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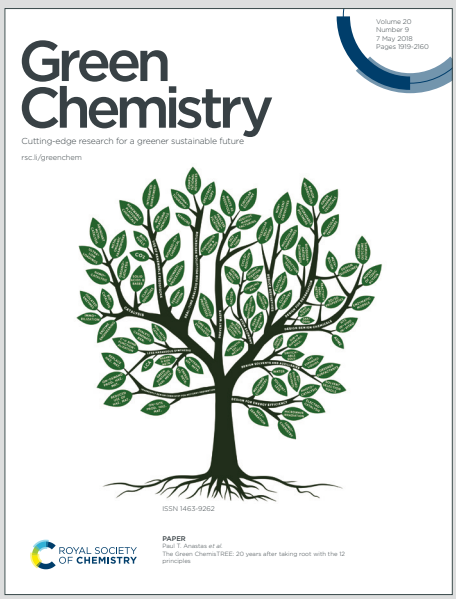

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PAPER

Synthesis of Hydroxyl-Containing Oxindoles and 3,4-Dihydroquinolin-2-ones through Oxone-Mediated Cascade Arylhydroxylation of Activated Alkenes

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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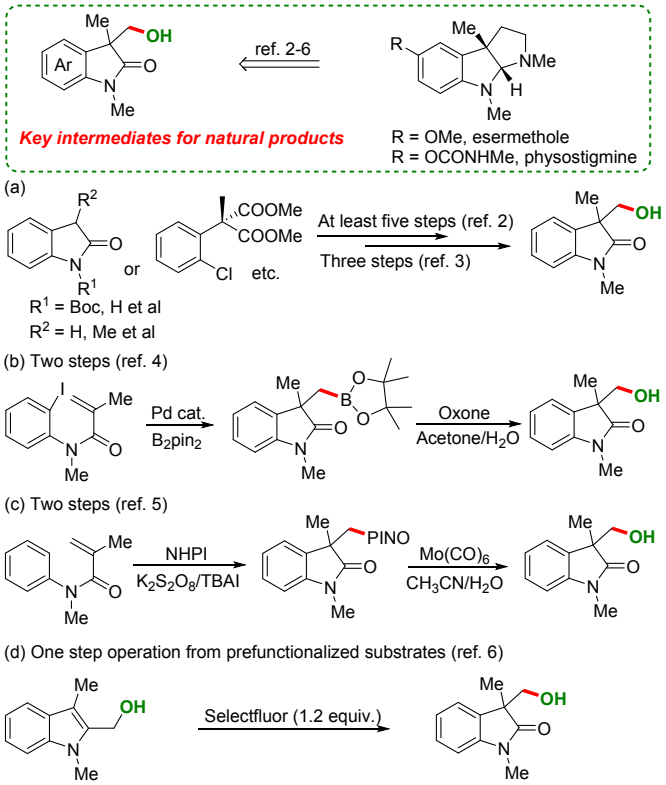
Hydroxyl-containing compounds are highly value-added organic molecules, and the establishment of novel methodologies for their elaboration is a long-standing challenge in organic synthesis. Here the first oxone-mediated direct arylhydroxylation of activated alkenes was developed for the synthesis of valuable hydroxyl-containing oxindoles and 3,4-dihydroquinolin-2-ones. The products were controlled by adjusting the structure of the starting alkenes. Moreover, the reaction was operated under simple conditions without any external additives or catalysts. Primary mechanistic studies showed that this reaction was a tandem process involving epoxidation and subsequent Friedel-Crafts alkylation, and oxone played a dual role (both the oxidant and proton source) in this process.

Introduction

3,3-Disubstituted 2-oxindoles exist extensively in a variety of bioactive molecules as one kind of important five-membered fused nitrogen-heterocycles.[1] Among them, the quaternary 3-hydroxymethyl-2-oxindoles are particularly attractive, because they are very valuable for the synthesis of natural product esermethole and physostigmine.[2-6] As illustrated in Scheme 1, a number of multistep reactions have been developed for the production of 3-hydroxymethyl-2-oxindoles, but these approaches usually suffer from low atom economy and require poisonous reagents or expensive metal catalysts (Scheme 1a).[2,3] In 2015, the Pd-catalyzed Heck/borylation of *N*-(2-iodophenyl)acrylamides was demonstrated as an indirect approach for producing 3-hydroxymethyl-2-oxindoles (Scheme 1b).[4] Recently, we reported an oxidative radical aminooxyarylation of activated alkenes, affording products that could be further converted into 3-hydroxymethyl-2-oxindoles in an aqueous acetonitrile solution (Scheme 1c).[5] An oxidative rearrangement strategy was also developed for the direct assembly of 3-hydroxymethyl-2-oxindoles, the reaction relied on a prefunctionalized 2-hydroxymethylindole substrate and needed to use the environmentally unfriendly organic fluorine reagent as the oxidant (Scheme 1d).[6] Thus, more economical, practical and eco-friendly synthetic strategies for 3,3-disubstituted 2-oxindoles are highly desirable.



Scheme 1 Preparation of 3-hydroxymethyl-2-oxindoles

The 1,2-difunctionalization of alkenes can incorporate two functional groups into a molecule in one pot with high atom- and step-economic efficiency and thus is recognized as a powerful method for building the highly value-added molecules.[7] During the past decades, much effort has been devoted to this field, and many

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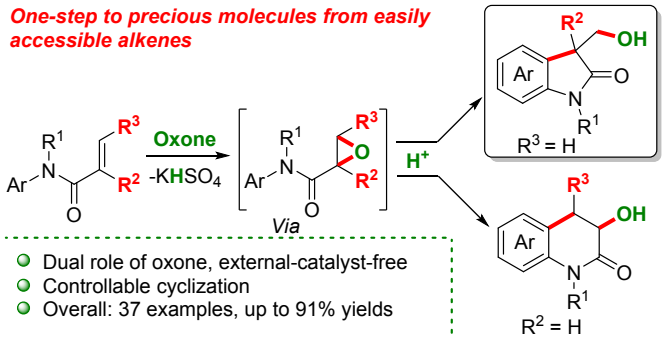
†Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

transition metal-catalyzed and metal-free methods have been developed, achieving dicarbofunctionalization,[8] carboheterofunctionalization[9] and diheterofunctionalization.[10] The direct arylhydroxylation of alkenes is an important method for the synthesis of hydroxyl compounds. However, only few examples were reported. In 2013, Jiao's group described that phenyl hydrazines could oxidatively couple with styrenes to produce the corresponding arylhydroxylating products.[11] Three years later, a similar arylhydroxylation reaction was accomplished by Heinrich's group using aryldiazonium salts as a radical source under thermal induced conditions.[12] In 2018, Buchwald *et al.* reported a new version of arylhydroxylation reaction of dehydroalanine with aryldiazonium salts through a catalytic redox process using ferrocene.[13]



Scheme 2 Oxone-mediated intra-molecular direct arylhydroxylation of activated alkenes

Oxone is a cheap, stable, easy to handle and nontoxic inorganic oxidant.[14] The oxidation reactions with oxone as the oxidant have been extensively studied over the past years. However, to the best of our knowledge, the dual role of oxone in organic transformations has rarely been reported.[15] We herein reported an intra-molecular arylhydroxylation[16] reaction (Principle 8, Reduce Derivatives) for the synthesis of hydroxyl-containing heterocycles with oxone as the sole oxidant under the transition-metal-free conditions (Principle 3, Less Hazardous Chemical Syntheses). This reaction was a cascade epoxidation/Friedel-Crafts alkylation process. In the reaction, the oxone not only acted as an oxidant for the epoxidation of alkenes but also served as the proton source for the subsequent ring-opening Friedel-Crafts alkylation (Principle 1, Prevention). This reaction provided a versatile and simple platform for the selective construction of 3-hydroxymethyl-2-oxindoles and 3-hydroxy-3,4-dihydroquinolin-2-ones[17] with step- and atom-economy (100% with respect to *N*-arylacrylamides, Principle 2, Atom Economy). It should be noted that the halocarbocyclizations of *N*-arylacrylamides with halogenation reagents in the presence of a large excess of oxidants have been developed for the construction of 3-halomethyl-2-oxindoles[18] and analogues.[19] These products might be further transformed into the corresponding hydroxyl derivatives via extra reaction procedures. However, the requirement of stoichiometric halogenation reagents not only increased the manufacturing cost but also led to producing copious halide waste. Mechanistic studies showed that halonium ions were the key intermediates in these reactions.

Results and discussion

Table 1. Optimization of the arylhydroxylation of activated alkene **1a**[a]

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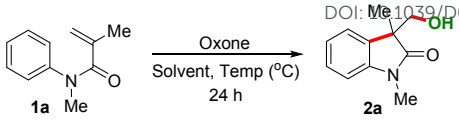


Entry	Oxone (equiv.)	Solvent	Tem. (°C)	Yield (%)[b]
1	2.0	MeCN	80	55
2	2.0	DCE	80	trace
3	2.0	Benzene	80	trace
4[c]	2.0	DMSO	80	N.R.
5	2.0	DMF	80	trace
6	2.0	EtOAc	80	trace
7[c]	2.0	THF	80	N.R.
8[c]	2.0	PhCN	80	N.R.
9	2.0	MeCN	90	74
10	2.0	MeCN	100	63
11	1.5	MeCN	90	70
12	1.2	MeCN	90	61
13[d]	2.0	MeCN	90	57
14[e]	2.0	MeCN	90	71
15[f]	2.0	MeCN	90	74

[a] Reaction conditions: a mixture of **1a** (0.3 mmol), oxone in solvent (3.0 mL) was heated at the indicated reaction temperature under the air atmosphere for 24 h. [b] Isolated yield. [c] N.R. = no reaction. [d] 12 h. [e] 30 h. [f] Under N_2 atmosphere.

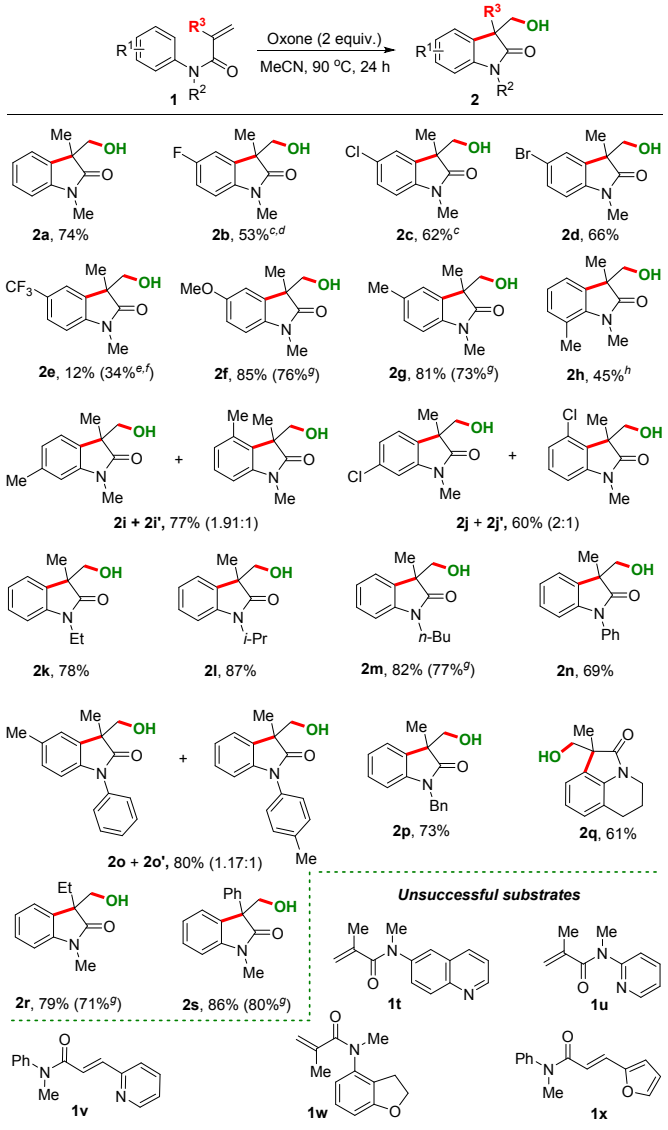
Heating the mixture of activated terminal alkene **1a**, oxone (2 equiv.) in MeCN at 80 °C for 24 h under air atmosphere resulted in the formation of the desired 3-hydroxymethyl-2-oxindole **2a** in 55% yield (Table 1, entry 1). Next, a series of solvents were investigated. MeCN seemed to be essential to this reaction, since no or only a trace amount of product could be detected in other solvents such as DCE, benzene, DMSO, DMF, EtOAc, THF and PhCN (entries 2-8). When the reaction was carried out at 90 °C, the yield of **2a** increased to 74% (entry 9); however, further elevating the reaction temperature to 100 °C lead to slight decrease of the yield (entry 10). To our satisfaction, a good yield (70%) was also achieved by reducing the amount of oxone to 1.5 equiv. (entry 11); however, when 1.2 equiv. of oxone was used, the yield of **2a** decreased to 61% (entry 12). The reaction time was also screened with 24 h being suitable for this reaction (entries 9, 13 and 14). Finally, the same yield of **2a** was obtained under N_2 atmosphere (entry 15).

With the optimal reaction conditions in hand, the substrate scope was subsequently investigated. As shown in Table 2, this reaction showed relatively high functional group tolerance. For example, F, Cl, Br, CF_3, MeO and Me all were compatible under the reaction conditions (**2b-2g**). It should be noted that the yield was affected by the electron density of benzene ring. When the electron-deficient substrates were used, the yield decreased. Prolonging the reaction time could improve the yields to some extent. The results were consistent with the proposed mechanism as described below, because the Friedel-Crafts alkylation took place more readily at the electron-rich benzene. In the cases of the *N*-methyl-*N*-phenylmethacrylamides bearing strong electron-withdrawing fluoro or trifluoromethyl substituent on the phenyl ring (**1b** or **1e**), the epoxides **2b'** and **2e'** were formed in 26% and 40% yield, respectively. The steric hindrance also affected the reaction. For example, when *ortho*-methyl derivative was used under the

standard conditions, the corresponding cyclizing product (**2h**) was given in 45% yield; the epoxide **2h'** was also isolated in 38% yield. When the substrates bearing *meta*-group were used, a mixture of regioisomers were generated with the cyclization preferentially occurring at the *para*-position of *meta*-group (**2i** and **2j**).[20] The *N*-substituent was subsequently investigated, and all selected derivatives could be converted into the expected arylhydroxylated products in good to high yields (**2k-2q**). As expected, a mixture of regioisomers was given when the substrate bearing two *N*-aryl groups (**2o**) was applied. Worth noting is that a three cyclic product was produced in a good yield when the tetrahydroquinoline derivative was used under the reaction conditions (**2q**). The substituent effect at the *α*-position of the acrylamide moiety was also investigated. It was found that both ethylacrylamide and phenylacrylamide showed high reactivity in this arylhydroxylation (**2r** and **2s**). A series of heteroaromatic substrates were also explored under the standard conditions. However, the *N*-heteroaromatic substrates failed to produce the desired products, which might be caused by the formation of heteroaromatic onium salt between *N*-heteroaromatic substrates and potassium bisulfate. The *O*-heterocycles gave a complex mixture of unidentified products. As demonstrated in Table 1, the reaction of **1a** with 1.5 equiv. of oxone could also provide a satisfactory yield (entry 11). We also evaluated the reaction efficiency of several well performed substrates under the reaction conditions, and the results were listed under the corresponding products (**2f**, **2g**, **2m**, **2r** and **2s**) in Table 2.

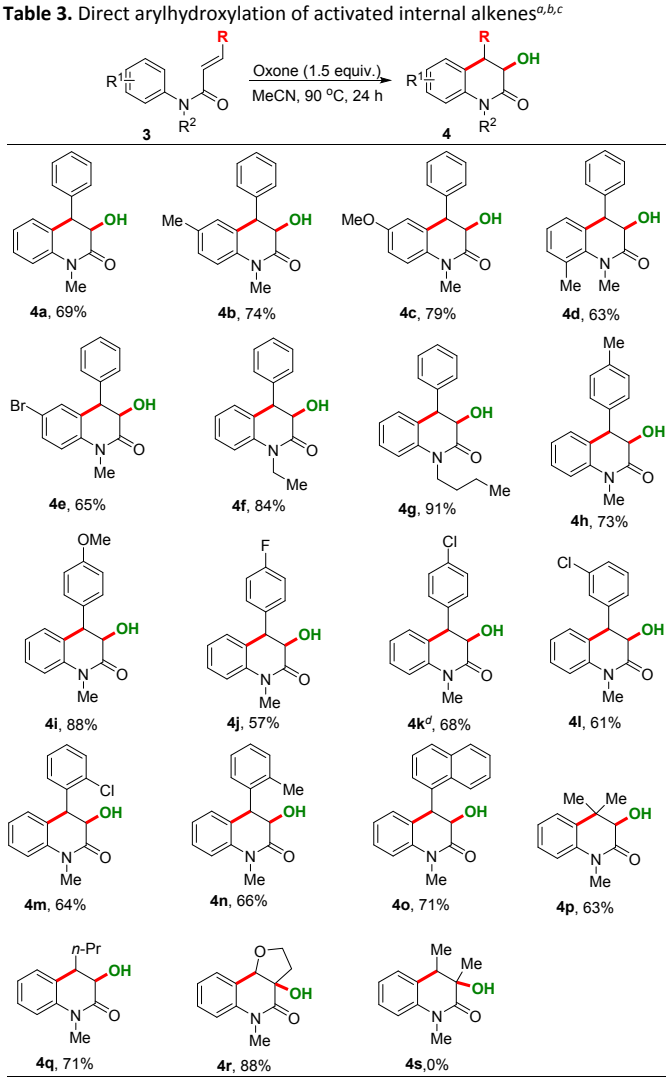
We then investigated the internal alkenes.[21] Interestingly, not the five-membered cyclic oxindoles, but the six-membered cyclic 3,4-dihydroquinolin-2-ones were produced under the reaction conditions. As illustrated in Table 3, a variety of six-membered cyclic hydroxyl-containing products including those with functional groups were generated in good to high yields (**4a**-**4o**). The studies on the

Table 2. Direct arylhydroxylation of activated terminal alkenes[a,b]



[a] Reaction conditions: a mixture of **1** (0.3 mmol), oxone (2 equiv.) in MeCN (3.0 mL) was heated at 90 °C under air atmosphere for 24 h. [b] Isolated yields. [c] 30 h. [d] Epoxide **2b'** was also isolated in 26% yield. [e] 40 h. [f] Epoxide **2e'** was also isolated in 40% yield. [g] Using 1.5 equiv. of oxone. [h] Epoxide **2h'** was also isolated in 38% yield.

Table 3. Direct arylhydroxylation of activated internal alkenes[a,b,c]



[a] Reaction conditions: a mixture of **3** (0.3 mmol), oxone (1.5 equiv.) in MeCN (3.0 mL) was heated at 90 °C under air atmosphere for 24 h. [b] Isolated yields. [c] Only trans isomers were observed. [d] The trans isomer of **4k** was confirmed by single-crystal X-ray diffraction analysis.

N-substituent effect showed that both ethyl and *n*-butyl groups promoted this reaction (**4f** and **4g**). Again, the heavier the electron density is, the easier Friedel-Crafts alkylation occurs. The electron effect on the aryl group connected with the carbon-carbon double bond was also studied and showed that higher yields were obtained with the electron-rich substrates (**4h**-**4o**). It was deduced that the electron-rich aryl group could promote the cleavage of C-O bond during the ring-opening Friedel-Crafts alkylation, and thus enhanced the yield. Acrylamide substrates with alkyl substituents on the β-position of vinyl group gave the desired products (**4p** and **4q**) in good yields. *N*-Methyl-*N*-phenyl-4,5-dihydrofuran-3-carboxamide also produced the expected cyclizing product 3,4-dihydroquinolin-2-one product (**4r**) in 88% yield. Unluckily, acrylamide bearing methyl groups on both α- and β-position of vinyl group afforded a complex mixture of unidentified products under the reaction conditions (**4s**).

As shown in Figure 1, the structure of product **4k** was confirmed by single-crystal X-ray diffraction analysis, clearly showing that phenyl and hydroxyl groups were not on the same side of ring (CCDC 2012568; for details, see the ESI†). The result indicated that this reaction exhibited high *trans*-selectivity in the ring-opening Friedel-Crafts alkylation.

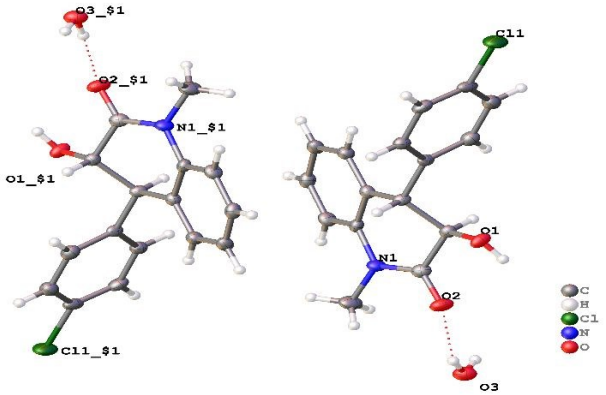
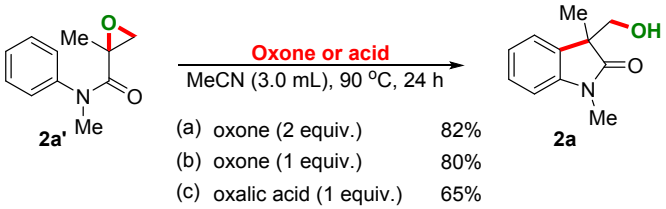


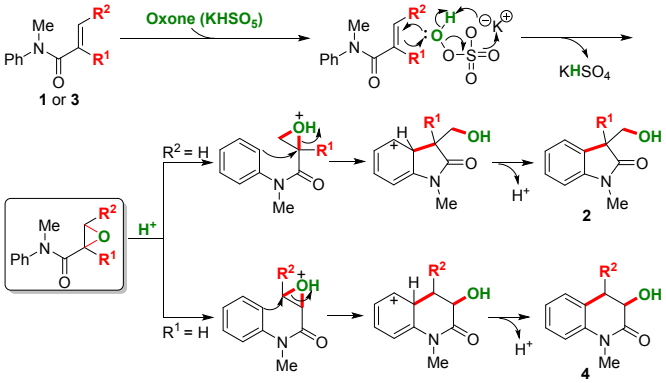
Figure 1 Molecular structure of product **4k** (one crystal water is attached).

In order to gain some mechanistic information, several control experiments were conducted (Scheme 3). During the reaction process, epoxide product **2a'** was detected by GC-MS (for details, see the ESI†). Previous work has showed that oxone is an effective oxidant for the epoxidation of alkenes.[14a] Therefore, combining with the electron effect described above, it was deduced that epoxides might be the key intermediate in this reaction. We also synthesized compound **2a'**[22] and found that it indeed could be converted into the corresponding oxindole **2a** under the current reaction conditions (Scheme 3a). This reaction could also take place readily with oxone or oxalic acid (1 equiv.) (Scheme 3b and 3c).



Scheme 3 Control experiments

On the basis of these results and previous related literatures,[14a,23] the arylhydroxylation of activated alkenes would take place through a tandem process involving epoxidation and subsequent Friedel-Crafts alkylation, and oxone acted as a dual role mediator in this tandem process (Scheme 4). It should be noted that the ring-opening Friedel-Crafts alkylation of arenes with epoxides determined the regioselectivity to produce either five-membered cyclic hydroxyl-containing oxindole or six-membered cyclic hydroxyl-containing 3,4-dihydroquinolin-2-ones.



Scheme 4 Proposed mechanism

Conclusions

In summary, we have described for the first time an oxone-mediated cascade arylhydroxylation of activated alkenes, and both the valuable hydroxyl-containing oxindoles and 3,4-dihydroquinolin-2-ones could be readily prepared by adjusting the structure of the starting alkenes. The efficiency and practicality of this new methodology were well demonstrated with (1) 37 examples, (2) wide functional group tolerance and generally good yields (up to 91%), and (3) successful integration of epoxidation and ring-opening Friedel-Crafts alkylation as a one-pot reaction, achieving one step synthesis of high value-added molecules, especially 3-hydroxymethyl-2-oxindoles, from easily accessible alkenes. The present method is of great value from the viewpoint of green chemistry and organic synthesis because of using cheap and non-toxic oxone as a dual role mediator under additional additives- and catalysts-free conditions.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We gratefully acknowledge financial support from the Project for Basic Research and Frontier Exploration of Science and Technology Commission of Chongqing (no. cstc2018jcyjAX0419 and cstc2019jcyj-msxm1275), the Science and Technology Research Program of Chongqing Municipal Education Commission (no. KJ1601202 and KJQN201901422), the Natural

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