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Visible-light promoted arene C–H/C–X lactonization *via* carboxylic radical aromatic substitution†

Qi Yang,‡[a,b] Zongbin Jia,‡[a,b] Longji Li,[a,b] Long Zhang[a,b,c] and Sanzhong Luo *[a,b,c]

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We report herein a photocatalytic arene lactonization *via* carboxylic radical aromatic substitution. This procedure is characterized by its ability to cleave inert C–X bonds (X = H, F, Cl, Br, O, S) under mild and oxidant-free conditions, thus furnishing a general and operationally simple synthetic protocol for diverse substituted coumarins.

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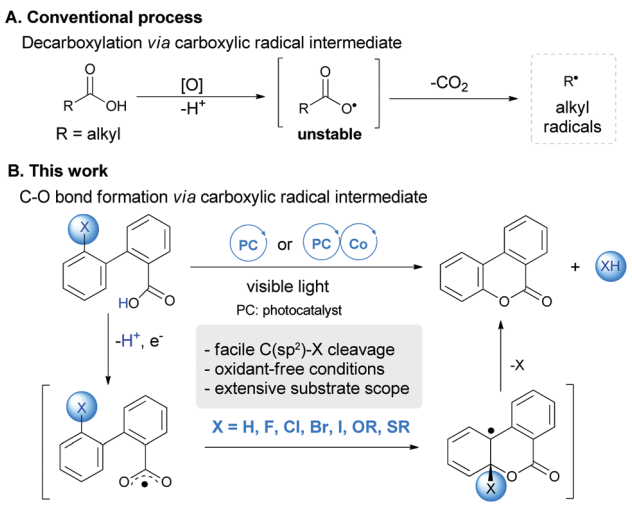
Introduction

Redox transformation of carboxylic acids is an ancient, yet fundamental transformation, as carboxylic acids are readily available from nature or the chemical industry. A prominent early example can be traced back to Kolbe electrolysis developed in 1840s,[1] when organic synthesis was born. Upon oxidation by either a chemical or electrochemical approach, aliphatic carboxylic acids undergo facile decarboxylation *via* transient carboxylic radical species (Scheme 1A). This process underlies many of the synthetically useful radical reactions such as the Hunsdiecker reaction and the Barton reaction.[2] Recently, visible light mediated photoredox catalysis has been developed as an enabling approach for radical decarboxylation, setting the basis for a number of intriguing C–X/C–C bond formations with the *in situ* generated alkyl radical species following decarboxylation.[3,4] It is noted that the direct radical decarboxylation of unsaturated acids, such as aryl and alkenyl acids, is more sluggish than their aliphatic homologues,[5,6] which usually requires high temperature or transition-metal assistance.[7] Capitalizing on this feature, we herein uncovered a distinctive reactivity of unsaturated carboxylic acids, which underwent radical aromatic substitution instead of decarboxylation, resulting in atom-economical and straightforward synthesis of coumarins *via* C–H or C–X bond cleavage (Scheme 1B).

Substitutional coumarin derivatives are widely found in natural and bioactive molecules, as well as in fluorescent materials, axially chiral products, and molecular rotary motors.[8] Direct arene C–H oxidative lactonization of 2-alkenylbenzoic acids represents one of the most straightforward approaches for the synthesis of coumarins.[9] However, most of the available methods require stoichiometric or excess amounts of oxidants under harsh conditions, thus limiting the scope as well as the applicability. Recently, Gonzalez-Gomez and coworkers reported a photo-catalytic dehydrogenative lactonization of 2-arylbenzoic acids by utilizing peroxysulphates as the oxidants with an organic photoredox catalyst.[9h] However, this method still required an excess of chemical oxidant and the protocol was not workable for alkenyl carboxylic acids. Recently, we reported an oxidant-free asymmetric cross-dehydrogenative coupling by merging a photocatalyst and a cobalt catalyst.[10] The combination of the photocatalyst



Scheme 1 Hydrodecarboxylation and dehydrogenation of carboxylic acid *via* radical intermediates.

[a]*Key Laboratory for Molecular Recognition and Function, Institute of Chemistry, Beijing, 100190, China. E-mail: luosz@iccas.ac.cn; http://luosz.iccas.ac.cn*
[b]*University of Chinese Academy of Sciences, Beijing, 100490, China*
[c]*Collaborative Innovation Center of Chemical Science and Engineering, Tianjin, 300071, China*

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‡These authors contributed equally to this work.

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and the cobalt complex has been shown to mediate efficient hydrogen-evolution accompanying C–X/C–C bond formations.[11] In order to expand this strategy to radical carboxylic acid transformations, an oxidant-free C–H lactonization process was developed, leading to the facile formation of coumarins under rather mild conditions. This method was not limited to C(sp^2)–H bond cleavage, and the radical aromatic substitution could be well applied to other C(sp^2)–X bonds, including the most challenging C(sp^2)–F bond.[12] Very recently, Weaver and Hashmi have independently achieved mild C–F bond functionalization of multifluoroarenes by photocatalysis and the reactions were proposed to proceed *via* an arene C–F radical anion in a formal S_NAr-type pathway.[13] We report herein a mechanistically distinctive radical substitution with an arene C–F bond.

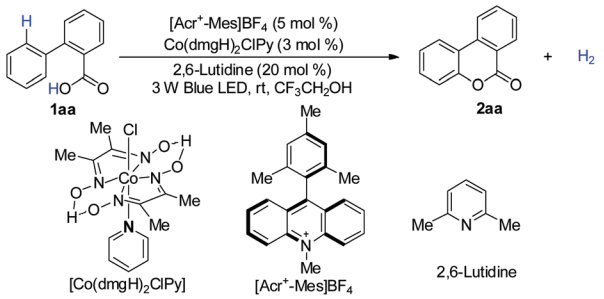
Results and discussion

We first explored the proposed arene lactonization using 2-phenylbenzoic acid **1aa** as the model substrate. We envisioned using [Acr$^+$-Mes]BF_4 in the reaction for its strong absorption band in visible light (λ_{max} = 430 nm) and high excited state reduction potentials (>2.0 V *vs.* SCE).[14a] In further optimizations, the best results were obtained with a quantitative conversion (Table 1, entry 1). Variation of photocatalysts (Table 1, entries 2 and 3), bases (Table 1, entries 4 and 5) and solvents (Table S2†) led to a decrease in the yield of **2aa** and H_2 evolution. It is interesting that, under sunlight irradiation, **2aa** was obtained with 88% yield and 95% H_2 after 5 h (Table 1, entry 8). Control experiments revealed that photocatalyst, cobalt catalyst, and visible light were essential in the whole reaction (Table 1, entries 10–12), and no reaction or a poor yield was observed in their absence.

Under optimized conditions, the scope was then examined. Diverse substituted benzoic acids furnished the corresponding benzocoumarins in good to excellent yields (Scheme 2). 2-Pyrrolyl benzoic acid also furnished the desired product (Scheme 2, **2as**). The reaction worked equally well on a gram scale (Scheme 2, **2aa**). 4-Arylcoumarins (neoflavones), as the family members of flavonoids, are widely distributed in natural products and exhibit promising biological activities.[8] A variety of 2-substituted cinnamic acids, including alkyl and unsymmetrical phenyl substituted aryl acids,[8h] gave the corresponding cyclization products without isomerization of the double bond (Scheme 3), which makes it possible to construct diverse unsymmetrical 4-substituted coumarins.

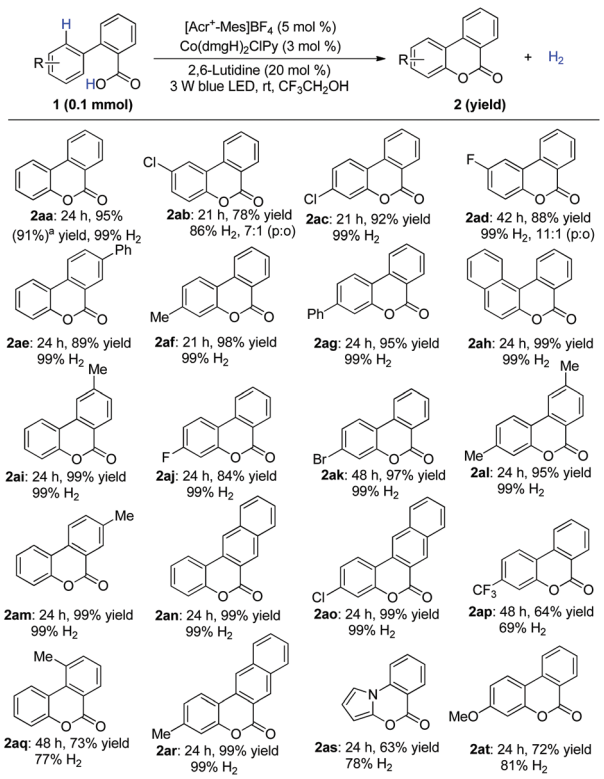
To explore the synthetic potential of arene lactonization, a series of *ortho*-enyl benzoic acids were synthesized and tested under standard conditions (Scheme 4). **2ca**, **2cb** and **2cc** could be obtained as five-*exo* adducts. It is interesting that the cyclization of **1cc** resulted in double bond migration, and **1cd**

Table 1 Screening and optimization[a]



Entry	Variation from standard conditions	Yield[b] (%)	H_2 [c] (%)
1	None	99 (95[d])	>99
2	Eosin Y instead of [Acr$^+$-Mes]BF_4	Trace	Trace
3	$Ru(bpy)_3(PF_6)_2$ instead of [Acr$^+$-Mes]BF_4	Trace	Trace
4	DBU instead of lutidine	90	95
5	Cs_2CO_3 instead of lutidine	76	83
6	2,6-Lutidine (100 mol%)	99	>99
7	2,6-Lutidine (10 mol%)	86	90
8	Under sunlight (5 h)	88	95
9	No 2,6-lutidine	60	31
10	No Co(dmgH)$_2$ClPy	22	Trace
11	No [Acr$^+$-Mes]BF_4	n.r.[e]	n.d.[f]
12	In the dark	n.r.	n.d.

[a] Reaction conditions: **1aa** (0.1 mmol), [Acr$^+$-Mes]BF_4 (5 mol%), 2,6-lutidine (20 mol%) and Co(dmgH)$_2$ClPy (3 mol%) were added to 1.0 mL CF_3CH_2OH, then deaerated and irradiated for 24 h by using a 3 W blue LED. [b] Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [c] Determined by gas chromatography using methane as an internal standard. [d] Isolated yield. [e] n.r. = no reaction. [f] n.d. = no detection.



Scheme 2 Scope of substituted 2-arylbenzoic acids. [a] 8 mmol scale, [Acr$^+$-Mes]BF_4 (3 mol%), Co(dmgH)$_2$ClPy (1.5 mol%) and 2,6-lutidine (20 mol%) under 30 W blue LED.

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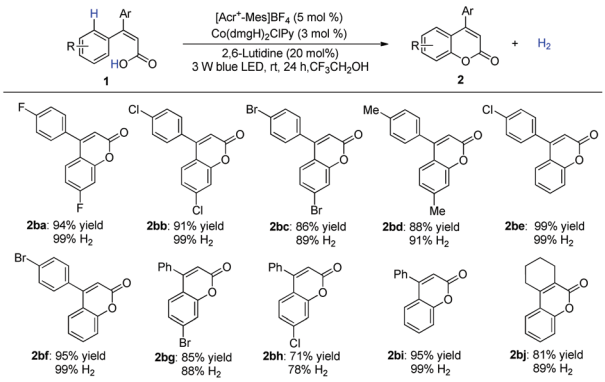
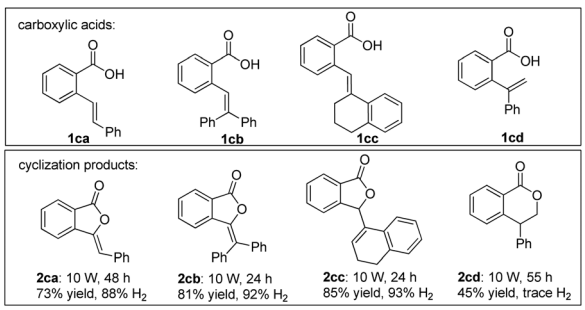


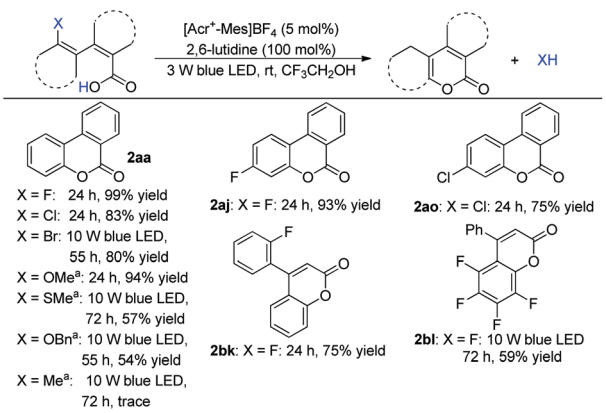
Scheme 3 Scope of aryl cinnamic acids.



Scheme 4 Scope of *ortho*-enyl benzoic acids.

reacted to form a six-*endo* adduct **2cd** without hydrogen evolution. In the latter case, the reaction likely proceeded *via* an *anti*-Markovnikov hydrocarboxylation process.[14b]

During the study, we found that this method could even cleave C–F in the reaction. In this context, a cobalt catalyst was not necessary. This result promoted us to explore arene C–X radical substitutions further. Substituted biphenyl acid and 2-aryl cinnamic acid reacted to give the desired products in good yield (Scheme 5, **2aa**). Arene halides, including chloride and bromide, could be incorporated. Other C–X bonds such as phenol ether or thioether also reacted smoothly to give the



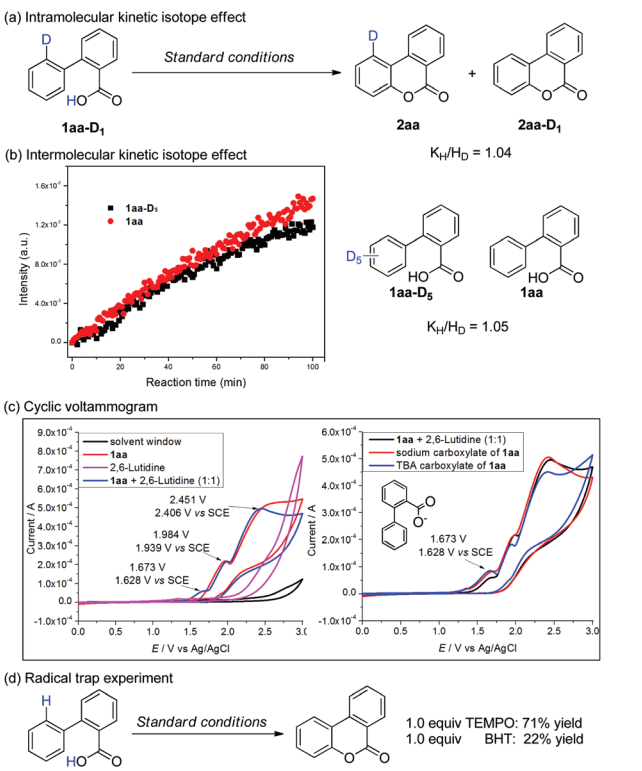
Scheme 5 C(sp^2)–X bond cleavage. [a] 20 mol% 2,6-lutidine was added.

lactonization adducts (Scheme 5). Control experiments revealed that no reaction was observed without a photocatalyst and visible light, which excluded an aromatic nucleophilic substitution process with the carboxylate as the attacking nucleophile.

To gain more insights into the mechanism, the kinetic isotope effect (KIE) experiments were examined by using *in situ* IR. A new peak at 1612 cm^{-1} belonging to the ester group of **2aa** could be observed accompanied by the consumption of **1aa** (Scheme 6b). The initial rate of oxidation of **1aa** *versus* its deuterated analogue **1aa-D$_5$** provided a KIE of 1.05. Similar k_H/k_D was obtained in mono-deuterated **1aa-D$_1$** (determined by ^{1}H NMR, Scheme 6a). Combined, these results suggested that C–H bond cleavage was not involved in the rate-determining step.

A cyclic voltammogram indicated that the oxidation potential of **1aa** is 1.939 V *vs.* SCE. Once 2,6-lutidine was added, a lower oxidative peak appeared at 1.628 V *vs.* SCE, which could be ascribed as the oxidation of carboxylate (Scheme 6c). Direct CV studies of purified sodium and ammonium tetrabutyl salts (TBA) of **1aa** showed nearly identical oxidative peaks (Scheme 6c).[4d] These results suggested that SET of carboxylate is more feasible than that of the arene ring under our catalytic conditions. In addition, control experiments indicated the inhibition effect of radical scavengers, such as TEMPO and BHT (Scheme 6d), which suggested that radical species were likely involved in this intramolecular radical process.

On the basis of the above observations, a plausible catalytic cycle is proposed in Scheme 7. Upon deprotonation, the car-



Scheme 6 Mechanism studies.

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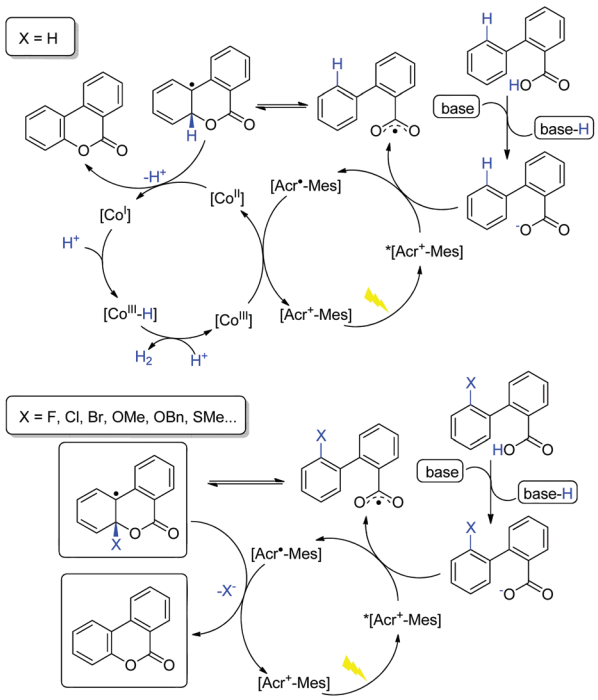

Scheme 7 Proposed mechanism.

boxylic acid is oxidized *via* SET by *[Acr$^+$-Mes], resulting in the formation of a carboxylic radical. The subsequent radical addition to an arene results in an aryl radical species and further oxidation by the cobalt catalyst leads to the desired product. The latter step may proceed *via* hydrogen atom abstraction (HAT) or e/H+ transfer sequence. The cobalt catalyst would serve as the proton and electron reservoir, leading to hydrogen release.[15,16] An alternative mechanism scenario involving nucleophilic addition of carboxylate to the arene radical cation,[11] though cannot be completely excluded, is not supported by the available experimental observations. In the C–X cleavage process in the absence of the cobalt catalyst, the generated aryl radical intermediate is reduced by [Acr$^•$-Mes], and elimination of X– gives the lactonization product (Scheme 7).

Conclusions

In summary, we have developed a visible-light promoted arene C–H/C–X lactonization *via* a carboxylic radical intermediate. This protocol constitutes a facile, environmentally benign, and general method for preparing diverse coumarin derivatives under mild reaction conditions. This oxidant-free system, mediated by a photocatalyst and a cobalt catalyst, offers a new strategy beyond traditional catalysis using stoichiometric or excess amounts of oxidants. We believe that the current strategy *via* carboxylic radicals will find more application in intermolecular C–H and C–X bond functionalization processes.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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