO)$_2PO_2H$	Blue LEDs, RT	0
8[d]	[$RuCl_2$(*p*-cymene)]$_2$	(PhO)$_2PO_2H$	Blue LEDs, RT	16
9[e]	[$RuCl_2$(*p*-cymene)]$_2$	(PhO)$_2PO_2H$	Blue LEDs, RT	0
10[f]	[$RuCl_2$(*p*-cymene)]$_2$	(PhO)$_2PO_2H$	Blue LEDs, RT	82
11	[$RuCl_2$(benzene)]$_2$	(PhO)$_2PO_2H$	Blue LEDs, RT	77
12	Ru(OAc)$_2$(*p*-cymene)	(PhO)$_2PO_2H$	Blue LEDs, RT	13
13	$RuCl_3 \cdot 3H_2O$	(PhO)$_2PO_2H$	Blue LEDs, RT	0
14	$Ru_3(CO)_{12}$	(PhO)$_2PO_2H$	Blue LEDs, RT	0
15	[$RuCl_2$(*p*-cymene)]$_2$	(PhO)$_2PO_2H$	No light, RT	0
16	[$RuCl_2$(*p*-cymene)]$_2$	(PhO)$_2PO_2H$	No light, 100 °C	22
17	[$RuCl_2$(benzene)]$_2$	(PhO)$_2PO_2H$	No light, 60 °C	trace
18[g]	[$RuCl_2$(*p*-cymene)]$_2$	(PhO)$_2PO_2H$	Blue LEDs, RT	30



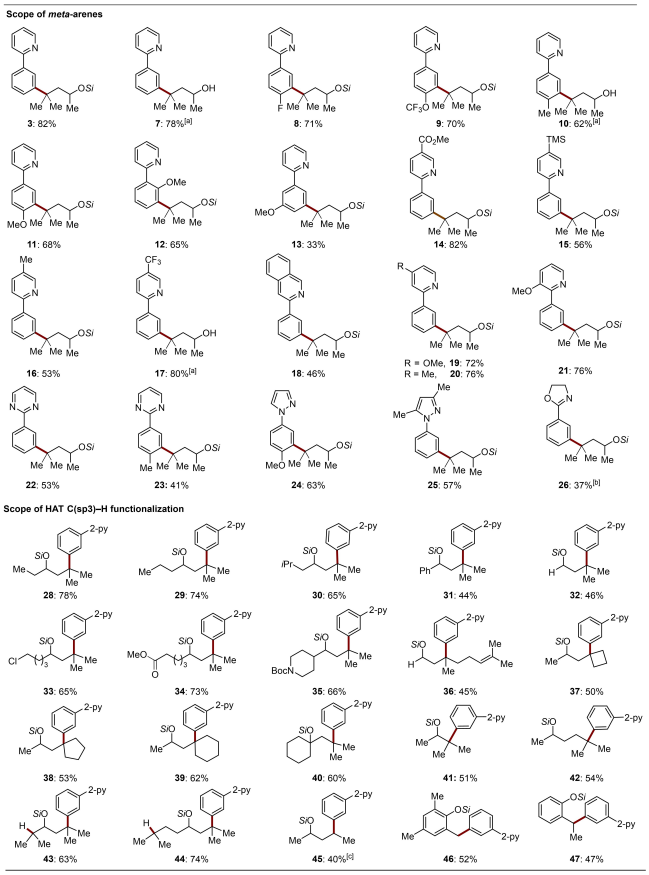
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), [Ru] (0.05 mmol), additive (0.1 mmol for PPh_3 and (*p*-$CF_3C_6H_4$)$_3$P, 0.15 mmol for the others), K_2CO_3 (1.0 mmol), 1,4-dioxane (2.0 mL), RT = 30–35 °C. [b] Yield of isolated products. [c] Using DCE as solvent. [d] Using DMAc as solvent. [e] Using KOAc as the base. [f] **2a** (1.0 mmol). [g] Using **4** instead of **2a**.

role of the light irradiation (Entries 15–17). Notably, the silyl methyl iodide **4**, which was previously ideal for remote C(sp^3)–H functionalization of alcohols by inter alia Gevorgyan,[12] was found to be less effective (Entry 18). Alcohols with a less sterically congested dimethyl silyl motif afforded a rather low yield and poor selectivity (see Supporting Information).

Reaction Robustness

With the optimized reaction conditions in hand, the viable substrate scope of the ruthenium-catalyzed twofold remote C(sp^2)–H/C(sp^3)–H activation was first examined with differently substituted arylpyridines **1** (Scheme 2). A range of arenes bearing electron-withdrawing or electron-donating groups could thus be selectively alkylated at the *meta*-position with high efficacy (**8–21**). Functional groups, including fluoro (**8**, **9**), ether (**11–13**), ester (**14**) and TMS (**15**) were well tolerated. Other heteroarenes, including pyrimidines (**22**, **23**) and pyrazoles (**24**, **25**), were identified as suitable orienting groups for the photo-induced ruthenium-catalyzed double remote C(sp^2)–H/C(sp^3)–H functionalizations. In contrast, substrates featuring oxazoline were not converted under the photochemical conditions. Instead, the desired product **26** could be obtained under thermal reaction conditions. Notably, the silyl auxiliary was easily removed within a one-pot procedure with the aid of TBAF to afford the corresponding *OH*-free alcohols **7**, **10** and **17**.

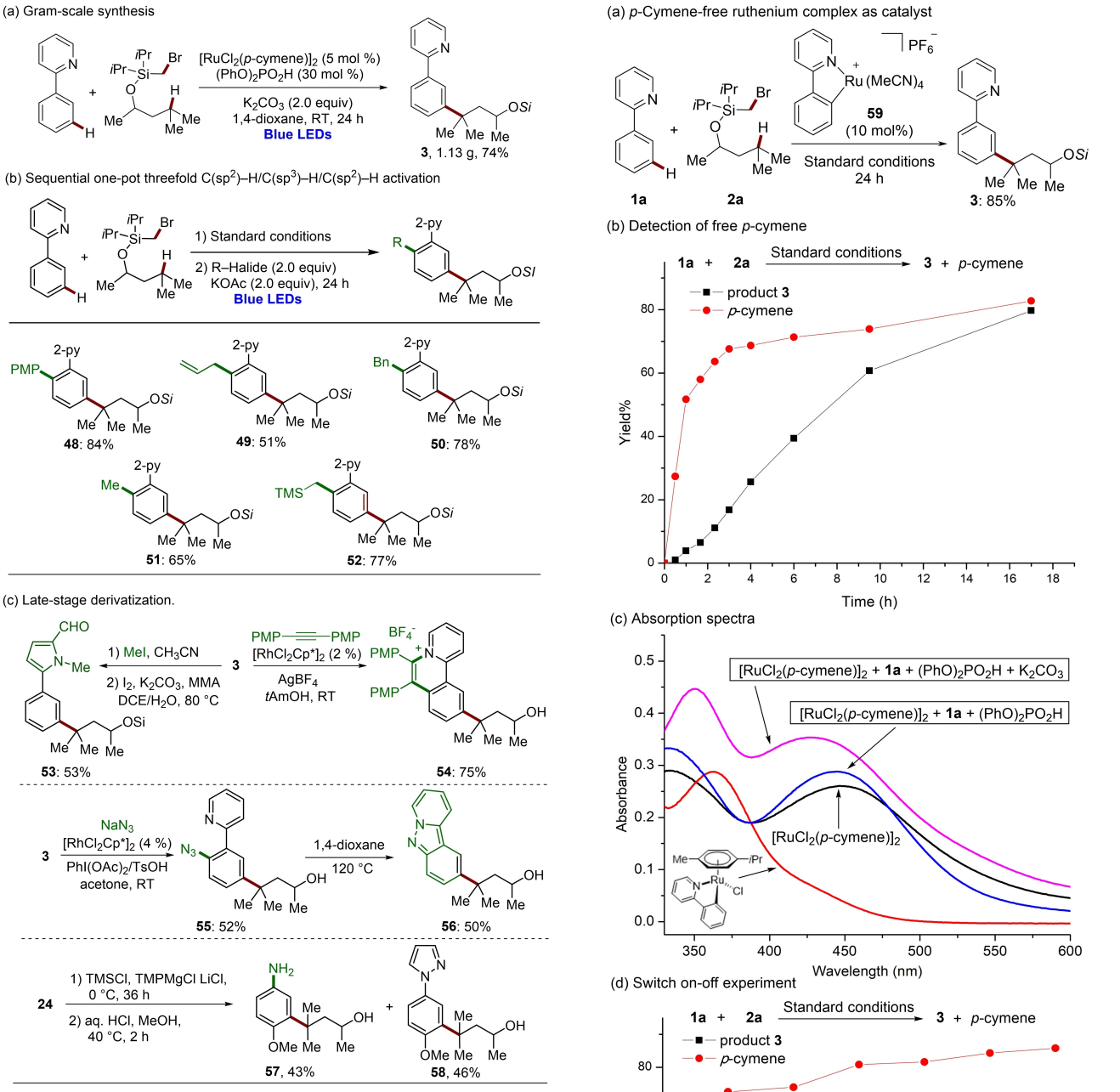
Thereafter, the scope of the double remote C(sp^2)–H/C(sp^3)–H functionalizations was further examined with various tethered silylethers (Scheme 2). Alcohols possessing phenyl (**31**), chloro (**33**), alkoxycarbonyl (**34**), and amino (**35**) substituted chains efficiently furnished the desired products with perfect regioselectivities. Primary alcohol smoothly underwent the γ-3°C–H arylation reaction in 46 % yield (**32**). Citronellol derivative was identified as a feasible substrate, leaving intact the otherwise reactive double bond (**36**). Cyclic alcohols, featuring 4- to 6-membered rings, also reacted well (**37–39**). Furthermore, γ-arylation of C–H bonds of tertiary alcohol proceeded efficiently (**40**). It is noteworthy that this transformation was not limited to γ-3°C–H activation. Indeed, substrates with tertiary β-H and δ-H proved also amenable, delivering the corresponding products **41**–**42** in a selective fashion. For the substrates that possess competitive β-H and δ-H sites, the reaction preferentially occurred at the γ-C–H sites to deliver products **43** and **44**. These findings are in good agreement with the previously observation that a silicon-based tether displays a preference for a 1,6-HAT over a 1,5-HAT or a 1,7-HAT for tertiary sites with similar BDE. A mixture of products **45** was obtained for the alcohol without remote tertiary C–H site. Gratifyingly, 2-alkylphenols were also suitable substrates for the remote C–H functionalization for the first time, affording the benzylic arylation products **46** and **47**.



Scheme 2. Ruthenium-catalyzed double remote C(sp^2)–H/C(sp^3)–H functionalization. Reaction conditions: Arene (0.5 mmol), alcohol derivative (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.025 mmol), $(PhO)_2PO_2H$ (0.15 mmol), K_2CO_3 (1.0 mmol), 1,4-dioxane (2.0 mL), blue light, RT, N_2, 24–48 h. [a] Work-up with TBAF (1.0 M in THF, 4.0 mL), see Supporting Information. [b] Arene (0.5 mmol), alcohol derivative (1.0 mmol), $Ru(OAc)_2(p\text{-cymene})_2$ (0.05 mmol), K_2CO_3 (1.0 mmol), 1,4-dioxane (2.0 mL), 90 °C, N_2, 24 h. [c] Mixture.

Late-Stage Derivatization

A gram-scale synthesis of product **3** was successfully performed to demonstrate the scalability of our approach, giving 1.13 g of the desired product **3** in 74 % yield (Scheme 3a). Furthermore, the double remote functionalization could be further cascaded. Thus, the merger of twofold remote C–H functionalization with a ruthenium-catalyzed *ortho*-C–H arylation (**48**), allylation (**49**), benzylation (**50**), methylation (**51**) or alkylation (**52**) proved to viable, notably without changing the nature of the catalyst or of the solvent (Scheme 3b). Thereby, a sequential threefold C–H transformation was achieved in a sustainable one-pot fashion, involving C(sp^2)–H/C(sp^3)–H/C-(sp^2)–H functionalizations. The pyridine ring could be efficiently converted into a variety of heterocycles, such as pyrrole **53**, polycyclic pyridinium salt **54** and indazole **56** (Scheme 3c), the structures of which are prevalent in bioactive compounds or light-emitting materials. In addi-



Scheme 3. Gram-scale synthesis and late-stage derivatization.

tion, the pyrazolyl motif was efficiently removed to deliver synthetically meaningful aniline **57** (Scheme 3c).

Mechanistic Studies

Since photo-induced ligand dissociation have been widely reported, we wondered whether *p*-cymene dissociation occurred from the ruthenium(II) complex during the catalysis. Hence, the arene-ligand-free ruthenacycle **59** was used. Indeed, the reaction selectively yielded the desired product **3** in high yield (Scheme 4a). In addition, monitoring the reaction by GC-MS showed that a signifi-

Scheme 4. Summary of key mechanistic findings.

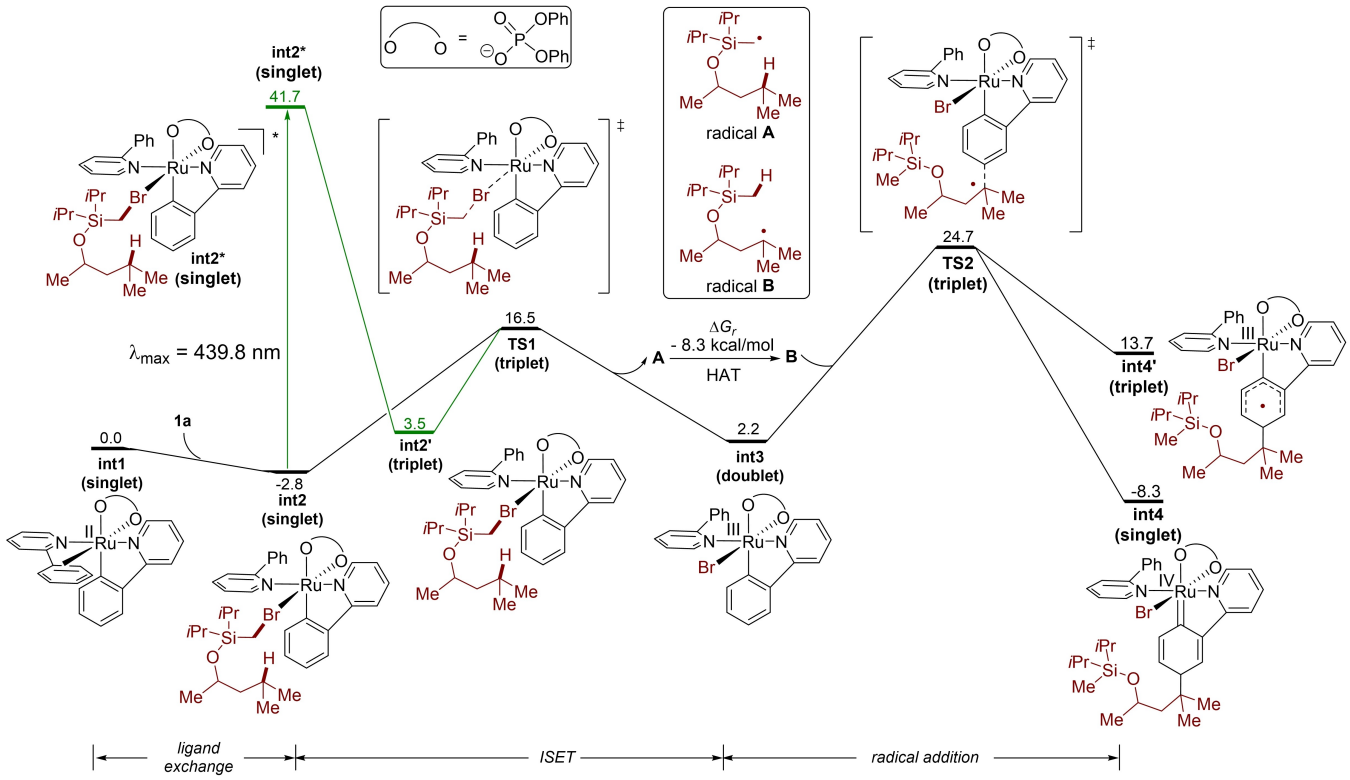


Figure 1. Computed free energy surface. Computational methods: PBE0-D3(BJ)/6–311+G(d,p)-SDD-SMD(1,4-Dioxane)//B3LYP-D3(BJ)/6-31G(d)-LANL2DZ.

cant amount of free *p*-cymene was released by the blue light irradiation in the initial phase of the reaction (Scheme 4b). UV/Vis absorption spectra of $[RuCl_2(p\text{-cymene})]_2$ featured broad absorbance in the region of 400–500 nm, which is in good agreement of the catalytic activity under blue-light irradiation (Scheme 4c). To further elucidate the role of the blue light, an on-off-experiment was conducted. Interestingly, the result demonstrated that the formation of the product **3** was only slightly suppressed in the absence of light during the latter phase of the transformation (Scheme 4d). Then, the reaction was conducted under the irradiation of blue light for only 2 h, and subsequently the light was switched off for 22 h, affording the desired product in 65 % yield (Scheme 4e).[17] These results show that continuous irradiation is not necessary, but is required initially for the decoordination of the *p*-cymene. This observation contrasts with the previously reported photo-induced ruthenium-catalyzed *ortho*-arylation of phenylpyridines.[18]

Computational Studies

To gain further insights into the details of the reaction mechanism, theory studies by means of density functional theory (DFT) calculations were conducted at the PBE0-D3(BJ)/6-311+G(d,p)-SDD-SMD(1,4-Dioxane)//B3LYP–D3(BJ)/6-1G(d)-LANL2DZ level of theory (Figure 1). The excitation of bromoalkane-coordinated ruthenacycle complex **int2** followed by intersystem crossing (ISC) leads to a long-lived triplet complex **int2′**. Next, inner-sphere electron transfer (ISET) to bromoalkane occurs through transition state TS1 to form radical **A** and ruthenium(III) intermediate **int3**. DFT results also showed that **int2** could be directly converted into **int3** in the absence of light excitation with a low barrier of only 19.3 kcal mol^{-1}. This is in good agreement with our experimental observation that the reaction kept going after discontinuation of the light irradiation (see above). Radical **A** easily converted to the tertiary carbon-centered radical **B** via intramolecular HAT. In addition, the radical attach product is significantly stabilized as the singlet metallacycle **int4** by 20 kcal mol^{-1} compared to corresponding triplet species **int4′**.

Proposed Mechanism

Based on our detailed experimental and computational findings, a plausible catalytic cycle commences by *ortho* C–H ruthenation and dissociation of *p*-cymene, thereby generating the catalytically competent complex **C** (Figure 2). Subsequently, single electron transfer (SET) occurs between intermediate C and substrate **2a** to generate the ruthenium(III) intermediate **E** and a silly methyl radical **A**. The newly formed radical **A** undergoes a HAT process to deliver the more stable distal carbon-centered radical **B**, followed by the immediate addition to

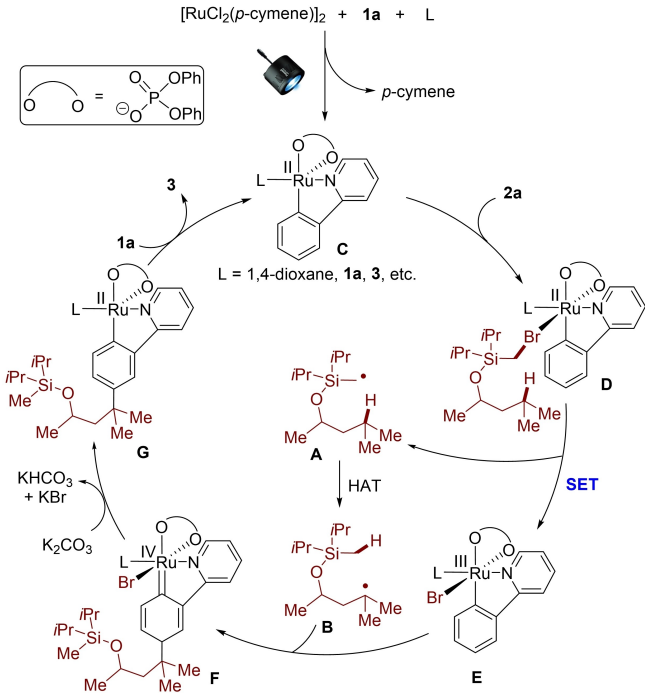


Figure 2. Proposed catalytic cycle.

intermediate **E** at the *para*-position to the C–Ru bond. Elimination of HBr by K_2CO_3 and ligand exchange delivers the double remote, *meta*-C(sp^2)–H/C(sp^3)–H functionalization product **3**, while at the same time regenerating the catalytically active species.

Conclusion

In summary, we have disclosed the merger of the ruthenium-catalyzed *meta*-C(sp^2)–H functionalization with an alkane hydrogen atom transfer (HAT) process. Thereby, we have established the twofold remote C-(sp^2)–H/C(sp^3)–H functionalizations via photo-induced radical relay, wherein an arene *meta*-C(sp^2)–H bond and a remote C(sp^3)–H bond of alkyl alcohols are selectively functionalized in a single operation by a single catalyst. The ruthenium catalysis was accomplished under exceedingly mild conditions at room temperature, while tolerating a broad range of otherwise sensitive functional groups. Mechanistic studies by experiment and theory were suggestive of an initial *p*-cymene decoordination from the ruthenium precatalyst to generate the catalytically competent ruthenacycle(II) complex. Given the current topical interest in modern radical HAT chemistry, we hope that our findings will inspire further studies towards multifold remote C(sp^2)–H/C(sp^3)–H functionalization manifolds.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: C–H Activation · Hydrogen Atom Transfer · *meta*-Functionalization · Photocatalysis · Ruthenium

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