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Transition-metal-free oxidative cyclization reaction of enynals to access pyrane-2-one derivatives†

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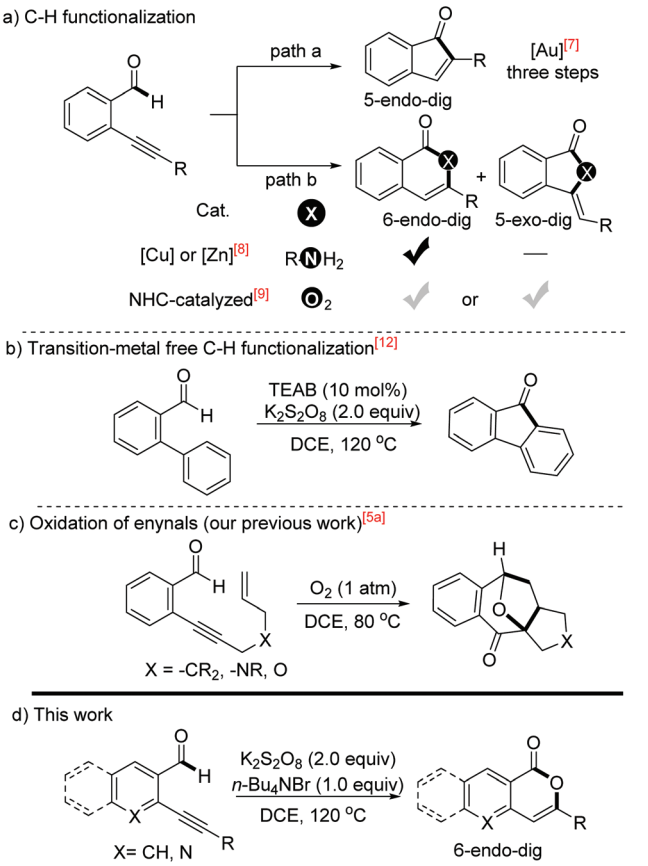
A novel and efficient metal-free C–H functionalization of enynals is developed to synthesize α-pyrone derivatives *via* the formation of two C–O bonds. In this project, $K_2S_2O_8$ has been introduced as an efficient oxygen source and C–H functionalization agent in regioselective oxidative cyclization reaction with a relatively broad substrate scope.

The universal application of enynals and related precursors in the synthesis of various hetero- and carbocyclic compounds makes them one of the most attractive families of organic molecules.[1] Yamamoto and co-workers were the first to use the unique features of these structures and their applications in a tandem nucleophilic addition reaction which leads to the alkenyl ether products.[2] In the last decade, enormous efforts have been made to promote applications of enynals as a reliable and beneficial precursor in the nucleophilic addition,[3] carbene-transfer,[1f,4] cycloadditions,[1g,5] and C–H functionalization[6] reactions. Unfortunately, despite the comprehensive use of C–H functionalization reactions in modern organic chemistry, these methods are restricted to scarce examples on enynals. In this context, cyclization of 2-cyclic acetal derivatives of enynals have been reported, with the aim of aldehyde moiety addition to the alkyne segments, *via* gold-catalyzed hydride shift.[7] This method provides a route to the C–H functionalization of enynals in three steps to synthesize indenones (Scheme 1a, path a). As another path for the C–H functionalization of enynals, isoquinolone scaffolds have been generated through an intramolecular 6-*endo-dig* addition of *in situ* formed hemiaminal moieties to the triple bonds and oxidation in the presence of different metal catalytic systems (Scheme 1a, path b).[8] Indeed, this reaction is another example of a nucleophilic addition reaction on *ortho*–alkynylaryl aldimines in which water reacts as a nucleophile.[2b]



Scheme 1 (a) C–H functionalization of enynals. (b) Metal-free C–H functionalization of aldehydes. (c) Oxidation of enynals. (d) Present work.

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Besides, the Youn group developed an NHC-catalyzed oxidative cyclization of *o*-alkynyl benzaldehydes to obtain phthalides and isocoumarins in which the regioselectivity was altered by changing the substitutions of the alkyne moiety (Scheme 1a, path b).[9]

Based on these reports, the development of new regioselective and transition metal-free strategies that lead to efficient and step-economical C–H functionalization reaction on enynal structures remains a significant challenge.

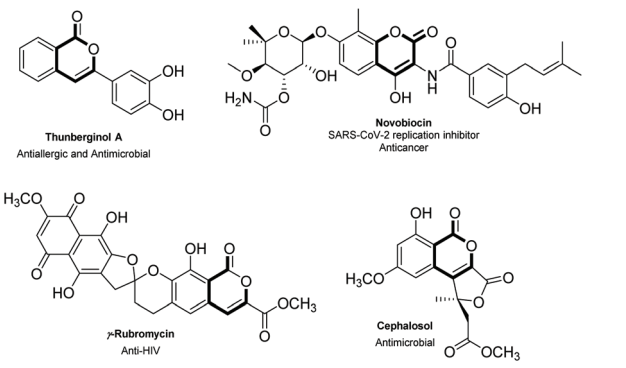
In recent years, aldehyde C–H functionalization has been considered one of the most important and practical atom economic strategies for C–C and C–heteroatom bond formations. Although reports around this field mostly were focused on metal-catalyzed reactions, in some cases, efficient transition metal-free methods were also reported.[10] In this regard, we reported a TBHP assisted radical reaction for the synthesis of indenones through the cyclization of aromatic acyl radical intermediates with alkynes.[11] In 2013, Glorius and co-workers established a new method for the synthesis of fluorenones involving the direct intramolecular coupling of aldehyde to phenyl group using $K_2S_2O_8$ as a radical initiator for acyl radical formation (Scheme 1b).[12] As a well-developed strategy in organic synthesis, it seems that acyl radical intermediates can help to remove restrictions of enynal C–H functionalization.

In our previous work, we developed oxidative oligocyclization of enynals and enynones with molecular oxygen through the radical cation chain oxidation mechanism (Scheme 1c).[5a] Benzannulated oxygen-bridged seven-membered ring systems have been generated in the presence of O_2 and $K_2S_2O_8$ as readily available oxidants. $K_2S_2O_8$ reacted as a cooxidant to increase the yields of reaction in the air condition. In the present work, we exhibit a different oxidative cyclization reaction of enynals in the presence of persulfate oxidant ($K_2S_2O_8$) and quaternary ammonium salt (TBAB) affording pyran-2-one derivatives (Scheme 1d). In addition to the synthetic perspective, pyran-2-one scaffolds are prevalent in natural and biologically active compounds, such as Thunberginol A,[13] γ-Rubromycin,[14] Cephalosol,[15] and Novobiocin[16] (Scheme 2).

To examine our hypothesis, 2-(phenylethynyl) quinoline-3-carbaldehyde 1a was used as a model substrate. Since potassium persulfate ($K_2S_2O_8$) and tetra-ethylammonium bromide (TEAB) have been introduced as an inexpensive and convenient couple to generating acyl radical spices in the intramolecular cyclization reactions,[12,17] the first reaction was carried out in the presence of $K_2S_2O_8$ and TEAB in DCE at 120 °C under the argon atmosphere (Table 1, entry 1). Surprisingly, oxidative cyclization product **2a** (instead of 5-*endo-dig* product) was obtained with exclusive regioselectivity in 12% yield.

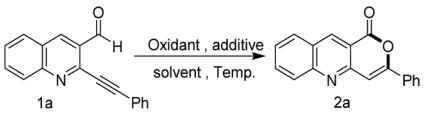
In the next step, the reaction was fulfilled in some other additives (also as phase-transfer catalysts), including TBAI, TBAB, and KBr. The best performance was obtained in the presence of TBAB. After an extensive oxidant screening (TBHP, oxone, BPO, *m*CPBA, $(NH_4)_2S_2O_8$, and $K_2S_2O_8$), as illustrated in Table 1, persulfates showed more reactivity for lactonization. In particular, $K_2S_2O_8$ was found to be the best choice to give **2a** in 82% yield (Table 1, entries 1–6). This result can be related to better solubility of potassium salts in organic solvent performing the efficient transformation.[18] Subsequently, the reaction was performed in various solvents with different polarities. However, these solvents were less efficient than DCE (see ESI, Table S2†). It is noteworthy that the reaction yield decreases by decreasing temperature and replacing argon with the air atmosphere. Therefore, the optimized conditions were confirmed to be 1.0 equiv. of 2-(phenylethynyl)quinoline-3-carbaldehyde 1a, 2.0 equiv. of $K_2S_2O_8$, and 1.0 equiv. of TBAB in DCE (0.2 M) at 120 °C (Table 1, entry 2).

As exhibited in Scheme 3, the scope and generality of the reaction have been examined with various substitutions on both alkyne and quinoline moiety in the optimized reaction condition. Quinoline with the various substituents at the different positions on the phenyl ring (such as Me, Et, isopropyl, OMe, and even aryl) afforded the desired products **2a–2i** in good to excellent yields (77–87%). The substrate **1j** containing *tert*-butyl



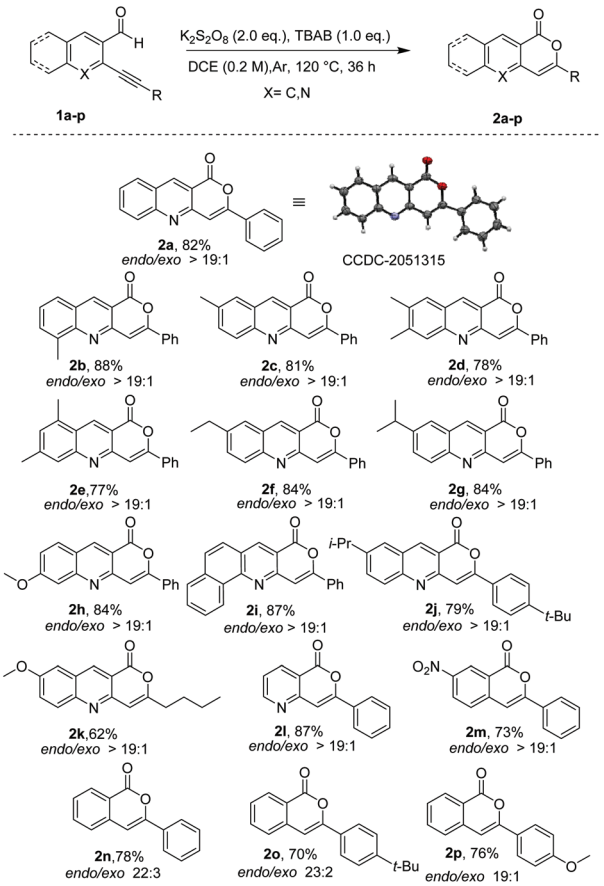
Scheme 2 Representative naturally and biologically active pyran-2-one.

Table 1 Optimization of the reaction conditions[a]



Entry	Oxidant	Additive	Solvent	Yield[b] (%)
1	$K_2S_2O_8$	TEAB	DCE	12
2	$K_2S_2O_8$	TBAB	DCE	82
3	$K_2S_2O_8$	TBAI	DCE	15
4	$K_2S_2O_8$	KBr	DCE	20
5	$K_2S_2O_8$	—	DCE	35
6	—	TBAB	DCE	ND[c]
7	Oxone	TBAB	DCE	30
8	BPO	—	DCE	ND
9	*m*CPBA	—	DCE	ND
10	$(NH_4)_2S_2O_8$	TBAB	DCE	72
11	TBHP	—	DCE	25

[a] Reaction conditions: **1a** (102.0 mg, 0.4 mmol), oxidant (2.0 equiv.), additive (1.0 equiv.), DCE (2.0 ml), under Ar atmosphere, 120 °C and 36 h. [b] Isolated yields, the diastereomer ratios (dr) were determined using ^{1}H-NMR and *endo*/*exo* is >19 : 1 in all cases (using vinylic hydrogen peaks). [c] ND = Not detected.

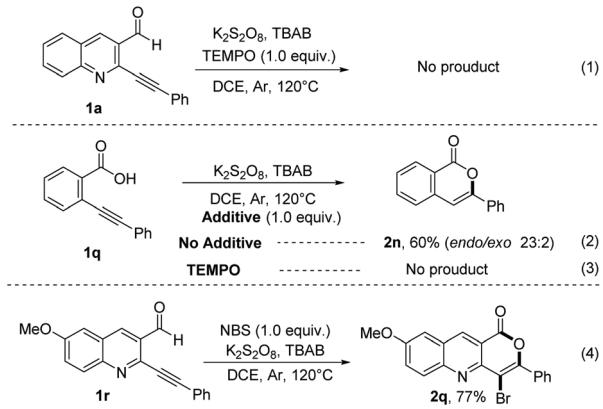


Scheme 3 Scope of the reaction.

substituent on the phenylacetylene segment reacted favorably and furnished the corresponding product **2j** in 79%.

The starting material with aliphatic alkyne **1k** also reacted smoothly to give the desired cyclization product **2k** in 62% yield. Then, the cyclization reaction of 2-(phenylethynyl) nicotinaldehyde **1l** was investigated under the optimal reaction condition. The desired product **2l** was obtained with 87% efficiency. To further generalize the scope of the reaction, this methodology was explored with 2-(phenylethynyl) benzaldehyde **1n** and some of its analogs **1m–1p**. In these cases, a small amount of the 5-*exo-dig* products **2n–2p** was observed, which may be related to the absence of pyridine as an electron-deficient group; hence, the carbon–carbon triple bond is not sufficiently polarized. This supposition was confirmed when an electron-withdrawing group was used on the phenyl ring of enynal, and only the 6-*endo-dig* product **2m** was obtained. For more confidence, the structure of **2a** was confirmed with the single-crystal X-ray analysis.

To elucidate the reaction mechanism, we designed some control experiments, as shown in Scheme 4. When the reaction was exerted in the presence of TEMPO (known as a radical scavenger), the yields decreased sharply, suggesting that this reaction involves radical intermediates (Scheme 4, eqn (1)). Afterward, the reaction of 2-(phenylethynyl)benzoic acid has been performed under the optimized conditions. The same

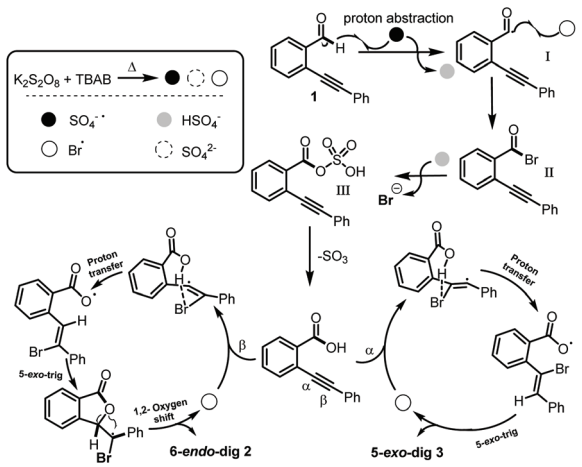


Scheme 4 Control experiments.

cyclization product **2n** represents carboxyl radical (or related compounds) as the possible intermediates, leading to final cyclization (Scheme 4, eqn (2) and (3)).

The experiment was carried out in the presence of *N*-bromosuccinimide (NBS) as a convenient source of the bromine radical in the reaction conditions; a product with a Br substituent on the pyrone ring confirms the presence of the vinyl radical intermediate in the reaction mixture, which was trapped with NBS (Scheme 4, eqn (4)). This novel reaction of enynals in the presence of NBS and $K_2S_2O_8$ is being studied in our research group.

Based on the pieces of evidence mentioned above and previous reports,[19] the plausible mechanism is depicted in Scheme 5. Initially, $K_2S_2O_8$ reacts with TBAB to generate the $(n\text{-}Bu_4N)_2S_2O_8$, producing the tetrabutylammonium sulfate radical anions (SRA) and the bromine radical at high temperatures. The *in situ* generated SRA reacts with enynal **1** to provide the acyl radical **I**. Afterward, the bromine radical combinates with acyl radical to generate acyl bromide **II**. The generated HSO_4^- attacks this acyl bromide to form intermediate **III**. The resulting intermediate can release sulfur trioxide through con-



Scheme 5 Plausible reaction mechanism.

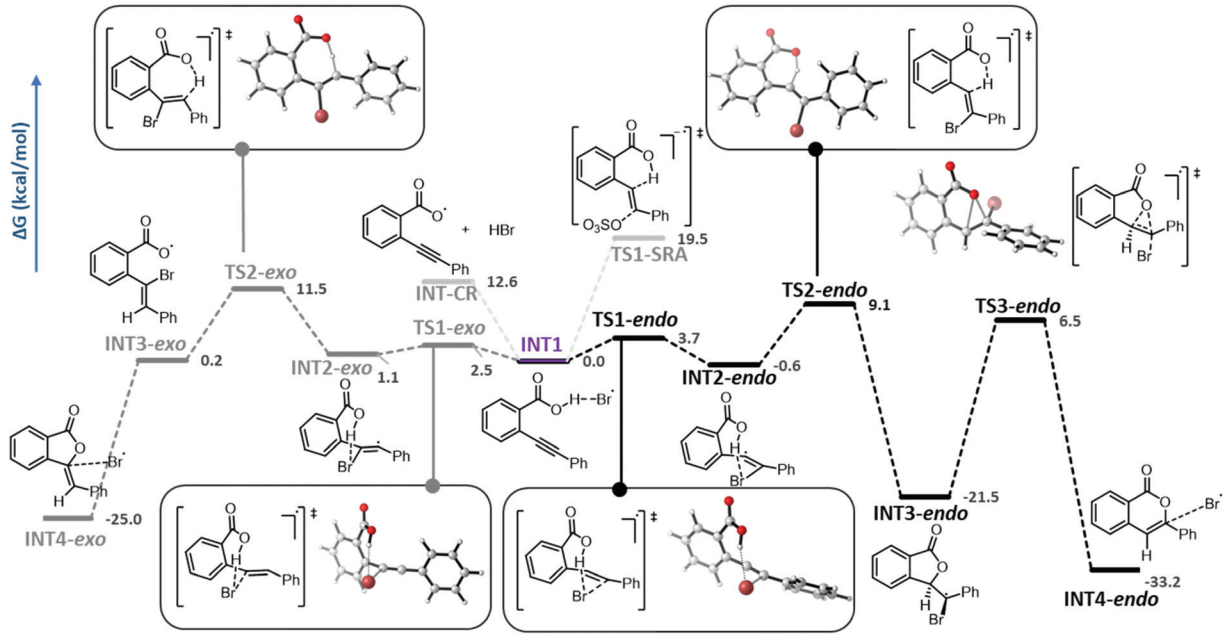


Fig. 1 Potential energy surfaces of the intramolecular cyclization of 2-(phenylethynyl)benzoic acid (all energies are in kcal mol^{-1}).

certed cleavage of the S–O bond and Hydrogen transfer. The intramolecular radical cyclization of the resulting compound takes place to form 6-*endo-dig* **2** or 5-*exo-dig* **3** products, depending on which carbon of triple bond is attacked.

To investigate the mechanism of intramolecular cyclization of 2-alkynyl benzoic acid as a critical step in determining diastereoselectivity, we carried out a series of density functional theory (DFT) studies at the UB3LYP/6-31G(d) level of theory using the Gaussian 09 package (Fig. 1).[20] 2-(phenylethynyl) benzoic acid has been selected as the model for 2-alkynyl benzoic acid intermediates. DFT calculation shows that carboxyl radical species (**INT-CR**) is unstable, about 12.6 kcal mol^{-1}, and the SRA needs 19.5 kcal mol^{-1} in case of addition to alkyne moiety (**TS-SRA**). In contrast, bromine radical is more reactive than SRA in case of addition to alkyne and just needs 3.7 and 2.5 kcal mol^{-1} to form **INT2**, which was probably trapped in control experiment **3** (**TS1-*endo*** and **TS1-*exo***, respectively). It seems that in the next step, intramolecular proton transfer controls the diastereoselectivity of the reaction. The intramolecular proton transfer of **INT2** is in favour of **TS2-*endo*** due to the strain of 6 and 7 membered ring TS (**TS2-*endo*** and **TS2-*exo***, respectively). The resulting carboxyl radicals lead to barrier-less 5-*exo-trig* cyclization (**INT3-*endo*** and **INT4-*exo***). Eventually, **INT3-*endo*** forms **INT4-*endo*** through an unprecedented 1,2-oxygen shift as the major product of the reaction. This investigation presents new reactivity of Br. as an alkyne activator.

Conclusions

The C–H functionalization of enynals was developed through an efficient and regioselective radical tandem lactonization, which avoids using expensive transition metal catalysts. This strategy provides the α-pyrone derivatives in high to excellent yields. The key feature of this C–H functionalization is the introduction of $K_2S_2O_8$ as an efficient and straightforward oxygen source. In addition, DFT calculation shows that alkyne groups can be activated using the bromine radical species in the intramolecular nucleophilic addition reactions.

Conflicts of interest

There are no conflicts to declare.

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