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Visible Light-Induced α-C(sp^3)−H Acetalization of Saturated Heterocycles Catalyzed by a Dimeric Gold Complex

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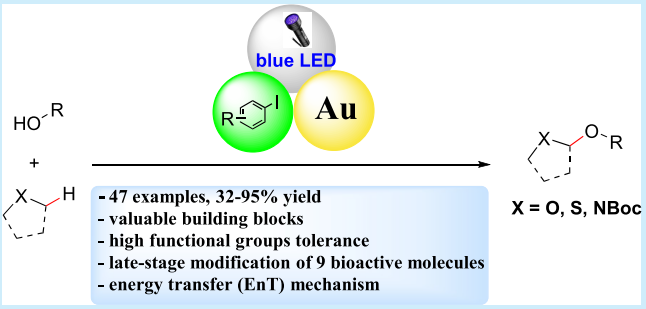
ABSTRACT: Saturated heterocyclic acetals are useful fragments in organic synthesis and other fields. Herein, C(sp^3)−H dehydrogenative cross-couplings of ethers, tetrahydrothiophenes, and pyrrolidines were achieved under visible light irradiation by using iodobenzene and an in situ-formed gold complex. The broad functional group compatibility and substrate scope indicate that our strategy is a promising way to synthesize acetal analogues. The method was successfully applied in late-stage modifications of bioactive molecules. Gram scale syntheses and mechanistic studies are also presented.



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Inspired by the demand for mild, straightforward, and environmentally friendly chemistry, synthetic chemists have devoted a great deal of effort to develop new ways to synthesize valuable products. Selective C−H bond functionalization has been recognized as a powerful and straightforward method.[1] Traditional ways are based on a preactivation of substrates, the requirement of specific and complex ligands, and the introduction of directing groups for the modulation of reactivity. All of this represents an obstacle for application. Because of the high reactivity of open-shell radicals,[2] radical-mediated C(sp^3)−H activation merged with hydrogen atom transfer (HAT) processes[3] have been developed as a promising solution for this problem.

Due to the mild and adjustable reaction conditions, photochemistry offers a new opportunity for radical chemistry.[4] In the past several years, our group has contributed to the development of light-driven organic synthetic methodologies.[5] The binuclear bis(diphosphine) complex [Au_2(μ-dppm)$_2$]Cl_2 [dppm = bis(diphenylphosphino)methane] has proven to be very useful in photocatalysis.[6] In most cases, UVA light was necessary to excite the gold complexes, which can be a drawback due to the fact that many functional groups also show absorption at this short wavelength, which can make applications more difficult and reduce the functional group compatibility. Recently, our group found two different strategies,[5e,g] which enabled a red shift and the excitation of gold complexes under blue light-emitting diode (LED) irradiation. One of the pathways took advantage of the coordination of a ligand (Ph_3P or mercaptan) to the [Au_2(μ-dppm)$_2$]Cl_2 complex, and another pathway was based on the use of a base (Na_2CO_3) as an additive. Herein, we continue to apply this new strategy by combining a dinuclear gold catalyst and a base to in situ form a new gold catalyst for new transformations.

Acetals derived from cyclic ethers are useful fragments for organic synthesis and other applications. Several drugs that contain this motif are applied to treat diseases (Figure 1). There are also other applications based on structures containing this motif, such as liquid crystal display devices[7] and DNA sequencing.[8] In addition, hydroxyl groups can be protected as tetrahydrofuranyl ethers in multistep organic syntheses as well as in peptide, nucleotide, carbohydrate, terpenoid, and steroid chemistry.[9] There are different strategies for the preparation of cyclic ether acetals;[10] the most direct way uses THF in the presence of single-electron oxidants via radical pathways. Most of the protocols use CCl_4 or similar perhalomethanes[10a−c] to promote the reaction, but these kinds of reagents were almost completely banned from use, even in research, because of toxicity and safety concerns. Hypervalent iodine compounds can also serve as the oxidant for this transformation, but high temperatures or microwave conditions are needed.[10d,g] In 2018, Toste and co-workers presented a new route[11] by using diaryliodonium chlorides as the HAT reagent in combination with CFL as the light source; however, the methodology was restricted to cyclic ether substrates, and no other heterocycles were reported. In addition, an excess of 2.5 equiv of diaryliodonium chloride was needed. On the basis of our previous report,[5g] iodobenzene

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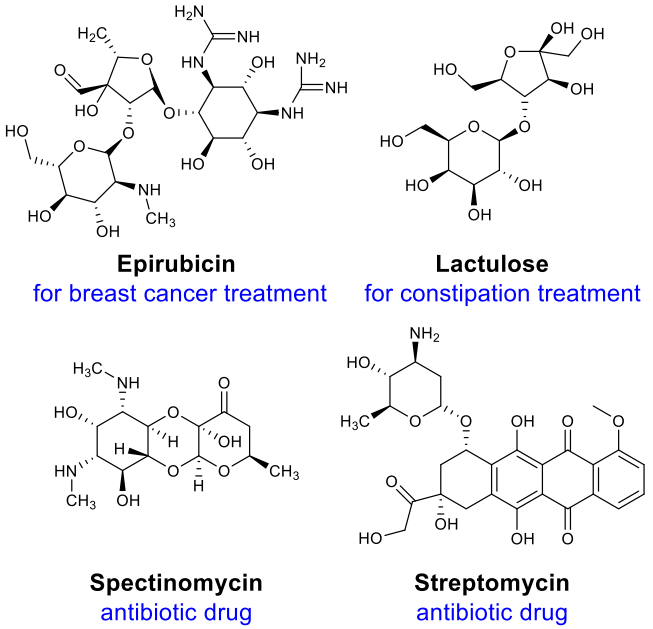


Figure 1. Selection of acetal-containing drugs.

can be excited to form an aryl radical and an iodine radical by an energy transfer (EnT) process with a newly formed gold complex. On the basis of this principle, we assumed that THF acetals might be accessible by the reaction of simple iodobenzene with THF. The formed aryl radical should quickly be trapped by THF to form an α-heteroatom-stabilized alkyl radical. The latter could then recombine with the iodine radical to form 2-iodotetrahydrofuran. A nucleophilic attack then might give rise to the desired products, a strategy different from that in Toste's report.

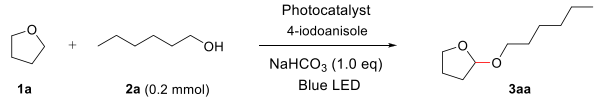
In our initial experiments, we found 4-iodoanisole to be a suitable precursor for this transformation in the presence of the gold catalyst, but the yield was only 38% (Scheme 1, entries 1, 2, and 5) after irradiation for 24 h. A catalyst screening using different counteranions (entries 3−4) enabled an increase in the yield to 60%, with OTf^- being the best choice. A slight increase in the amount of 4-iodoanisole (entries 6−8) and an extended irradiation time (entry 12) further improved the reaction. Attempts to lower the catalyst load failed (entries 10 and 11). We found the condition shown in entry 12 to be the optimum conditions {1.0 equiv of $NaHCO_3$, 1.5 equiv of 4-iodoanisole, and 1.0 mol % $[Au_2(\mu\text{-dppm})_2](OTf)_2$ irradiated by blue LED lights for 36 h}. On the basis of entries 7 and 9, we found reducing the amount of THF does not influence the yield, but using less ether could reduce cost and is beneficial for large scale reactions. We used 0.2 mL of THF for further experiments. The use of simple PPh_3AuCl or other widely applied photocatalysts, like $[Ir(ppy)_2(dtbbpy)]PF_6$, $[Ru(bpy)_3](PF_6)_2$, Eosin Y, or Mes-Acr-$Me^+BF_4^-$, instead of the $[Au_2(\mu\text{-dppm})_2]Cl_2$ complex, resulted in none of the desired product (entries 13−17, respectively). Decreased yields were obtained upon irradiation with CFL or UVA light (entries 20 and 21). The control experiments shown in entries 1, 5, 18, and 19 prove that all of the parameters are significant for a successful transformation.

With the optimal conditions in hand, we then explored the scope of this reaction. Different kinds of primary and secondary alcohols underwent the desired C(sp^3)−H acetalization (Scheme 2). Both linear and cyclic allylic alcohols (**3d**, **3e**, and **3g**) gave moderate yields. No racemization was observed for substrates with chiral centers (**3c** and **3h**). Differently substituted phenylethanol derivatives bearing halogens at different positions (**3i** and **3j**) and a trifluoromethyl (**3l**) group were all tolerated. A wide variety of benzylic alcohols (**3m**−**3s**) reacted well, showing no large difference in yield. The less nucleophilic phenol also reacted with THF to the desired product in 35% isolated yield, but this compound decomposed after storage at 4 °C for 2 days. Even medically relevant heteroaromatic alcohols, which are notoriously problematic in many photoredox protocols, performed well under our reaction conditions, including thiophene, furan, and pyridine (**3u**−**3w**, respectively; 45−65% yields).

We next evaluated other commonly used cyclic ethers instead of THF for this acetalization. Tetrahydropyran also reacted adjacent to the oxygen atom in 48% yield (**3x**). The diminished reactivity compared to THF might result from stereoelectronic factors. On the other hand, we found different aryl iodides influence the yield, maybe because of polarity match. On the basis of condition optimization, 2-chloroiodobenzene was better than others. In the case of 1,4-dioxane (**3y**), despite a comparable steric demand, the second oxygen atom was not functionalized. For 2-methyltetrahydrofuran, only the less hindered position reacted to give **3z**.

Next we expanded the application of this C−H functionalization strategy toward the synthesis of thioacetals and α-alkoxypyrrolidines (Scheme 3). Like the sulfur analogues of acetals, thioacetals have potential applications in pharmaceutical development and alcohol protection.[12] A variety of alcohols, including simple alkyl alcohol (**4a**), cinnamyl alcohol (**4b**), benzyl alcohols (**4d** and **4e**), and heterocyclic benzyl alcohol (**4f**), all directly reacted with thiophene in our new photoredox C−H activation (functionalization) route in moderate yields (33−62%). The oxidation of pyrrolidine to

Scheme 1. Select Optimization Results and Control Studies[a]



Entry	**1a** (mL)	4-iodoanisole	photocatalyst	Time (h)	Yield of **3aa**
1	0.3	0	2.5 % $[Au_2(\mu\text{-dppm})_2]Cl_2$	24	n.d.[b]
2	0.3	1.0 eq	2.5 % $[Au_2(\mu\text{-dppm})_2]Cl_2$	24	38%
3	0.3	1.0 eq	2.5 % $[Au_2(\mu\text{-dppm})_2](NTf_2)_2$	24	53%
4	0.3	1.0 eq	2.5 % $[Au_2(\mu\text{-dppm})_2](OTf)_2$	24	60%
5	0.3	1.0 eq	0	24	n.d.
6	0.3	1.2 eq	2.5 % $[Au_2(\mu\text{-dppm})_2](OTf)_2$	24	80%
7	0.3	1.5 eq	2.5 % $[Au_2(\mu\text{-dppm})_2](OTf)_2$	24	98%
8	0.3	2.0 eq	2.5 % $[Au_2(\mu\text{-dppm})_2](OTf)_2$	24	97%
9	0.2	1.5 eq	2.5 % $[Au_2(\mu\text{-dppm})_2](OTf)_2$	24	93%
10	0.2	1.5 eq	1.0 % $[Au_2(\mu\text{-dppm})_2](OTf)_2$	24	82%
11	0.2	1.5 eq	0.5 % $[Au_2(\mu\text{-dppm})_2](OTf)_2$	24	58%
12	0.2	1.5 eq	1.0 % $[Au_2(\mu\text{-dppm})_2](OTf)_2$	36	98%(95%)[c]
13	0.2	1.5 eq	1.0 % PPh_3AuCl	36	n.d.
14	0.2	1.5 eq	1.0 % $[Ir(ppy)_2(dtbbpy)]PF_6$	36	n.d.
15	0.2	1.5 eq	1.0 % $[Ru(bpy)_3](PF_6)_2$	36	n.d.
16	0.2	1.5 eq	1.0 % Eosin Y	36	n.d.
17	0.2	1.5 eq	1.0 % Mes-Acr-$Me^+BF_4^-$	36	n.d.
18	Conditions as in entry 12 but no $NaHCO_3$				n.d.
19	Conditions as in entry 12 but no light (r.t. and heated to 65°C)				n.d.
20	Conditions as in entry 12 but using CFL instead of Blue LED				52%
21	Conditions as in entry 12 but using UVA instead of Blue LED				60%

[a]Yield determined by ^1H NMR analysis using 1,2,4,5-tetramethylbenzene as the internal standard. [b]n.d. = not detected. [c]Isolated yield.

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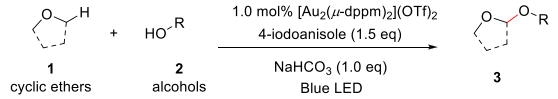
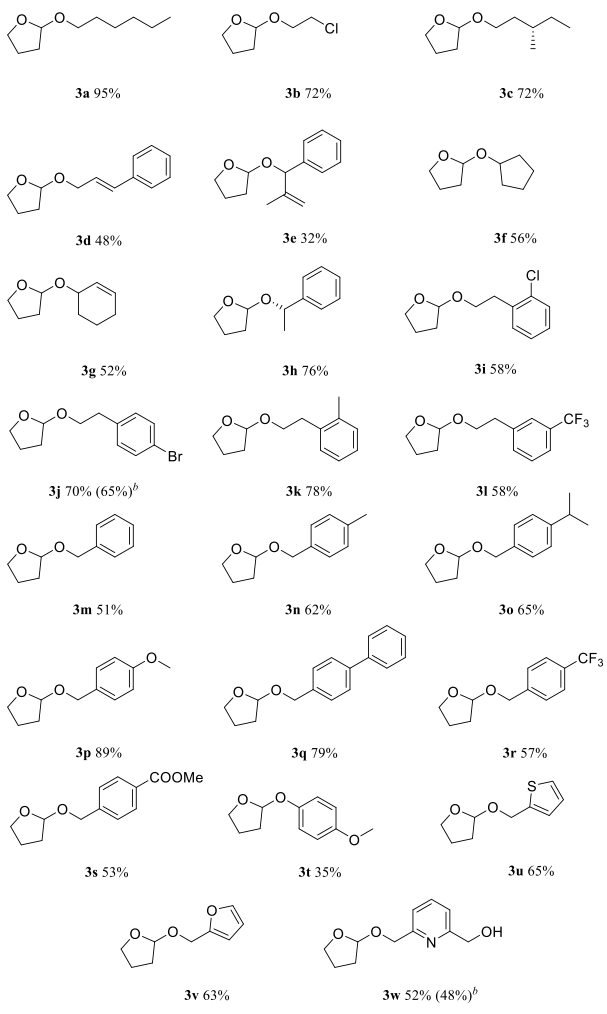
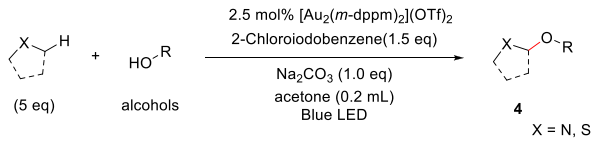
Scheme 2. Scope of sp^3 C−H Acetalization of Ethers[a]

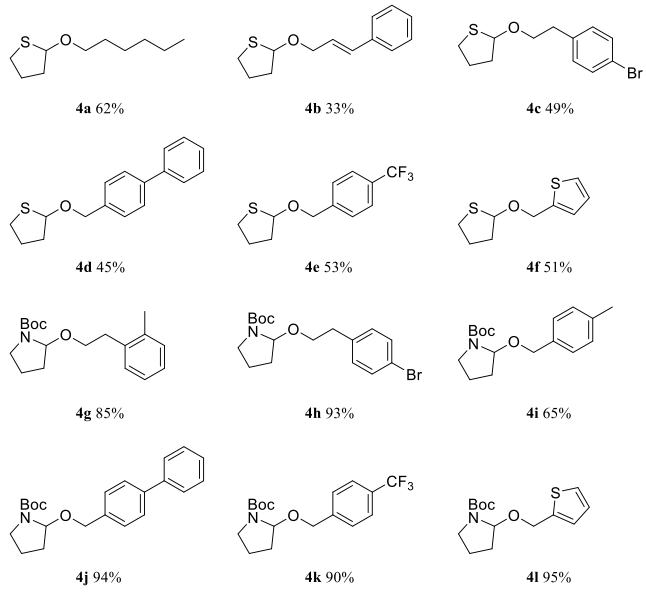




[a]Reactions were performed on a 0.2 mmol scale by following general procedure A. Yields are isolated yields. [b]Reactions were performed on a 2.0 mmol scale, and the irradiation time was 60 h. [c]Reactions were performed on a 0.2 mmol scale, using 2-chloroiodobenzene instead of 4-iodoanisole, using 0.2 mL of acetone as solvent, and 5 eq of ethers was added. [d]Reactions were performed on a 0.2 mmol scale, using 2-chloroiodobenzene instead of 4-iodoanisole, using 0.2 mL of 1,4-dioxane as solvent.

Scheme 3. Scope of sp^3 C−H Acetalization of Thioethers and Amides[a]





[a]Reactions were performed on a 0.2 mmol scale by following the general procedure. Yields are isolated yields.

α-alkoxypyrrolidines has been utilized as a starting step for the synthesis of cyclic lactams, alkaloids, and even the antimalarial agent isofebrifugine.[13] For this kind of transformation, researchers usually use prefunctionalization.[14] Only a few publications[15] have reported the direct modification of pyrrolidines through electrochemical pathways; however, special liquid electrolyte systems are needed. Various α-alkoxypyrrolidines were achieved by our strategy. Halogen (**4h**), trifluoromethyl (**4k**), and heterocycles (**4l**) were compatible, and the yields were >90%.

Furthermore, we could demonstrate that this methodology can be applied for late-stage modifications of some bioactive molecules (Figure 2). Carbohydrates and nucleosides are common substances in living organisms, and site-selective modifications of those compounds offer exciting possibilities for both organic synthesis and pharmaceutical development. Compounds **5**−**7** further demonstrate the broad applicability of our strategy. Ezetimibe is a medication used to treat high blood cholesterol levels and certain other lipid abnormalities. The compound includes two hydroxyl groups, but the aliphatic alcohol was selectively converted while the phenolic hydroxyl remained under our reaction conditions (**8**). Another medicinal compound, podophyllotoxin (**9**), and the natural products 5α-cholestan-3β-ol (**10**), (−)-menthol (**11**), and (−)-borneol (**12**) also underwent this α-C(sp^3)−H acetalization reaction. In addition, the late-stage modification of (−)-ambroxide by using acetone as solvent was also successful and the desired product was obtained in 62% yield (**13**). Although 5.0 equiv of ether was necessary, >3.0 equiv could be recovered during the purification. These applications clearly suggest that our strategy is a promising synthetic method and a late-stage modification tool for natural products and drug molecules.

After the successful construction of acetals and related analogues through the dehydrogenation cross-coupling between saturated heterocyclic rings and alcohols, other control experiments were conducted to gain deeper insight into the

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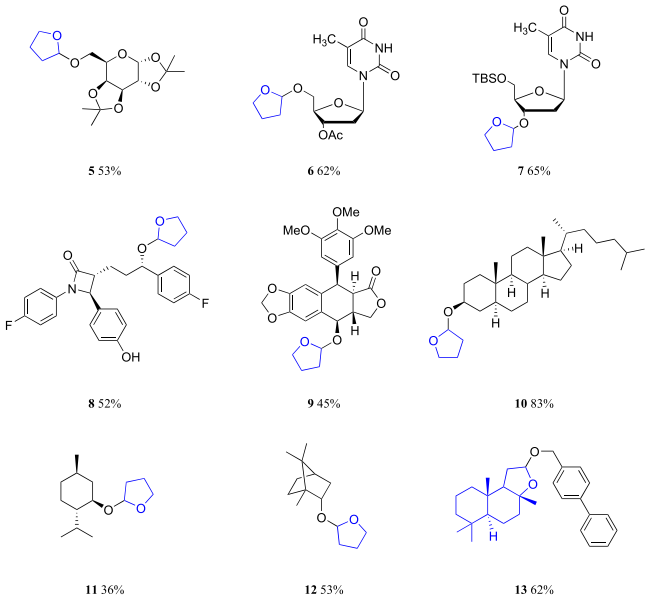
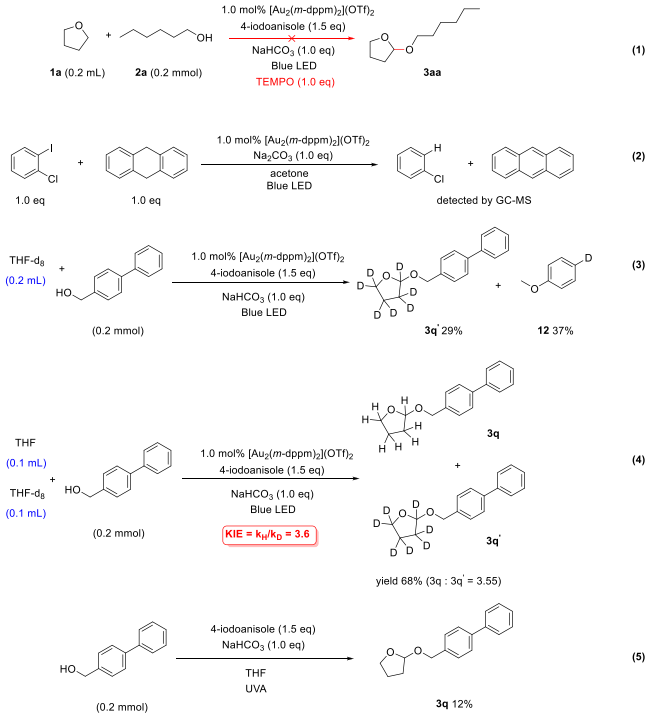


Figure 2. Selective late-stage modification of bioactive molecules. Reactions were performed on a 0.2 mmol scale (see the Supporting Information for detailed procedures). Yields are isolated yields.

mechanistic pathway. The transformation was completely inhibited when 1.0 equiv of the radical scavenger TEMPO was added. For the reaction system shown in Scheme 4 (eq 2),

Scheme 4. Mechanistic Experiments



if a gold catalyst and a base were present, the aryl radical derived from the aryl iodide by blue LED irradiation would be captured by HAT from 9,10-dihydroanthracene (DHA) to generate chlorobenzene. These two inhibition experiments suggest that a radical process is involved and that alcohols are not participating in the radical-forming process. The yield dropped to 29% when THF-d_8 was used as solvent, and deuterated compound **12** was detected, which verifies that a hydrogen atom transfer (HAT) had occurred after the generation of the phenyl radical. In addition, a significant kinetic isotope effect (KIE = 3.6) was recorded, providing evidence that the C−H bond cleavage event might constitute the rate-determining step. Finally, the reaction was conducted under UVA in the absence of a gold catalyst. As demonstrated in Scheme 4 (eq 5), **3q** was obtained in only 12% yield compared to 79% yield under our standard condition. It is well-known that aryl iodobenzene would split into two free radicals under UVA irradiation.[16] Having in mind our previous research,[5g] we rationalized that iodobenzene homolysis was also a possible route for this transformation, but unlike for the reported energy transfer process, direct UVA irradiation was inefficient for this transformation. The quantum yield [Φ = 13.5% (see the Supporting Information)] indicates that a radical chain mechanism is not involved in the transformation.

On the basis of previous studies[5g] and our experiments, this transformation should follow an energy transfer process. The possible mechanism is shown in Figure 3. A new gold complex

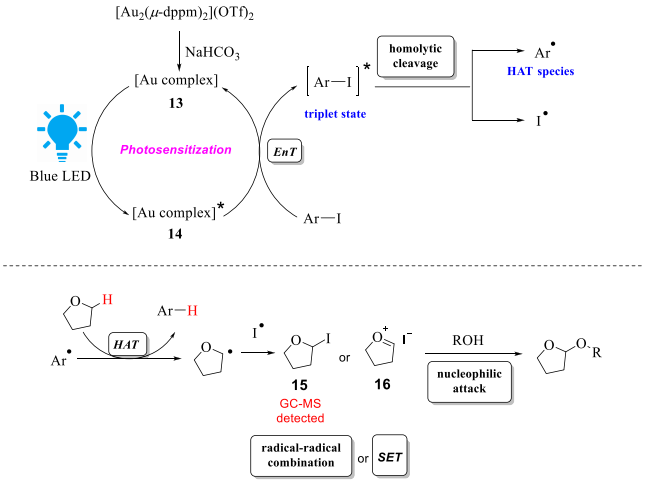


Figure 3. Proposed mechanism.

13, formed in situ by the combination of [$Au_2(\mu$-dppm$)_2$]-(OTf)$_2$ and $NaHCO_3$, can be photoexcited to **14** under blue LED irradiation. Then, the iodobenzene converts to its photoexcited triplet state through an energy transfer process (EnT), followed by a homolytic cleavage generating an aryl radical and an iodine radical. In the THF solvent cage, the aryl radical is then quickly trapped by THF via a HAT process. Subsequently, the produced THF radical undergoes radical−radical recombination with the iodine radical, leading to 2-iodotetrahydrofuran **15** as the reactive intermediate. As an alternative, it might also be oxidized to an oxocarbenium ion **16**. As reported previously,[10] such α-halogenated ethers can easily be attacked by alcohols to deliver the corresponding acetals.

In summary, C(sp^3)−H dehydrogenative cross-couplings on ethers, tetrahydrothiophene, and pyrrolidines were successfully performed with a dimeric gold catalyst, iodobenzene, and blue LEDs. The wide functional group compatibility and a broad substrate scopes make our strategy appealing as a synthetic method with respect to acetals, thioacetals, and α-alkoxypyrrolidines. The applications and gram scale experiments also demonstrate a potential use of the strategy for late-stage modifications and the construction of other complex

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structures. On the basis of mechanistic study, the energy transfer process between the excited newly formed gold complex and iodobenzene was important for the following HAT process and finally built the products. More detailed studies are underway in our lab, especially on highly selective C−H functionalization controlled by the electronic effects of different kinds of aryl iodides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01924.

Experimental procedures and compound characterization (PDF)

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Notes

The authors declare no competing financial interest.

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