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Late-Stage Functionalization of Arylacetic Acids by Photoredox-Catalyzed Decarboxylative Carbon–Heteroatom Bond Formation

Yota Sakakibara,[a] Eri Ito,[a] Tomohiro Fukushima,[a,b] Kei Murakami,*[a] and Kenichiro Itami*[a,b]

Abstract: The rapid transformation of pharmaceuticals and agrochemicals enables access to unexplored chemical space and thus has accelerated the discovery of novel bioactive molecules. Since arylacetic acids have been regarded as privileged structures in bioactive compounds, new transformations of these structures would contribute to drug/agrochemical discovery and chemical biology. Herein, we report carbon–nitrogen and carbon–oxygen bond formation through the photoredox-catalyzed decarboxylation of arylacetic acids. The reaction shows good functional group compatibility without pre-activation of the nitrogen- or oxygen-based coupling partners. Under similar reaction conditions, carbon–chlorine bond formation was also feasible. This efficient derivatization of arylacetic acids allows us to synthesize pharmaceutical analogues and bioconjugates of pharmaceuticals and natural products.

The late-stage functionalization of pharmaceutical and agrochemical molecules has been regarded as a promising way to accelerate the discovery of new bioactive compounds.[1] Such rapid and straightforward transformations allows for the generation of a new family of potential bioactive molecules from pharmaceutical molecules to access unexplored regions of chemical space. Analogues of pharmaceuticals differ in structure from the original molecule, but they generally meet criteria for bioactive molecules, such as Lipinski's rule.[2] Therefore, these analogues would have potential to control different life phenomenon to express novel bioactivity. A recent study has revealed that analogues of pharmaceutical compounds can be used for other biological applications. For example, we have shown that analogues of Celecoxib, a non-steroidal anti-inflammatory drug, were found to enhance stomatal development in plants (Figure 1A) even though higher plants do not possess orthologs of the originally target gene in human.[3] Since arylacetic acids have been regarded as privileged structures in pharmaceuticals and agrochemicals (Figure 1B), we envisioned that transforming the carboxyl group into other functionalities would allow for the synthesis of various analogues that would contribute drug/agrochemical discovery and chemical biology.[4]

Carboxylic acid moieties have long been utilized as a handle to construct chemical bonds through the Curtius rearrangement,[5] Hunsdiecker reaction,[6] and Barton decarboxylation.[7] Recent developments on photoredox-catalyzed reactions allow for the generation of radicals from carboxylic acids through single electron oxidation of carboxylates.[8,9] Generally, the thus-generated carbon radicals are nucleophilic and easily react with a variety of electrophilic heteroatoms or other radical acceptors.[10,11] Since nitrogen or oxygen atoms are inherently electronegative, additional steps to activate nitrogen or oxygen into radical acceptors are required.[12] In order to pursue streamlined chemical syntheses, a direct decarboxylative coupling of carboxylic acids with unactivated nitrogen or oxygen is highly sought after. In 2014, Lei reported a photoredox-catalyzed decarboxylative amination of α-keto acid.[13] Kiyokawa and Minakata reported Ritter-type decarboxylative amination with acetonitrile in the presence of $PhI(OAc)_2$ and I_2 as the oxidants under fluorescent lamp irradiation.[14] Quite recently, Fu, Hu and MacMillan reported novel copper/photoredox co-catalyzed decarboxylative aminations of carboxylic acids.[15]

During our study on photoredox-catalyzed carbon–nitrogen (C–N) bond formation,[16] we discovered that our photocatalytic systems could be applicable to the decarboxylative functionalization of arylacetic acids (Figure 1B).[17] Herein, we report C–N and C–O bond formation through photoredox-catalyzed decarboxylation of arylacetic acids. The reaction shows good functional group compatibility without pre-activation of the nitrogen- or oxygen-based coupling partner. Furthermore, our oxidative conditions were applicable for decarboxylative chlorination using tetrabutylammonium chloride as a safe and easy-to-handle Cl^- source.[9g,10c]

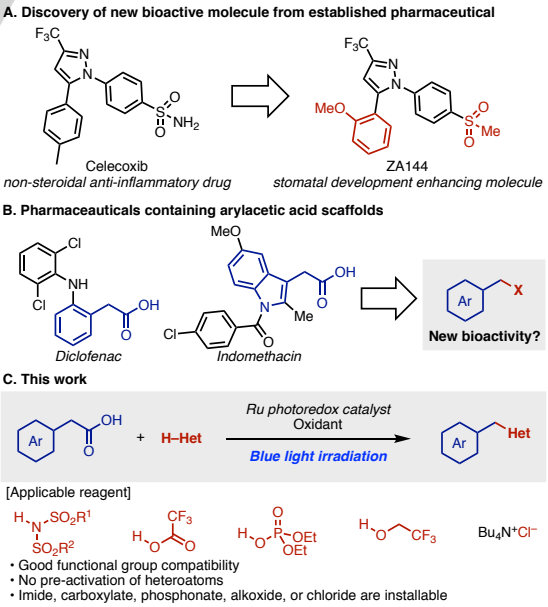

Figure 1. (A) An example of the discovery of new bioactive molecule from established pharmaceuticals. (B) Pharmaceuticals containing arylacetic acid scaffolds. (C) This work.

We launched our study from the reaction of biphenylylacetic acid (**1a**: felbinac, an anti-inflammatory drug) with $HN(SO_2Ph)_2$

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(**2a**) (Figure 2). The use of $[Ru(bpy)_3]Cl_2·6H_2O$ (catalyst) and hypervalent iodine-based oxidant 1-butoxy-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (IBB) under blue light irradiation proved to be particularly effective, affording the corresponding decarboxylative imidation product **3a** in 87% yield. Notably, both the catalyst and light are critically important for the reaction to proceed. Although hypervalent iodine $PhI(OAc)_2$, an analog of IBB, gave **3a** in good yield, other organic and inorganic oxidants were not effective in this transformation. Moreover, no C–H imidation products were observed.[16]

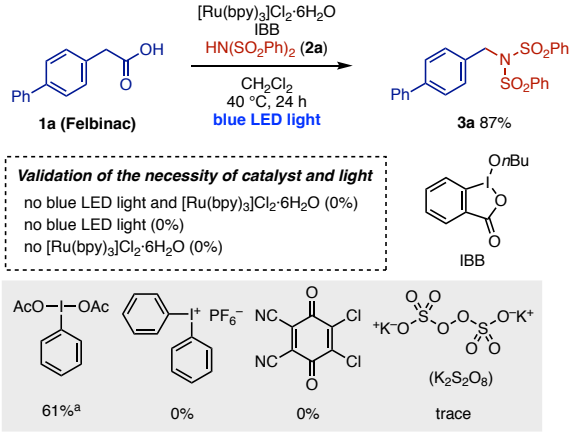


Figure 2. Validation of the necessity of catalyst and light, and the effect of oxidants.

A possible mechanism for the decarboxylative imidation is shown in Figure 3, which is based on our previous study on C–H imidation.[16] Firstly, carboxylic acid **1** reacts with IBB to give activated intermediate **A** *in situ* (see the Supporting Information (SI) for details). At the same time, the ruthenium catalyst is activated by irradiation of blue light to give Ru^{II}*. Then **A** reacts with Ru^{II}* to provide Ru^{III}, radical **B**, and *o*-iodobenzoate. Decarboxylation of **B** then occurs to give **D**. In parallel, Ru^{III} oxidizes imide **2a** to provide imidyl radical **E**.[18] The resulting proton might react with butoxide (*n*-BuO^-) or 2-iodobenzoate (**C**). Finally, a radical-radical coupling between **D** and **E** would produce **F**. The precise mechanism is not clear at this stage and other possible pathways from intermediate **D** might exist; for example, single electron transfer between **D** and **E** to furnish an ionic intermediate[19] that finally affords **F**. Judging from the results that other electron-deficient oxygen nucleophiles participate in the decarboxylative coupling (*vide infra*), this reaction pathway is also possible. The existence of radical intermediate **D** was proved through the reaction of cyclopropane-substituted arylacetic acid **4** as shown in Scheme 1. The reaction of **4** with **2a** gave ring-opening product **5** in 25% yield. This result clearly indicates intermediate **G** is generated from **4** under the reaction conditions, which then opens the 3-membered ring to afford **H** and eventually the imidated product **5**.

With the optimal reaction conditions in hand, we performed the decarboxylative imidation with a range of substrates (Figure 4A). Arylacetic acids having methyl, methoxy, or halogen (Cl, Br, or I) substituents were converted smoothly to **3b–j** in good to high yields. The yield of **3k** was low as the electron-withdrawing group decreases the reactivity by increasing the oxidation potential. Not only benzeneacetic acids but also other arylacetic acids (naphthalene, indole, and thiophene) gave products **3l–n**. Notably, no aromatic C–H imidation products were observed. Although a methyl group at the benzylic position did not retard the reaction (**3o**), the introduction of a bulkier phenyl group completely suppressed the reaction (**3p**).

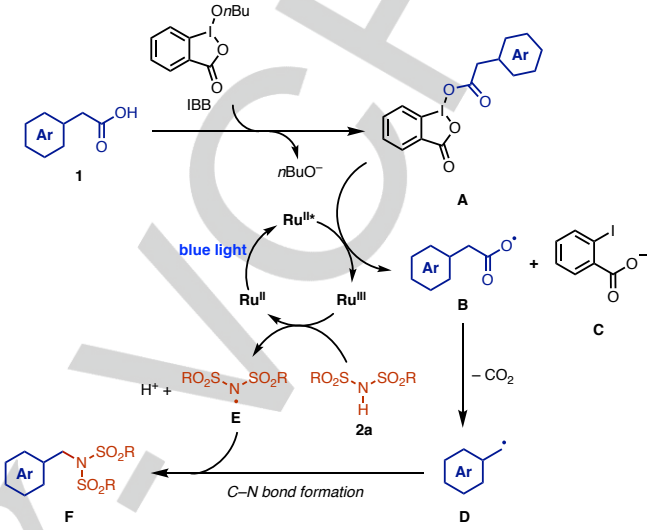
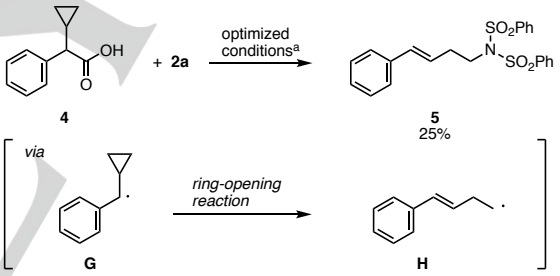


Figure 3. Possible mechanism of Ru-catalyzed decarboxylative imidation under blue LED light.



Scheme 1. Generation of benzyl radical under the conditions.

We then studied the scope of the imide substrate (Figure 4B). Diarylsulfonimides bearing a methyl or bromo-group smoothly afforded the corresponding products **6a–c** in high yields (87%, 78%, and 87%). A diarylsulfonimide with electronically opposing substituents (trifluoromethyl and methoxy) on either aryl ring gave the product **6d** in 64% yield. Not only aryl but also an alkyl-substituted sulfonimide worked nicely to give **6e** in 72% yield. The reaction of a cyclic sulfonimide gave **6f** in 45% yield. Saccharin, a cyclic imide, furnished the corresponding product **6g** in 51% yield, with concomitant formation of **6g'** in 22% yield.

Notably, nucleophiles other than imides are also applicable in this decarboxylative reaction. For example, trifluoroacetic acid and dibutylphosphonic acid coupled with **1a** to give the corresponding C–O coupling products **6h** and **6i** in 53% and 63%, respectively (Figure 4C). The reaction of **1a** with 2,2,2-trifluoroethanol afforded **6j** in 50% yield. Interestingly, the addition of sulfonimide **2a** accelerated the reaction as only 29% of **6j** was obtained without a catalytic amount of **2a**. Notably, tetrabutylammonium chloride can be used as a chloride source. The reaction provided the corresponding benzylic chloride **6k** in

84% yield. Although thiols were not directly installable with this reaction, a one-pot sequence of decarboxylative chlorination and S_N2 reaction of **1a** with 4-^{t}BuC$_6$H$_4$SH afforded **6l** in 60% yield (Figure 4D).

Our reaction can be applied to transformations of pharmaceuticals having functionalized arylacetic acid substructures (Figure 5). For example, the reaction of Diclofenac, which possesses a free N–H moiety, afforded the corresponding product **7a** in 59% yield. The reaction proceeded smoothly in a gram-scale to give **7a** in 1.02 g. Other pharmaceuticals such as Indomethacin, Flurbiprofen, Ibuprofen, Zaltoprofen, and Isoxepac were smoothly transformed into the corresponding benzylamine derivatives (**7b–f**) in good to high yields. The decarboxylative chlorination of Isoxepac also proceeded smoothly to afford **7g** in 82% yield. The resulting benzyl chloride **7g** can be used as an intermediate to conjugate with other bioactive molecules. S_N2 reactions with bioactive molecules such as Duloxetine, L-cysteine, vitamin E, and Celecoxib gave the corresponding conjugates **8a–d** in good yields (65%, 48%, 43%, and 62% yields, respectively). These overall transformations could be applicable in the area of pharmaceutical/agrochemical chemistry and chemical biology to accelerate the development of new biological compounds and tools as well as for affinity-probe-based identification of target proteins.[20]

In summary, we have developed a decarboxylative functionalization of arylacetic acids via oxidative carbon–heteroatom bond formation through photoredox catalysis. This method allows us to directly convert carboxylic acids into nitrogen, oxygen, or chlorine functionalities. Given the importance of arylacetic acids and the abundance of nucleophiles that are available today, this fundamental reaction will find significant utility in various fields to accelerate the discovery of new functional molecules and tools.

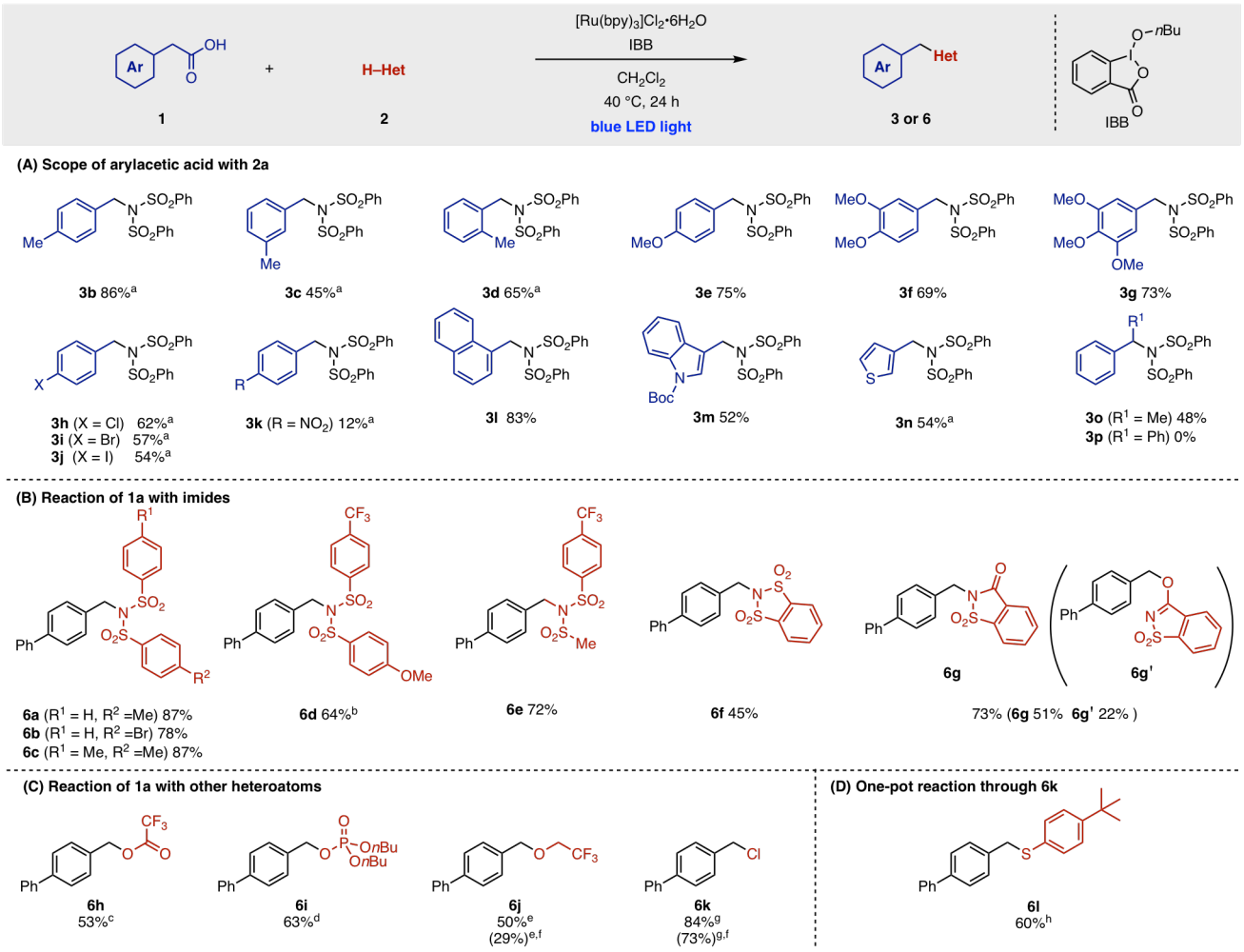


Figure 4. Scope of the substrate. Optimized reaction conditions: **1** (2.0 equiv), **2** (0.20 mmol), [Ru(bpy)$_3$]Cl$_2$·6H$_2$O (2.5 mol%), IBB (2.5 equiv), CH$_2$Cl$_2$ (4.0 mL) 40 °C, 24 h. Variation from optimized reaction conditions: [a] **1** (5.0 equiv), IBB (3.0 equiv). [b] 36 h. [c] CF$_3$CO$_2$H (0.20 mmol), IBB (2.0 equiv). [d] (*n*BuO)$_2$PO(OH) (0.20 mmol), IBB (2.0 equiv). [e] **1a** (0.20 mmol), CF$_3$CH$_2$OH (4.0 mL: solvent), IBB (2.0 equiv), HN(SO$_2$Ph)$_2$ (25 mol%). [f] ^{1}H NMR yield. Without addition of HN(SO$_2$Ph)$_2$. [g] Bu$_4$N$^+$Cl$^-$ (0.20 mmol), IBB (2.0 equiv), HN(SO$_2$Ph)$_2$ (25 mol%). [h] Bu$_4$N$^+$Cl$^-$ (0.20 mmol), IBB (2.0 equiv), HN(SO$_2$Ph)$_2$ (25 mol%), then 4-*tert*-butylbenzenethiol (1.0 equiv), NaH (10 equiv), DMF (4.0 mL), 2 h.

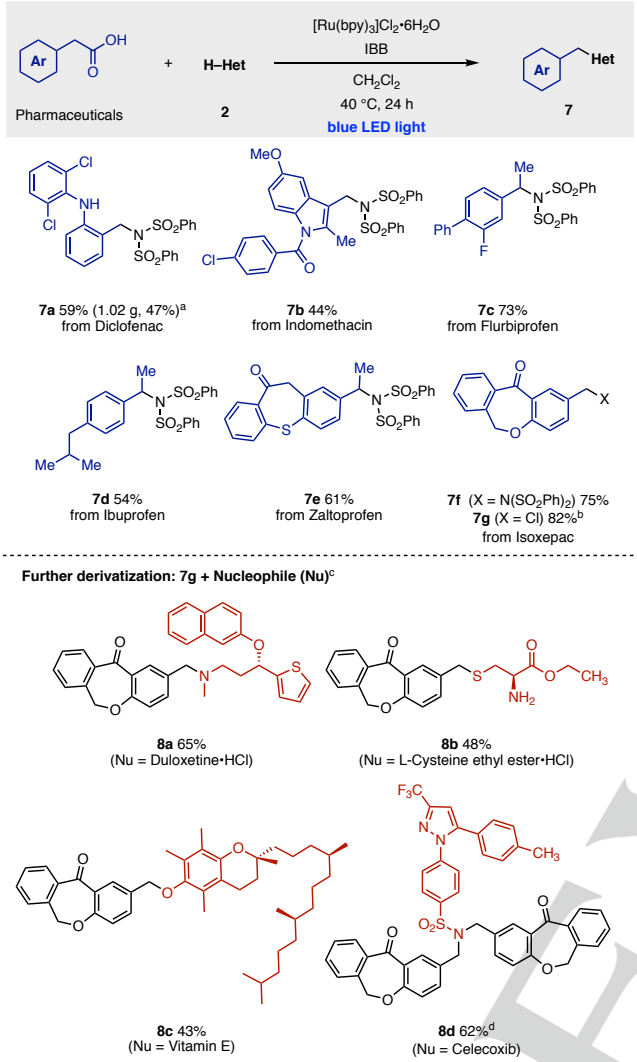


Figure 5. Transformation of pharmaceuticals. Optimized reaction conditions: **1** (2.0 equiv), **2** (0.20 mmol), $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ (2.5 mol%), IBB (2.5 equiv), CH_2Cl_2 (4.0 mL) 40 °C, 24 h. [a] Diclofenac (2.0 equiv), **2a** (4.0 mmol), $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ (2.5 mol%), IBB (2.5 equiv), CH_2Cl_2 (80 mL) 40 °C, 72 h. [b] Isoxepac (2.0 equiv), $Bu_4N^+Cl^-$ (0.20 mmol), IBB (2.0 equiv), $HN(SO_2Ph)_2$ (25 mol%), $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ (2.5 mol%), CH_2Cl_2 (4.0 mL) 40 °C, 24 h. [c] Nu (1.0 equiv), NaH (2.0 equiv), DMF (0.50 mL), 80 °C, 2 h. [d] Nu (0.50 equiv).

Acknowledgments

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Keywords: decarboxylation • photoredox catalyst • imidation • ruthenium catalyst • arylacetic acid

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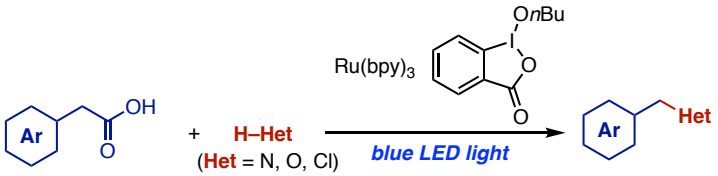

- *Wide-scope decarboxylative C–heteroatom bond formation*
- *Oxidative reaction with photoredox catalyst*

Decarboxylative Functionalization: Carbon–nitrogen, carbon–oxygen, and carbon–chlorine bond formation through photoredox-catalyzed decarboxylation of arylacetic acids is reported. The reaction shows good functional group compatibility without pre-activation of nitrogen- or oxygen-based coupling partner. This efficient derivatization of arylacetic acids allows synthesizing pharmaceutical analogues and bioconjugates of pharmaceuticals and natural products.

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