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Activation Relay on Rhodium-Catalyzed C−H Aminomethylation in Cooperation with Photoredox Catalysis

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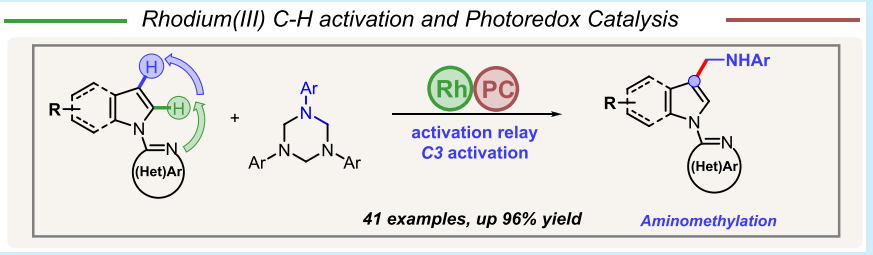
Supporting Information



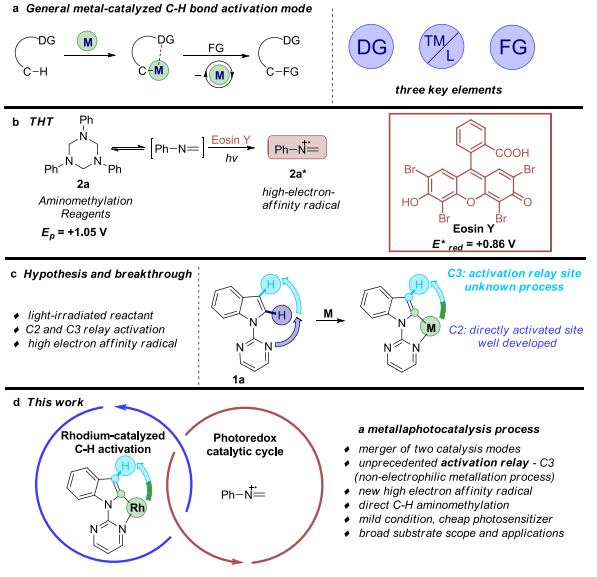
ABSTRACT: A site selective C−H aminomethylation at indole's C3 position has been achieved by merging rhodium(III)-catalyzed C−H activation and photoredox catalysis in a one-pot manner. An investigation of the mechanistic insights rationalized the essence of the activation relay and the combination mode.

Direct constructions of carbon−carbon (C−C) bonds and carbon−hetero (C−X) bonds from C−H bonds are highly efficient, atom- and step-economical processes.[1] Extensive research into the design of diversified directing groups (DG), ligands (L), and ingenious synthetic strategies and the development of transition metal (TM) catalysts such as palladium,[2] rhodium,[3,4] ruthenium,[5] and others[6] have made C−H bond activation more sophisticated and practical (Scheme 1a). Photoredox catalysis plays a pivotal role in synthetic events because it can provide easy access to reactive radical or cationic species under mild conditions from abundant and native functional groups (FG).[7] When these two powerful synthetic methods were taken together, innovative activation modes could be established in C−H bond functionalizations.[8]

The aminomethylated moiety, considered as the modified amino group, is a crucial component and functional group in a wide range of medicinally relevant compounds, including pharmaceuticals, agrochemicals, and bioactive natural products.[9] Amino reagents, such as organic azide,[10] dioxazolone,[11] and isocyanate,[12] have been extensively used to build C−N bonds in the C−H functionalizations. However, aminomethylation has been rarely reported in metal-catalyzed C−H bond activations.[13] Triphenylhexahydrotriazine (THT), an equivalent to imine, can be easily accessed from aniline and paraformaldehyde under mild conditions. As a tertiary amine or an imine equivalent (after dissociation), it can be excited and oxidized by a photosensitizer to generate the corresponding cationic radical intermediate **2a***, which is a highly electrophilic species (Scheme 1b).

Because the C−H bond of indole's C2 position can be activated by a transition metal catalyst with the assistance of an N-tethered directing group, we envisioned that the merger of these two catalytic cycles into one process would yield a new C−H bond activation mode for indole **1a** through an activation relay. This working hypothesis is based on the following. (i) In the classical activation mode, C−H bond functionalizations at indole's C2 position have been well developed using pyrimidine as the directing group.[14] The generation of a unique

Scheme 1. C−H Bond Activation and Our Working Hypothesis



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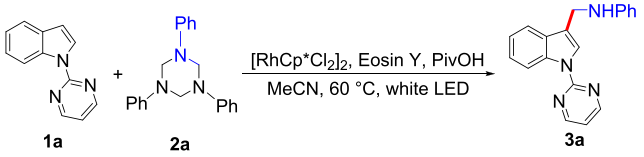
functionalization reagent (FG) upon photoredox catalysis might lead to a breakthrough with regard to the traditional activation modes. (ii) THT (E_p = 1.05 V) could be oxidized with an appropriate photosensitizer.[15] In this respect, we need to address several challenges to realize this breakthrough, such as the selection of the appropriate metal catalyst in the first step of C−H bond activation at the C2 position and the matched photosensitizer to generate the desired active imino species (Scheme 1c).

To our delight, the merger of these two catalysis modes is successful in the site selective C−H aminomethylation at the C3 poisition of indole using pyrimidine as a directing group (Scheme 1d). Because this occurrence of C3 aminomethylation of indole is initiated by Rh-catalyzed C−H bond activation at the C2 position, we termed this C−H activation mode the activation relay. In this C−H bond functionalization, we reckoned that the C3 position is also partially activated by the rhodium catalyst in the formed cyclometalated species. A further illustration of this concept will be presented in the mechanistic investigation section.

Our studies commenced with easily available indole **1a** (0.1 mmol, 1.0 equiv) and THT **2a** (0.05 mmol, 0.5 equiv) as the model substrates, $[Cp^*RhCl_2]_2$ and Eosin Y as the catalyst combination, and pivalic acid as an additive in acetonitrile (1.0 mL) at 60 °C upon irradiation with white light-emitting diode (LED) light for 5 h, giving desired aminomethylation product **3a** in 95% yield (Table 1, entry 1). The structure of product **3a** was

Table 1. Examination of the Reaction Conditions[a]



1a 2a 3a

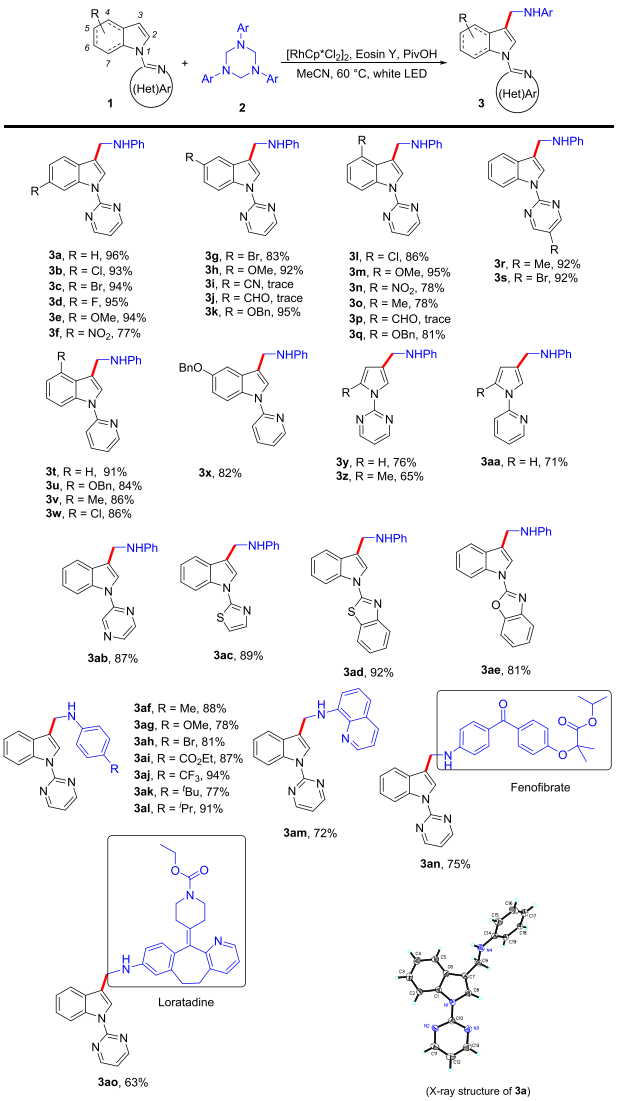
entry[b]	catalyst	yield (%)[c]
1	standard conditions	95
2	without $[RhCp^*Cl_2]_2$	0
3	without Eosin Y	0
4	without PivOH	33
5	*fac*-Ir(ppy)$_3$ instead of Eosin Y	17
6	Rose Bengal instead of Eosin Y	0
7	fluorescein instead of Eosin Y	0
8	other metal catalysts instead of $[Cp^*RhCl_2]_2$[d]	0
9	DCE instead of MeCN	93
10	25 °C instead of 60 °C	41

[a]Reaction conditions: **1a** (0.10 mmol), **2a** (0.05 mmol), PivOH (0.20 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), Eosin Y (20 mol %), MeCN (1.0 mL), 60 °C, 12 h, ambient atmosphere. [b]All of the reactions were carried out on a 0.10 mmol scale in solvent (1.0 mL) at 60 °C for 12 h unless otherwise specified. [c]Isolated yield. [d]Other metal catalysts are $[Cp^*IrCl_2]_2$, $[Cp^*Co(CO)I_2]$, and $[Ru(p\text{-cymene})Cl_2]_2$.

determined by its X-ray diffraction. The examination of the necessity of these catalysts revealed that the catalyst combination of $[Cp^*RhCl_2]_2$ and Eosin Y is essential in this reaction, indicating the activation relay at the C3 position through this cooperative catalysis (Table 1, entries 2 and 3). The use of pivalic acid can significantly improve the yield of **3a** (Table 1, entry 4). Other photosensitizers, including a metal−polypyridyl complex and organic dyes, were also examined, and we found that *fac*-Ir(ppy)$_3$ was less effective than Eosin Y; however, the use of Rose Bengal and fluorescein did not give the desired product (Table 1, entries 6−8). The use of organic dyes[16] as photosensitizera is our first choice because they are practically useful and much cheaper than metal−polypyridyl complexes such as *fac*-Ir(ppy)$_3$ and suitable for ambient atmosphere without deterioration. Eosin Y [$E^T(S^*/S^{\bullet-})$ = 0.86 V vs a saturated calomel electrode (SCE) in acetonitrile] has a wide range of applications and excellent catalyst performance in the family of xanthene dyes. Although its potential is lower than that of THT, Eosin still can oxidize THT due to its dissociation equilibrium in the solvent. The other transition metals were tested instead of Rh(III), but no reactions occurred using these metal catalysts (Table 1, entry 8). An examination of solvent effects revealed that 1,2-dichloroethane (DCE) is an alternative option in this transformation (Table 1, entry 9). Temperature is also crucial to this transformation because the reaction becomes sluggish if it is carried out at 25 °C (Table 1, entry 10). In addition, we have also tested several LEDs with different powers and identified no influence on the yield of **3a**.[17]

Having established the optimal reaction conditions, we next began to investigate the substrate scope of various substituted indoles, and the results are shown in Scheme 2. When indoles

Scheme 2. Substrate Scope



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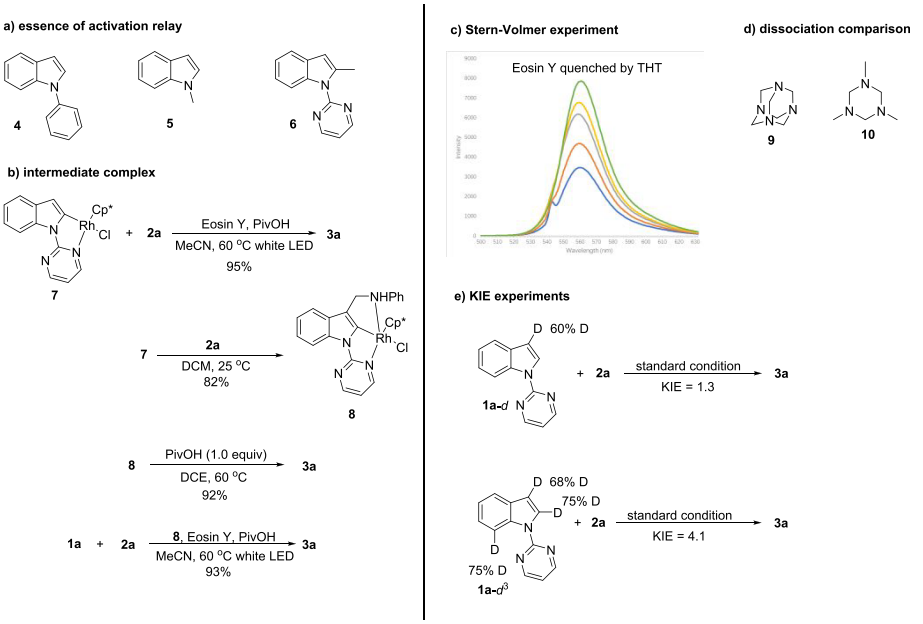
Scheme 3. Control Experiments



bearing a pyrimidine directing group were substituted with halogen atoms, Me, OMe, NO_2, and OBn at positions C4−C6, the reactions proceeded smoothly to furnish corresponding aminomethylation products **3** in moderate to good yields ranging from 77% to 96%. When indole was substituted with CN (substrate **1i**) and CHO (substrates **1j** and **1p**), no reaction occurred presumably due to the fact that they can interfere with the excited Eosin Y. We also examined the scope of other directing groups such as pyridine, other pyrimidine derivatives, and heterocycles containing a nitrogen atom. The use of pyridine as a directing group afforded aminomethylated products **3t**−**3x** with results similar to those seen upon using pyrimidine as a directing group. Other pyrimidine derivatives could also deliver desired products **3r** and **3s** in good yields under the standard conditions. To our delight, this protocol could be extended to other heterocycles containing a nitrogen atom. For example, indoles using pyrazine, thiazole, benzothiazole, and benzoxazole as directing groups afforded products **3ab**, **3ac**, **3ad**, and **3ae**, respectively, in good yields. The substrates could be changed from indole to pyrrole with pyrimidine or pyridine as a directing group, furnishing desired products **3y**−**3aa** in moderate yields ranging from 65% to 76%. In addition, we also investigated the scope of THTs. A range of THTs with a variety of substituents at the *para* position of the benzene ring was tested, affording desired products **3af**−**3al** in good yields ranging from 77% to 94%. The electronic property of these substituents did not significantly impact the reaction outcome regardless of whether they are electron-donating or -withdrawing ones. In the case of THT containing a heterocycle like quinoline, the reaction also proceeded efficiently, providing desired product **3am** in 72% yield. Furthermore, this novel aminomethylation process is compatible with the late-stage modification of two drugs, fenofibrate and loratadine, affording corresponding products **3an** and **3ao** in 75% and 63% yields, respectively. All of these results demonstrated a broad substrate scope and good functional group tolerance in this aminomethylation process.

To gain more insights into the reaction mechanism, several control experiments were performed. It has been well-known that indole can undergo electrophilic metalation, such as electrophilic palladation, at position C3 also to afford the C3-functionalized product.[18] Thus, we replaced the pyrimidine directing group with a benzyl group (substrate **4**) or methyl group (substrate **5**), which cannot be used as a directing group because neither has a coordination atom. We also introduced a methyl group at position C2 (substrate **6**) to block out the Rh(III)-catalyzed C−H bond activation forming cyclometalated species. These experiments all failed to give the corresponding products, suggesting that the C−H activation step is indispensable and the possibility of electrophilic metalation can be ruled out (see Scheme S1 for more details) (Scheme 3a).[18] Therefore, the activation relay is in principle not an electrophilic metalation pathway. Furthermore, according to ref 14d, we prepared the corresponding cyclometalated complex **7** in the C−H activation step and identified that treating complex **7** with **2a** could produce **3a** in 95% yield under the standard conditions (Scheme 3b). We next attempted to isolate the key intermediate of this reaction. Fortunately, stirring complex **7** and **2a** in DCM at room temperature gave complex **8** in 82% yield (Scheme 3b). Protonolysis of complex **8** by PivOH at 60 °C afforded desired product **3a** in 92% yield (Scheme 3b). Furthermore, complex **8** could be also used to replace $[Cp^*RhCl_2]_2$ as the catalyst, giving **3a** in 93% yield under otherwise identical conditions. All of these control experiments suggested that complex **8** may be the real active catalytic species in the mechanistic paradigm.

The Stern−Volmer experiment indicated that the fluorescence of Eosin Y was quenched by **2a**, suggesting the SET process between Eosin Y and **2a** gives a high-electron affinity cationic radical species **2a*** (Scheme 3c).[15,19] At the same time, the nucleophilicity of position C3 was enhanced in cyclometalated complex **7**.[20] The two factors resulted in site selective C−H activation taking place exclusively at position C3. Moreover, several other experiments were conducted to investigate the SET process of Eosin Y and **2a**. First, using hexamethylenetetramine **9** or methyl group-substituted THT **10** instead of THT, the reaction did not take place, perhaps because **9** and **10** are unable to dissociate to give the reactive monomer

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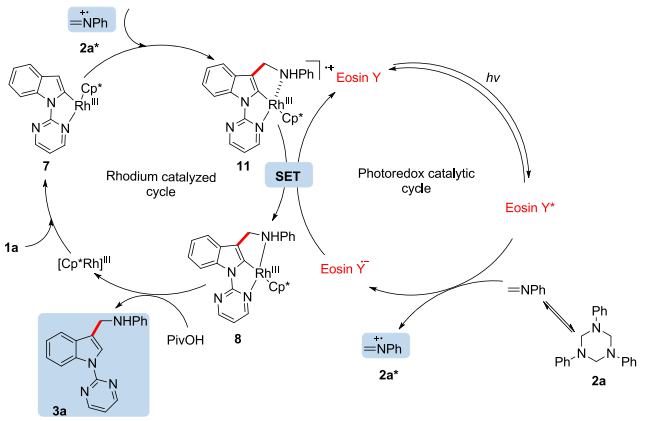
under the reaction conditions (Scheme 3d).[21] The kinetic isotope effect (KIE = 1.3) observed in parallel reactions using **1a** and **1a**-*d* suggested that C−H activation at position C3 is not the rate-limiting step (Scheme 3e). On the contrary, the kinetic isotope effect (KIE = 4.1) observed in parallel reactions using **1a** and **1a**-d^3 indicated that C−H bond activation at position C2 catalyzed by the Rh(III) catalyst was the rate-limiting step (Scheme 3e).

On the basis of generally accepted mechanisms of C−H bond activation and the conducted control experiments, a plausible mechanistic paradigm was proposed (Scheme 4). Eosin Y was

Scheme 4. Proposed Mechanism

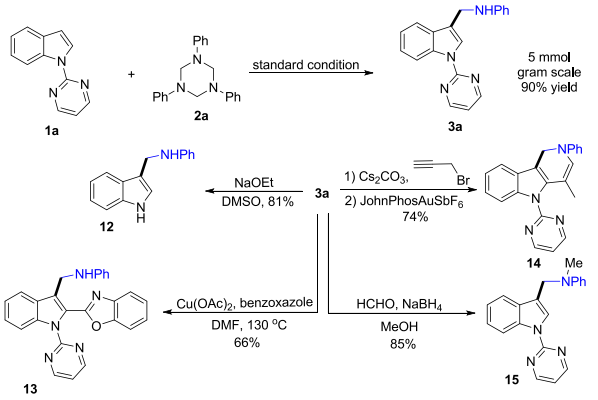


excited upon photoirradiation with LED light, and THT **2a** was oxidized by Eosin Y* to give cationic radical species **2a***, which is a high-electron affinity species. Substrate **1a** was activated by the rhodium(III) complex with the assistance of PivOH to deliver cyclometalated complex **7**, which reacted with **2a*** to afford rhodium species **11**. A SET process between **11** and Eosin $Y^{\bullet-}$ furnished rhodium(III) species **8** and regenerated Eosin Y. Rhodium(III) complex **8** underwent a proton demetalation by pivalic acid to regenerate the Rh(III) catalyst and release desired product **3a**. Increasing the reaction temperature could accelerate the proton demetalation process. High-electron affinity cationic radical species **2a*** and the activation relay dominated this specific site selectivity.

The synthetic utility of obtained aminomethylation product **3a** was briefly examined. This new aminomethylation procedure could be conveniently performed in a gram scale manipulation, giving desired product **3a** in 90% yield. Removal of a pyrimidine directing group was readily achieved upon treatment with NaOEt in DMSO to afford corresponding product **12** in 81% yield. Considering the fact that C2 unsubstituted indole can undergo a C−H bond activation process again, we introduced a benzoxazole moiety at position C2 under the catalysis of $Cu(OAc)_2$ to afford product **13** in 66% yield.[22] Treatment of **3a** with propargyl bromide in the presence of Cs_2CO_3 and subsequently with a gold(I) catalyst gave carbazole derivative **14** in 74% yield. In addition, reductive amination of **3a** with formaldehyde and $NaBH_4$ in methanol provided methylated product **15** in 85% yield (Scheme 5).

In summary, we have successfully developed a cooperative catalytic system by merging rhodium-catalyzed C−H activation and photoredox catalysis into one reaction system in a unique way. The site selective aminomethylation for the C−H bond at indole's C3 position can be achieved using THT as the reactant and using $[Cp^*RhCl_2]_2$ as the C−H bond activation catalyst at

Scheme 5. Synthetic Application



position C2 as well as using Eosin Y as a photosensitizer in the photoredox catalysis. Efforts to apply this novel metal-laphotocatalysis to synthesize other useful compounds are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01261.

Experimental procedures and characterization data for all compounds (PDF)

Accession Codes

CCDC 1552046 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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