# Photo-Induced Ruthenium-Catalyzed C–H Benzylations and Allylations at Room Temperature

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*Dedicated to the memory of Prof. Dr. Klaus Hafner.*

**Abstract:** The ruthenium-catalyzed synthesis of diarylmethane compounds was realized under exceedingly mild photoredox conditions without the use of exogenous photocatalysts. The versatility and robustness of the ruthenium-catalyzed C–H benzylation was reflected by an ample scope, including multifold C–H functionalizations, as well as transformable pyrazoles, imidates and sensitive nucleosides. Mechanistic studies were indicative of a photoactive cyclometalated ruthenium complex, which also enabled versatile C–H allylations.

## Introduction

Transition metal-catalyzed C–H activation has evolved as a powerful platform in molecular syntheses.[1] Thus, C–H activation has been identified as an atom- and step-economic strategy with applications ranging from material sciences to drug discovery and crop protection,[2] with major progress in ruthenium catalysis.[3]

Diarylmethanes are important structural motifs in various compounds of relevance to biology (Figure 1a).[4] Valuable approaches for their syntheses include $S_EAr$ Lewis acid-catalyzed Friedel-Crafts benzylations, often leading to regioisomeric mixtures and over benzylation.[5] Furthermore, nucleophilic additions of often sensitive organometallic reagents, along with subsequent reduction,[6,4b] as well as transition metal-catalyzed cross-coupling reactions have been devised.[7] However, these procedures are associated with considerable limitations, such as significant stoichiometric waste formation and lengthy synthesis. Ruthenium-catalyzed benzylations of arenes offer the possibility for more efficient syntheses.[8] Despite major advances, *ortho*-selective benzylations require harsh reaction conditions, namely high reaction temperatures of typically 100 °C (Figure 1b).[8d]

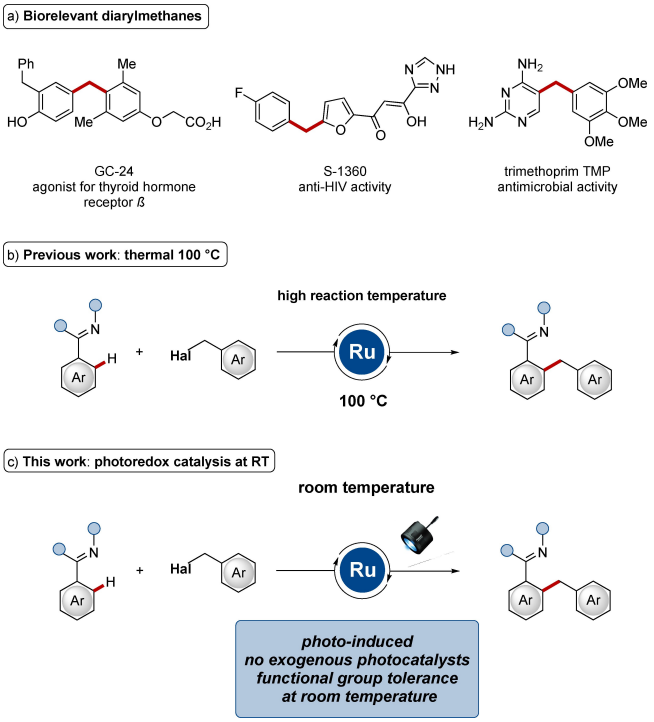


**Figure 1.** a) Biological active diarylmethanes. Ruthenium-catalyzed C–H benzylations: (b) under thermal reaction conditions and (c) under mild photoredox conditions.

Visible-light metallaphotoredox catalysis constitutes a sustainable approach to allow for transformations under mild conditions.[9] Major contributions in this area were thus made by among others Akita,[10] MacMillan,[11] Molander,[12] Glorius,[13] König[14] and Doyle,[15] towards metallaphotoredox catalysis. Here, exogenous photocatalysts, such as ruthenium or iridium complexes, are usually required in these photoredox transformations. In sharp contrast, Ackermann and Greaney addressed this drawback very recently by remote C–H

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alkylations[16] as well as *ortho*-selective C–H arylations,[17] through exogenous photocatalyst-free ruthenium catalysis.

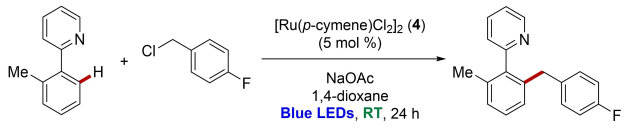
Within our program on photo-induced C–H activation,[18] we have now developed unprecedented photo-induced C–H benzylations and allylations at ambient temperature (Figure 1c). Notable features of our method include (i) versatile photo-induced ruthenium(II/III) catalysis, (ii) visible-light-enabled C–H benzylations and allylations, and (iii) mechanistic findings into exogenous photocatalyst-free conditions for the (iv) efficient assembly of diarylmethanes.

## Results and Discussion

We commenced our studies by probing various reaction conditions to enable the desired visible-light-induced ruthenium-catalyzed benzylation of arene **1a** with benzyl chloride **2a** (Table 1).[19] The reaction in the presence of $[Ru(p\text{-cymene})Cl_2]_2$ (**4**) as the catalyst and NaOAc as the base in 1,4-dioxane under blue light irradiation delivered the desired *ortho*-benzylated product **3aa** in 83% yield at room temperature (entry 1). Other solvents, such as 1,2-DCE or PhMe, were also potent reaction media, albeit giving reduced yields (entries 2–3). Different carboxylate bases, such as KOAc and NaOPiv, led to slightly lower efficacy (entries 4–5). When a catalytic amount of carboxylic acid additive AcOH and $K_2CO_3$ were employed, the efficacy was significantly diminished (entry 6). The cyclometalated complex $[(C\Lambda N)Ru(MeCN)_4][(PF_6)]$[20] delivered the product **3aa** albeit with reduced yield (entry 7). The cationic ruthenium (II) complex $[Ru(NCtBu)_6][PF_6]_2$ as well as other ruthenium sources, such as $RuCl_3{\cdot}nH_2O$ and $Ru_3(CO)_{12}$, failed to efficiently catalyze the reaction (entries 8–10). Control experiments verified the essential role of the ruthenium catalyst (entry 11), the base (entry 12) and the photo irradiation (entry 13).

With the optimized conditions in hand, the versatility of the photo-induced ruthenium-catalyzed benzylation reaction was examined with differently substituted benzyl chlorides **2** (Scheme 1). Arenes with electron-donating and electron-withdrawing substituents were fully tolerated in all positions of the

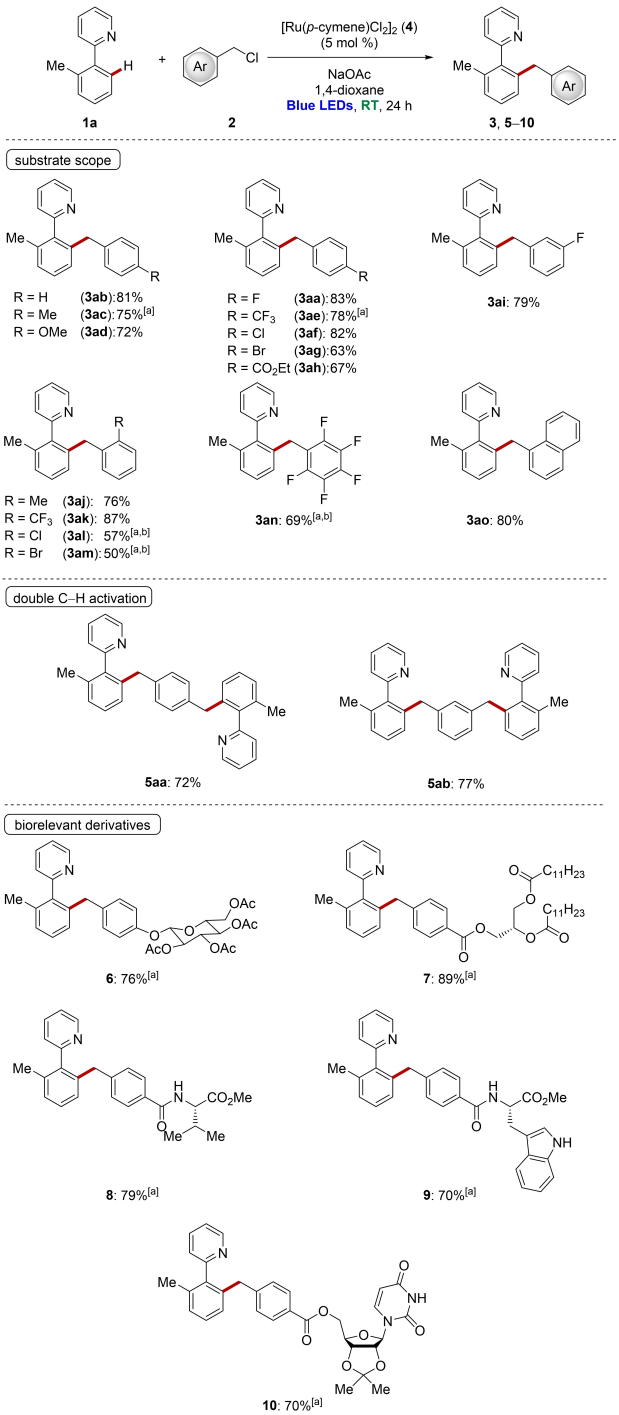
**Table 1.** Optimization of photo-induced C–H benzylation.




1a 2a 3aa

| Entry | Deviation from the standard conditions | Yield [%][a] |
|---|---|---|
| 1 | none | 83 |
| 2 | PhMe instead of 1,4-dioxane | 45 |
| 3 | 1,2-DCE instead of 1,4-dioxane | 76 |
| 4 | KOAc instead of NaOAc | 74 |
| 5 | NaOPiv instead of NaOAc | 77 |
| 6 | $AcOH/K_2CO_3$ instead of NaOAc | 24[b,c] |
| 7 | $[(C\Lambda N)Ru(MeCN)_4][(PF_6)]$ instead of **4** | 66[d] |
| 8 | $[Ru(NCtBu)_6][PF_6]_2$ instead of **4** | – |
| 9 | $RuCl_3{\cdot}nH_2O$ instead of **4** | 8[c] |
| 10 | $Ru_3(CO)_{12}$ instead of **4** | 3[c] |
| 11 | no [Ru] | – |
| 12 | no NaOAc | 8[c] |
| 13 | no light | – |

[a] Reaction conditions: **1a** (0.50 mmol), **2a** (0.75 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol%), NaOAc (1.00 mmol), 1,4-dioxane (2.0 mL), 30–33 °C, 24 h, under $N_2$, blue LEDs; yield of isolated products. [b] AcOH (30 mol%) and $K_2CO_3$ (1.00 mmol). [c] The conversion was determined by $^1H$ NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [d] $[(C\Lambda N)Ru(MeCN)_4][(PF_6)]$ (10 mol%) without light ($C\Lambda N{=}C_6H_4(CH_2)NMe_2$).




**Scheme 1.** Photo-induced ruthenium(II)-catalyzed C–H benzylation at room temperature. [a] Regioisomers (3–8%) were also formed.[19] [b] $ArCH_2Br$ was used.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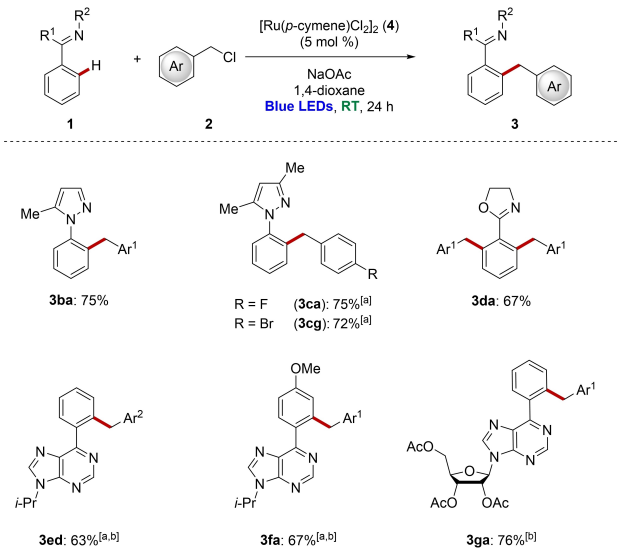
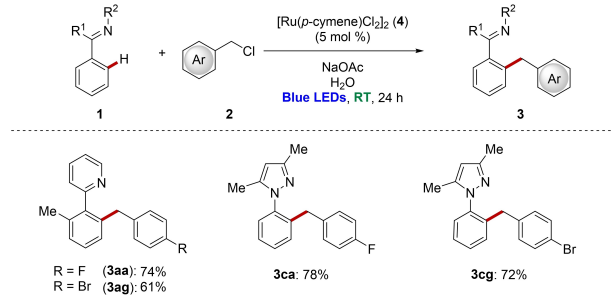
electrophile substrate (**3aa**–**3an**). The ruthenium-catalyzed benzylation proved to be widely applicable and substrates with sensitive functional groups, such as ester (**3ah**), chloro (**3af**, **3al**) and bromo (**3ag**, **3am**) were efficiently converted. Furthermore, the ruthenium catalysis at ambient temperature proved to be applicable to twofold C–H functionalization to furnish products **5aa** and **5ab**. The broad functional group tolerance was further demonstrated with electrophiles bearing sensitive, biorelevant moieties, such as monosaccharide (**6**), triglyceride (**7**), amino acids (**8**, **9**) as well as nucleosides (**10**).

The C–H benzylation under irradiation of blue LED was not restricted to the assistance of pyridines (Scheme 2). In contrast, also transformable pyrazoles (**3ba**-**3cg**), oxazoline (**3da**) and biorelevant purines (**3ed**-**3ga**) were identified as suitable substrates under the exogenous photocatalyst-free conditions.[21]

The photo C–H activation reaction could also be efficiently performed on water (Scheme 3) as a non-toxic medium. It is noteworthy that the sensitive bromo-substituted benzyl chloride **2g** was selectively transformed.




**Scheme 2.** Scope for visible-light-enabled ruthenium-catalyzed C–H benzylations. $Ar^1 = 4\text{-}C_6H_4F$, $Ar^2 = 4\text{-}C_6H_4OMe$ [a] Regioisomers (2–7%) were also formed.[19] [b] 1,2-DCE as solvent.

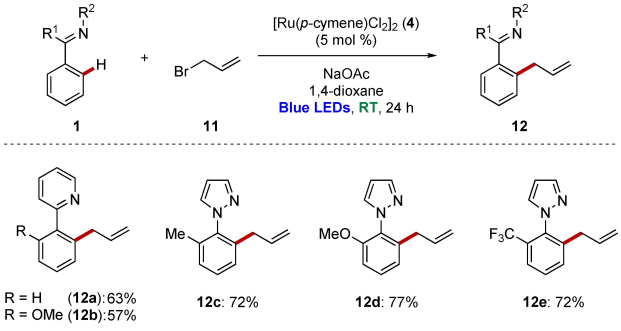



**Scheme 3.** Examples for photo-induced C–H benzylation on water.

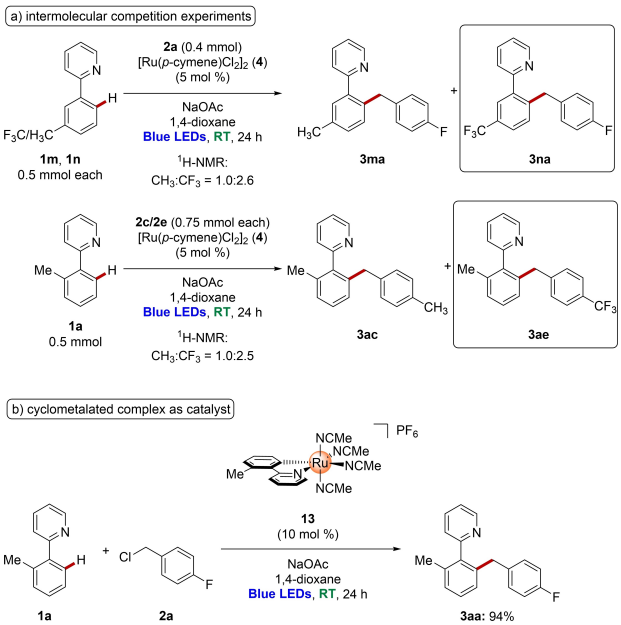
The versatility of the room-temperature photochemical C–H functionalization was further demonstrated by C–H allylations of arenes **1** with allyl bromide (**11**) at ambient temperature (Scheme 4). Electron-donating as well as electron-withdrawing substituents on the arenes **1** were notably fully tolerated.

Given the synthetic utility of our room-temperature C–H benzylation and allylation, we became interested in rationalizing its mode of action. To this end, intermolecular competition experiments were performed (Scheme 5a), and the reaction of the *meta*-substituted arenes **1** showed a preference for the electron-poor substrate **1n**. Electronically different benzyl chlorides **2** were employed in the competition experiment, revealing a more efficient conversion of the electron-poor substrate. Arene-free ruthenacycles **13**[20,22] likewise delivered the corresponding product **3aa** (Scheme 5b). These findings were suggestive of a carboxylate-ligated, arene-ligand-free ruthenacycle as a key intermediate in the C–H benzylation.

To further elucidate the key role of the blue light irradiation, an on/off experiment was conducted (Figure 2). The formation of the *ortho*-benzylated product was strongly suppressed in the




**Scheme 4.** Scope for photo-induced C–H allylation.




**Scheme 5.** Key mechanistic studies.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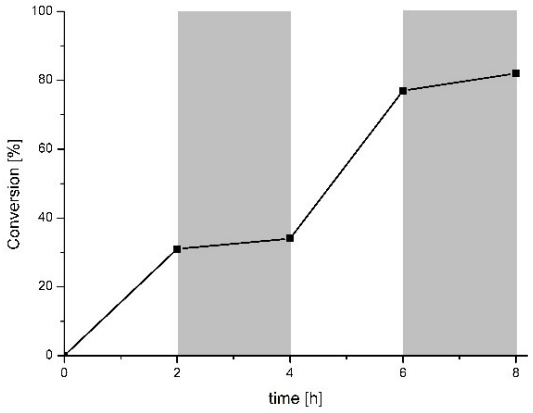
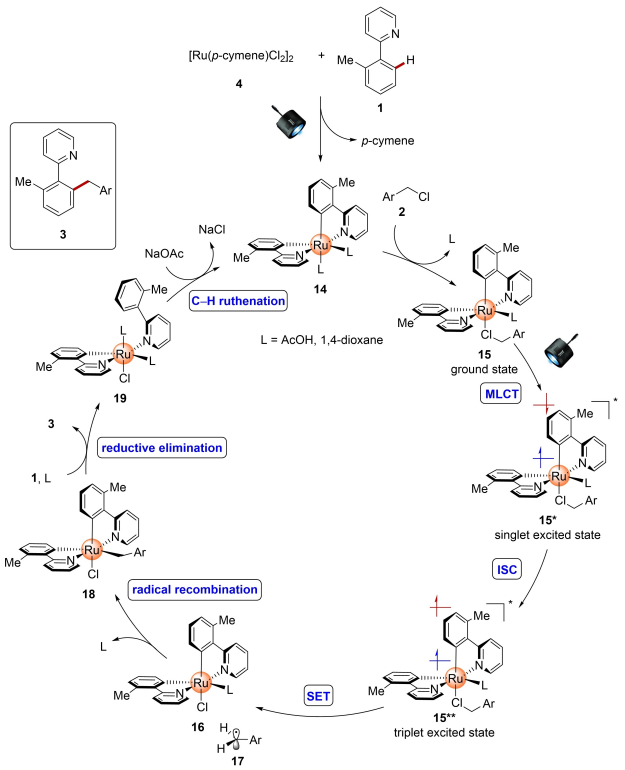



**Figure 2.** On/off experiment.

absence of light, being indicative of the C–H benzylation not being a radical chain process. In addition, reactions in the presence of radical scavengers led to the formation of the corresponding product in significantly reduced yields.[19]

Based on our mechanistic studies and previous findings,[17a,16a] a plausible catalytic cycle is proposed in Scheme 6. The mechanism commences by dissociation of the *p*-cymene ligand from the precursor and twofold carboxylate-assisted C–H ruthenation generates the biscyclometalated species **14**. After coordination of the benzyl chloride **2**, the ruthenium complex **15** is formed, which can be excited by absorption of blue light to the singlet excited species **15***. Subsequent relaxation through intersystem crossing (ISC) results in a long-lived triplet ruthenacycle **15****. An inner-sphere electron transfer (ISET) to benzyl chloride yields a benzyl radical **17** and the ruthenium(III) intermediate **16**. Fast radical recombination affords the stable ruthenium(IV) complex **18**, which undergoes reductive elimination and ligand exchange, delivering the benzylated product **3** and and the monocyclometallated species **19**, which undergoes C–H activation, regenerating the catalytically active complex 14.




**Scheme 6.** Plausible catalytic cycle.

## Conclusion

We have developed the unprecedented visible-light-enabled ruthenium-catalyzed C–H benzylations at ambient temperature. This robust, versatile photoredox C–H activation featured ample scope under exceedingly mild conditions. The excellent functional group tolerance was demonstrated by late-stage transformations of biorelevant substrates.

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## Conflict of Interest

The authors declare no conflict of interest.

**Keywords:** C–H activation · diarylmethane · photocatalysis · photoredox · ruthenium

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