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Direct C-H Arylation of Aldehydes by Merging Photocatalyzed Hydrogen-atom Transfer with Palladium Catalysis

Lu Wang,[a,b,†] Ting Wang,[c,e,†] Gui-Juan Cheng,[c] Xiaobao Li,[a] Jun-Jie Wei,[b] Bin Guo,[b] Caijuan Zheng,[a]

Guangying Chen,[a] Chongzhao Ran,[d] Chao Zheng[a, d*]

[a]Key Laboratory of Tropical Medicinal Resources Chemistry of Ministry of Education, Key Laboratory of Tropical

Medicinal Plant Chemistry of Hainan Province, College of Chemistry and Chemical Engineering, Hainan Normal University,

Haikou 571158, China

[b]Center of Cyclotron and PET Radiopharmaceuticals, Department of Nuclear Medicine and PET/CT-MRI Center, The First

Affiliated Hospital of Jinan University, 613 West Huangpu Road, Tianhe District, Guangzhou 510630, China

[c]Warshel Institute for Computational Biology, School of Science and Engineering, School of Life and Health Sciences, The

Chinese University of Hong Kong, Shenzhen, 518172, PR China

[d]Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital and Harvard Medical School,

Boston, MA, 02129, USA

[e]Department of Chemistry, University of Science and Technology of China, Hefei, 230026, PR China

Supporting Information Placeholder

ABSTRACT: Herein we report that merging palladium catalysis with hydrogen-atom transfer (HAT) photocatalysis enabled direct arylations and alkenylations of aldehyde C-H bonds, facilitating visible-light catalyzed construction of a variety of ketones. Tetrabutylammonium decatungstate (TBADT) and anthraquinone (AQ) were found to act as synergistic hydrogen-atom transfer photocatalysts. DFT calculations suggested a $Pd^0–Pd^{II}–Pd^{III}–Pd^I–Pd^0$ pathway and revealed that regeneration of the Pd^0 catalyst and the photocatalyst occurs simultaneously in the presence of $KHCO_3$. This regeneration features a low energy barrier, promoting efficient coupling of the palladium catalytic cycle with the photocatalytic cycle. The work reported herein suggests that further applications of HAT photocatalysis in palladium-catalyzed cross-coupling and C-H functionalization reactions show great promise to be successful.

KEYWORDS: palladium catalysis, HAT photocatalyst, hydrogen-atom transfer, C-H functionalization, ketone synthesis, DFT calculation

Aldehyde C–H bonds can be directly functionalized by coupling them with a carbon electrophile, such as readily available aryl and alkenyl halides under palladium catalysis, as an ideal way to synthesize ketones[1-11], which are ubiquitous functionalities with important applications in pharmaceuticals, natural products, organic materials, photosensitizers, flavors, and fragrances[12-14]. Due to its high bond dissociation energy and low acidity, aldehyde C-H bond structure is particularly challenging to alter under palladium catalysis[15-19]. Kuninobu and Kanai recently reported a palladium-catalyzed aldehyde C-H arylation at high temperature, wherein a newly designed ligand was used to facilitate deprotonative C-H functionalization of the aldehyde C-H bond on a Pd^{II} center to achieve a variety of ketone syntheses[15]. However, this protocol exploiting picolinamide ligand gave diminishing yields of aliphatic aldehydes featuring C-H bonds of high pKa. Other methods for direct arylations of aldehyde C-H bonds include palladium catalysis with pyrrolidinones as examined by Xiao[16], nickel catalysis through a carbonyl Heck mechanism as reported by Newman[4, 20], and most recently, disclosed iridium photoredox catalysis merged with nickel as well as HAT catalysis by MacMillan[2].

Our on-going interest in developing palladium catalyzed synthesis of carbonyl compounds from halides, as well as our recent discoveries of palladium catalysis under visible light[21-23], inspired us to propose that a combination of suitable HAT photocatalyst and palladium catalyst would enable direct functionalization of aldehyde C-H bonds with aryl halides under mild reaction conditions, as depicted in Fig. 1. In this scheme, the photo-excited HAT catalyst (**II**) abstracts formyl hydrogen to generate an acyl radical, which is subsequently trapped by a palladium species (**VI**) and undergoes reductive elimination to form an acyl–carbon bond. The reduced HAT photocatalyst (**I**) may further reduce the palladium (**III**) species (**VII**) or Pd (**I**) species through proton elimination, thereby completing the palladium

catalytic cycle. With this hypothesis in mind, we focused our efforts on tetrabutylammonium decatungstate (TBADT) [24-28] and anthraquinone (AQ), which were discovered to be viable HAT photocatalysts[29-30] to merge with palladium catalysis for direct aldehyde C-H arylations and alkenylations to synthesize ketones. Aryl halides and aryl triflates were both suitable substrates. The reactions reported herein represent a new type of relay catalysis. Our findings suggest great promise for further applications of HAT photocatalysis in conjunction with palladium catalyzed cross-coupling as well as C-H functionalization reactions.

(a) *Structures of HAT photocatalysts*

tetrabutylammonium decatungstate (TBADT)   anthraquinone (AQ)
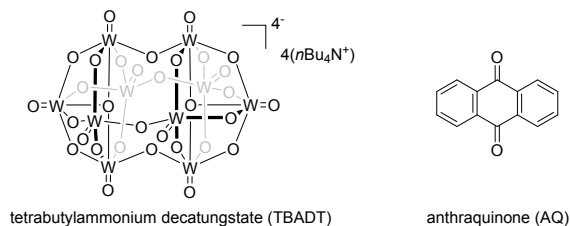
(b) *Proposed catalytic cycles for the aldehyde C-H arylation*
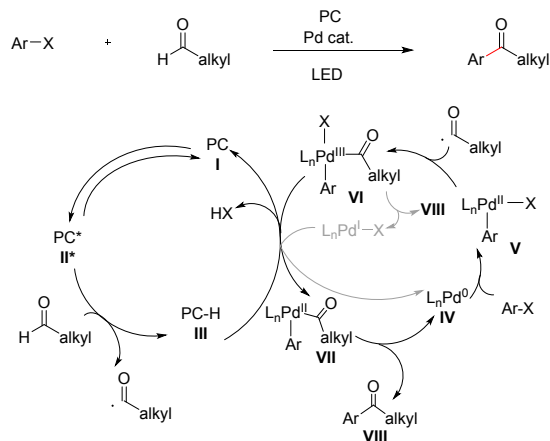
Figure 1. Merging HAT photocatalysis with Pd catalysis for C–H arylation of aldehyde.

Screening of reaction conditions for C-H arylation of aldehyde.

A series of commercially available diaryl ketones and organic dyes were screened for their ability to absorb light and activate C-H. TBADT and AQ were predicted to be good candidates for direct C-H arylations of aldehydes (Scheme S1). The optimized reaction conditions were identified and are given by the equation at the top of Table 1. A slight reduction in yield was observed when the amount of aldehyde **2** was adjusted to be stoichiometrically equal to that of aryl **1** (entry 2). Exchanging Pd(OAc)$_2$ for other palladium catalysts (entries 3 and 4) failed to initiate the reaction. Judicious selections of phosphine ligands and bases are evidently crucial to achieve desirable reactivities (entries 5-8). Acetone was demonstrated to obtain superior yields compared to other aprotic polar solvents, such as acetonitrile or DMA, which retarded the reaction effectiveness (entries 9 and 10). Extending the reaction time and reducing the concentration were both found enhance yield (entries 11 and 12). In addition, no reaction occurred in the absence of light irradiation. Control experiments also verified the indispensable roles of the photocatalyst, palladium catalyst, and ligand in initiating the reaction (entries 13-15), indicating that a direct radical redox pathway is impossible. Reactivity was completely quenched in an oxygen atmosphere, probably reflecting the reaction of triplet oxygen with the excited photoredox catalyst or a reactive intermediate such as acylpalladium species (entry 16).

Table 1. Optimization of the reaction conditions[a]

entry	variations from indicated conditions	yield (%)[b]
1	none	71
2	**2** (100 mol%)	62
3	Pd$_2$(dba)$_3$ instead of Pd(OAc)$_2$	trace
4	Pd(PPh$_3$)$_4$ instead of Pd(OAc)$_2$	n.r.
5	BINAP instead of Xantphos	13
6	Ni-Xantphos instead of Xantphos	56
7	K$_2$CO$_3$ instead of KHCO$_3$	trace
8	NaHCO$_3$ instead of KHCO$_3$	51
9	acetonitrile instead of acetone	18
10	DMA instead of acetone	43
11	t = 48 h	82
12	5 mL of acetone, t = 48 h	88
13	without TBADT	n.r.
14	without light	n.r.
15	without Pd(OAc)$_2$	n.r.
16	with Air	n.r.

[a]Reaction performed at ambient temperature under argon atmosphere and irradiation by Kessil lamp. [b]Yields determined by ^{1}H NMR using diphenylmethane as an internal standard.

In addition, this transformation was entirely suppressed with addition of stoichiometric amount of TEMPO as acyl-TEMPO species was observed (see Supporting Information).

Remarkably, the optimization of AQ gave similar results, although notably, AQ was equally effective in response to irradiation by 427 nm light. Control experiment showed that the reaction did not proceed at all in the absence of AQ (see Supporting Information). These conditions are depicted in Fig. 2.

Figure 2. Optimized conditions for HAT/Pd catalyzed C-H arylation of aldehyde.
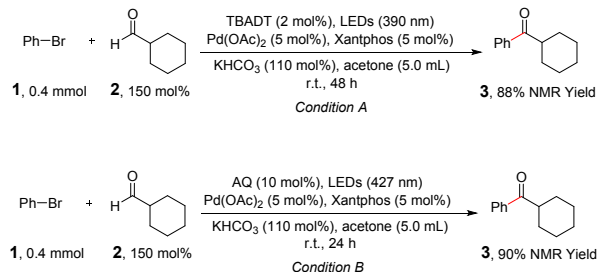
Scope of substrates with alkyl/aryl aldehydes. The scope of compatible aldehyde structures was revealed to be broad (Fig. 3). Acyclic secondary aldehydes (**5**, **7**), linear primary aldehydes (**4**, **8**), and even sterically bulkier primary aldehyde (**6**) could all be readily converted into their corresponding ketone products. Moreover, alkyl aldehydes with a diverse array of functional
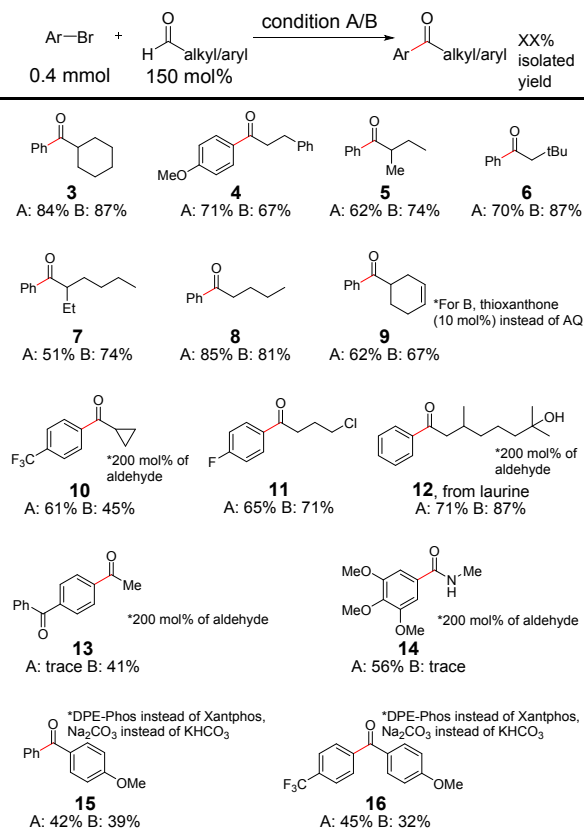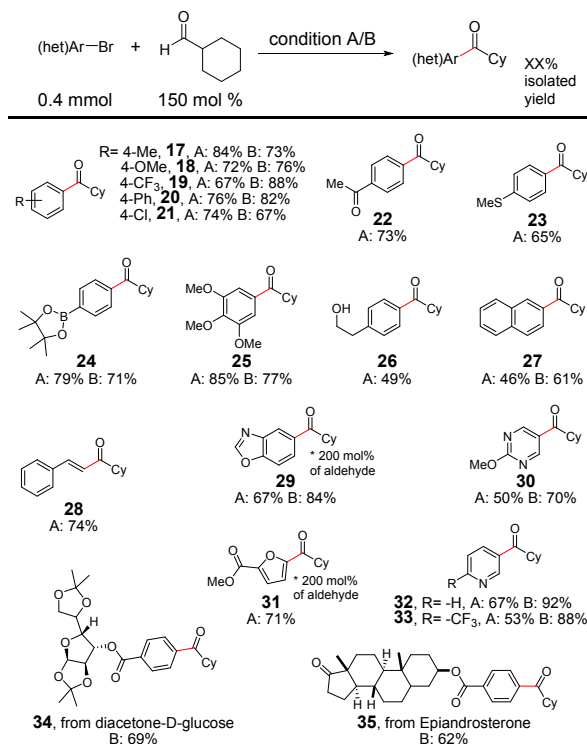
Figure 3. Substrate scope with respect to aldehyde.

groups, including carbon-carbon double bonds (**9**, **10**), cyclopropane (**10**), halides (**11**), and alcoholic hydroxyl groups in bio-perfume (**12**), were demonstrated to be suitable substrates. A thioxanthone photocatalyst also enabled a satisfactory yield (66%) of 9 to be obtained. Acetaldehyde (**13**), which is extremely volatile, delivered a somewhat lower yield. Notably, the aldehyde group of N-methylformamide (**14**) was found to be capable of serving as the coupling partner. Moderate yields were obtained for 4-methoxybenzaldehyde (**15-16**). For bezaldehyde and 4-trifluoromethylbenzaldehyde, the C-H arylation reactions with 4-bromoanisole were not successful. The very similar BDEs of C(O)-H bonds of aliphatic aldehyde and benzaldehyde will not cause a large difference in HAT rate.[17] We consider a possible explaination for the poor performance of aryl aldehydes is a concomitant decarbonylation process of ArC(O)–Pd species that poisons the palladium catalyst.

Scope of substrates with (hetero)aromatic bromides. Suitable precursors for the reaction system (Fig. 4) included a variety of aryl as well as heterocyclic bromides, which exhibited excellent functional group compatibility, tolerating substituted groups that are both electron withdrawing and donating (**17-23**), as well as aryl boronates (**24**), alkyl alcohol (**26**), and bromostyrene (**28**). It is noteworthy that these precursors accommodated the electrophilic sites susceptible to cross coupling reactions, such as aryl chlorides (**21**), preserving the opportunity for further functionalization. Even without additional photocatalyst, the aryl bromides containing

Figure 4. Substrate scope with respect to aryl/heterocyclic bromides.

diaryl ketone structure **22** could furnish a remarkable yield of 12%, indicating the potential for these species to effectively function as their own photocatalysts. In case where AQ was added, the yield could be increased to 73%. Interestingly, modification of the aryl bromides with natural drug molecules still obtained satisfactory yields of the corresponding products (**34**, **35**), marking a convenient springboard for biological structural editing. Several heteroaromatic bromides were also tested and found to obtain moderate to good yields of ketones with benzoxazolyl (**29**), pyrimidinyl (**30**), furanyl (**31**), and pyridyl (**32**, **33**) moieties. Altogether, these results demonstrated the complementarity of our protocol with iridium polypyridyl complexes, classical photocatalysts well known for their relatively low yields from electron-rich heteroaromatic substrates, presumably due to competitive single electron transfer (SET) processes.[31-35]

Extending the substrate scope with aryl iodides and triflates. Consideration was also given to the reactivities of aryl iodide and aryl triflate substrates, which produced relatively lowerproduct yields relative to those given by aryl bromide substrates with otherwise identical substituents. This finding is intriguing since reactivity towards oxidative addition was anticipated to be higher for aryl iodide than for aryl bromide.[36-37] Auspiciously, the addition
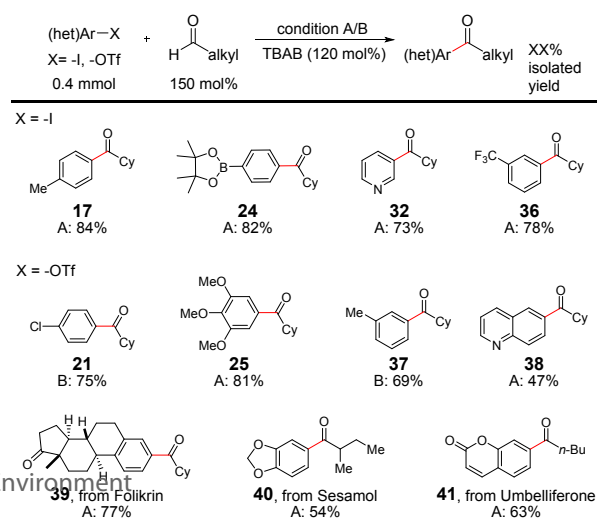
Figure 5. Substrate scope with respect to aryl iodide and aryl triflates.

of tetrabutylammonium bromide (TBAB) reduced arylation reaction time to 24 h under condition A with TBADT as the photocatalyst, as shown in Fig. 5. Moreover, yield was also greatly improved. For instance, the yield of **36** increased from 41% to 84%, possibly reflecting that the bromine radical produced by TBAB promotes C-H bond activation.[38] Furthermore, aryl iodides and aryl triflates, specifically electron-rich aryls (**17**, **25**, **37**), halogens (**36**, **21**), heteroaromatics (**32**, **38**), and boronates (**24**), were found to give satisfactory yields and good functional group compatibility. We also demonstrated the synthesis of additional natural products, which were achieved at satisfactory yields (**39**, **40**, **41**). The array of feasible reactions, including but not limited to the acylation of aryl halides and phenolic derivatives, will undoubtedly broaden the range of possible applications of this synthetic approach.

Investigation of reaction mechanism via density functional theory (DFT) calculations. DFT calculations enabled insight into the mechanisms for the generation of ketone products and for the coupling of the palladium catalytic cycle and the photocatalytic cycle. As shown in Fig. 6, abstraction of hydrogen from an aldehyde by the excited AQ reagent (*[AQ]) was the proposed origin of the acyl radical, and therefore accompanied the generation of an AQ-H radical.[28,39-41] Calculations indicated two plausible pathways for the generation of the aromatic ketone products[42-57] (Fig. 6 and Fig. 7). In path A, oxidative addition of Pd[0] catalyst precursor with aryl halide leads to a Pd[II] intermediate **INT1A**, which is then oxidized by the acyl radical to form a Pd[III] intermediate **INT2** (i.e. Pd[0]-Pd[II]-Pd[III] path). Alternatively, the Pd[0] precursor might first combine with the acyl radical to form an acyl-Pd[I] complex **INT1B**, which subsequently undergoes oxidative addition with the aryl halide to generate **INT2** (path B, Pd[0]-Pd[I]-

At this point in the reaction, we must turn our attention to the essential task of regenerating the Pd[0] catalyst and the photocatalyst (AQ) from **INT3** and AQ-H radicals, respectively, to complete the palladium catalytic cycle and the photocatalytic cycle. Because the presence of a base was found to be indispensable in order to obtain a product, we speculated that the base (i.e. KHCO₃) may play a key role in regenerating catalysts (dashed box in Fig. 6). Computational

Pd[III] mechanism). Computational results suggested that the free energy barriers of oxidative addition (**TS1A**) and the radical combination step (**TS2A**) for pathway A are 11.0 and 12.1 kcal/mol, respectively. Meanwhile, in pathway B the oxidative addition step (**TS2B**) must overcome a free energy barrier of 21.0 kcal/mol, indicating that pathway A is more favorable. The
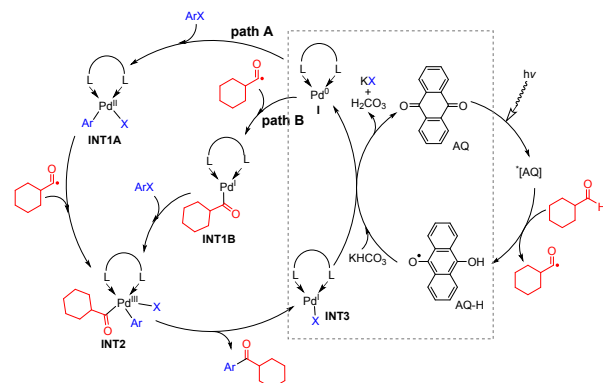
Figure 6. Proposed cross-coupling of aromatic ketones by photoredox/palladium dual catalysis.

generated Pd[III] intermediate **INT2** subsequently undergoes reductive elimination via **TS3** to produce the aromatic ketone product and the Pd[I]-Br complex **INT3**. This step is highly exergonic (ΔG‡ = −40.3 kcal/mol).

deprotonation is quite facile, rendering it much more favorable than the stepwise process (blue path in Fig. 7). **TS6** begets a triplet Pd[I]-AQ-radical **INT6**, which rapidly undergoes internal electron transfer to become a stable singlet Pd[0]-AQ intermediate **INT7**. Finally, AQ dissociates from **INT7** to regenerate the Pd[0] catalyst and photocatalyst, completing the palladium catalytic cycle and the photocatalytic cycle. The computed barrier for AQ dissociation is
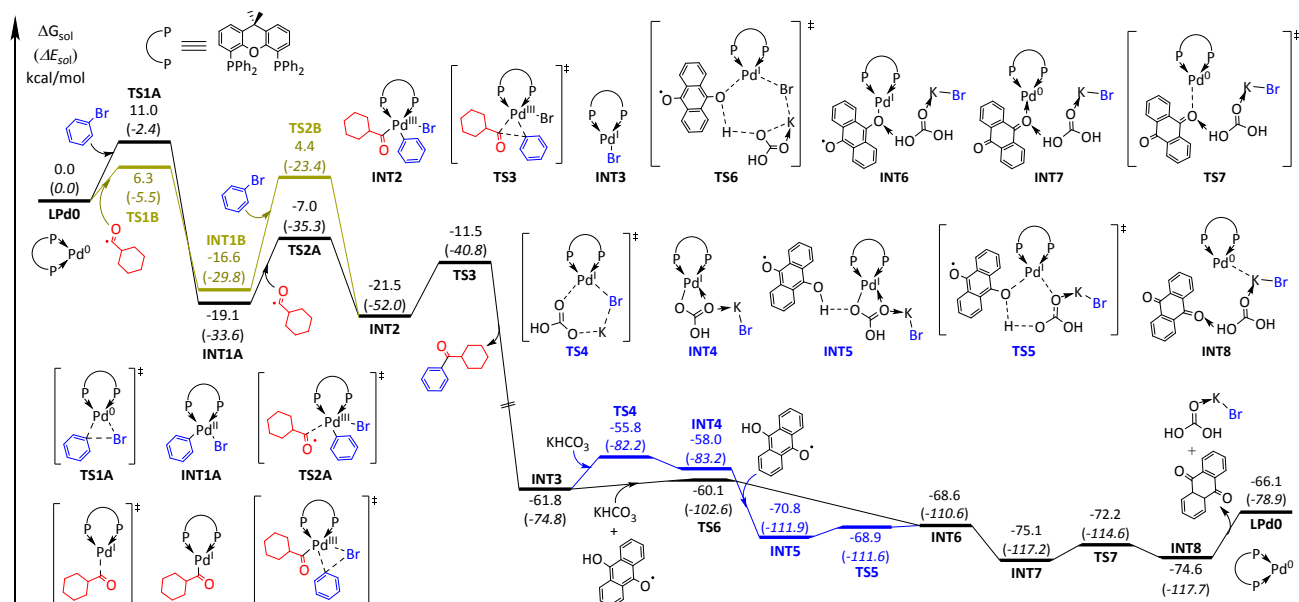
Figure 7. DFT-computed energy profiles of HAT/Pd dual catalysis for direct C-H arylation of aldehydes

results revealed an intriguing transition state **TS6** in which the base abstracts a Br atom from the Pd[I]-Br complex and a proton from AQ-H in a concerted manner. With an energy barrier of only 1.7 kcal/mol, this process for simultaneous dehalogenation and

only 2.9 kcal/mol.

Therefore, DFT calculations provide supporting evidence that the reaction pathway involves the oxidative addition of aryl halide, acyl radical combination, and reductive elimination and

regeneration of Pd[0] catalyst and AQ reagent (black path, Pd[0]–Pd[II]–Pd[III]–Pd[I]–Pd[0]). With an overall barrier of only 12.1 kcal/mol, the full reaction is remarkably facile, as indicated by its efficiency even in mild conditions. Furthermore, computational results suggest that Pd[0] catalyst and AQ photocatalyst are readily regenerated simultaneously in the presence of KHCO$_3$, promoting the efficient coupling of the palladium catalytic cycle and the photocatalytic cycle and accounting for the critical role of the base. Although literatures reported by Gevorgyan[53], Shang[45], and Glorius[54] recently revealed that phosphine coordinated palladium catalyst can be photoexcited under visible light, the energy profiles of our calculation results showed the reaction pathway without photoactivation of palladium was energetically feasible. And the control reaction (Table 1, Entry 13; S12, Entry 10) with no photocatalyst, which shows that any photoactivity of the palladium catalyst is not sufficient to promote the reaction. Thus, the mechanistic complexity of photoexcited palladium complex was not taken into consideration in the DFT studies.

Gram-scale HAT/Pd catalyzed C-H arylation of aldehyde. The synthetic utility of our reaction systems was further demonstrated in gram-scale preparations, wherein the scale-up was found to be well accommodated (Fig. 8). 0.96 g of product (**24**) was obtained from a pinacol-protected 4-bromobenzeneboronic acid substrate with only a slightly reduced reaction yield (76%). Haloperidol (**42**), a quintessential butyrylbenzene antipsychotic drug molecule,[56] can be synthesized efficiently by this protocol within two steps in a total yield of 61%. These results help illustrate the promising feasibility of this new approach in an industrial context, wherein the light-facilitated synthesis of the desired molecules could be achieved in a relatively short reaction scheme.
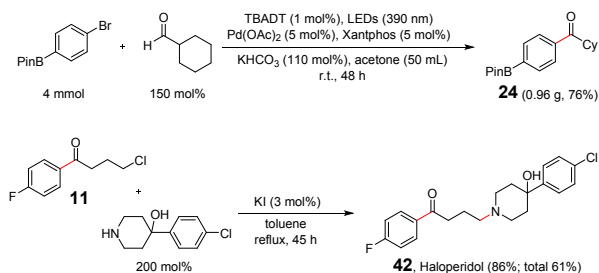
Figure 8. Application of the HAT/Pd catalyzed C-H arylation of aldehyde.

Merging HAT photocatalysis with palladium catalysis and exploiting the aldehyde moiety to serve as a nucleophile enabled mild synthesis of ketones featuring a broad scope of aryl and alkenyl halides as well as aryl triflates. Moreover, the disclosed synthetic method is suitable for gram-scale preparations. DFT calculations suggested that the catalytic reaction proceeded along the Pd[0]–Pd[II]–Pd[III]–Pd[I]–Pd[0] pathway, which involves a sequence comprised of oxidative addition of aryl halide, acyl radical combination, reductive elimination, and regeneration of palladium catalyst and photocatalyst. In addition, computational results revealed that Pd[0] catalyst and HAT photocatalyst regenerate simultaneously in the presence of KHCO$_3$, and that the energy barrier to this concerted regeneration is low, promoting the efficient coupling of the palladium catalytic cycle and the photocatalytic cycle. These results suggest that visible light-facilitated HAT and palladium catalyses show great promise for application in developing new types of cross coupling and C-H functionalization reactions.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures including preparation and purification of reacting substrates, optimization of parameters for the C-H arylation of aldehyde, characterization of new compounds and ^{1}H and ^{13}C spectra of characterization. Details of the analysis of DFT calculations. This Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.xxxxxxx. (pdf files)

The Supporting Information is available free of charge on the ACS Publications website.

AUTHOR INFORMATION

Corresponding Author

*zhengchao@hainnu.edu.cn (C. Zheng);

ORCID

Lu Wang: 0000-0002-8049-1991

Chao Zheng: 0000-0002-2179-8096

Author Contributions

[†]L.W. and W.T. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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