RSC Advances

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2016, **6**, 74917

Received 23rd June 2016
Accepted 2nd August 2016

DOI: 10.1039/c6ra16266e

www.rsc.org/advances

Selectfluor-mediated highly selective radical dioxygenation of alkenes†

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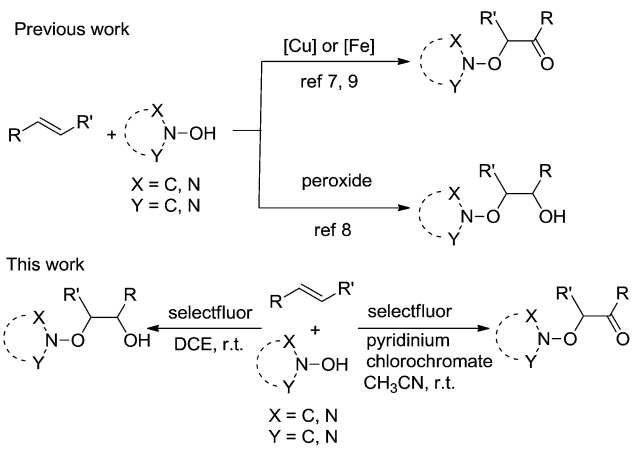
A practical and simple selectfluor mediated highly selective radical dioxygenation of alkenes was achieved under mild conditions. Various hydroxylamines, such as *N*-hydroxyphthalimide (NHPI), *N*-hydroxybenzotriazole (HOBt) and *N*-hydroxysuccinimide (NHSI), could react smoothly with alkenes to give β-oxo alcohols and α-oxy ketones in good to moderate yields. The reaction mechanism was primarily investigated and a radical process was proposed.

Alkenes are the most ubiquitous prochiral functional groups, and direct difunctionalization of alkenes (whereby two functional groups are added to the same double bond) has attracted considerable attention in organic synthesis.[1] Following the pioneering work of Sharpless and co-workers,[2] metal-free as well as transition-metal-catalyzed difunctionalization of alkenes, such as dioxygenation,[3] aminooxygenation, diamination, aminohalogenation, fluoroamination, azidooxygenation and carboamination have been intensively studied.[4] Among which, the selective and sustainable dioxygenation of alkenes is a valuable synthetic tool for the preparation of 1,2-diols, α-hydroxyketones, and 1,2-dicarbonyl compounds, which have high utility in organic synthesis.[5] Although there have been significant developments in this area in recent decades, the development of selective dioxygenation reactions remains challenging. For example, current methods suffer from the use of toxic and/or expensive transition metals or require dialkylperoxides as initiators.

N-Hydroxyphthalimide (NHPI) is not only a cheap, nontoxic catalyst for C–H bond functionalization by using an *in situ* generated phthalimide *N*-oxyl (PINO) radical, but also a precursor of oxime ethers.[6] Recently, Punniyamurthy,[7a] Woerpel,[7b] Liang,[7c] and Tang[7d] independently reported transition-metal catalysed oxidation of alkenes using molecular oxygen and NHPI. Similarly hydroxamic acid derivatives are also used as radical precursors for dioxygenation of alkenes in the works of Alexanian[8] and Lei *et al.*[9] As part of our continuing interest in employing efficient *O*-centered radical precursors, such as NHPI, *N*-hydroxybenzotriazole (HOBt), *N*-hydroxysuccinimide (NHSI) and hydroxamic acid derivatives, for the construction of a C–O bond directly from a C–H bond,[10] we present herein our recent progress in selectfluor-mediated[11] highly selective radical dioxygenation of alkenes, in which versatile β-oxo alcohols and α-oxy ketones can be synthesized in a single process (Scheme 1).

The initial screening studies were carried out using styrene (**1a**) and *N*-hydroxybenzotriazole (**2a**, HOBt) as model substrates. As shown in Table 1, use of $FeCl_2$ as a catalyst and selectfluor as oxidant at room temperature for 12 h in MeCN produced the desired product **3a** in 47% yield together with the corresponding products **4a** (entry 1). The solvent was found to have a significant influence on the reaction efficiency. The results showed that DCE is a highly effective solvent, affording the product **3a** with the highest isolated yield (Table 1, entry 2–4). Surprisingly, control experiment in the absence of Fe catalyst significantly improved the yield of **3a** to 93% yield with high



Scheme 1 Direct dioxygenation of alkenes using hydroxylamines.

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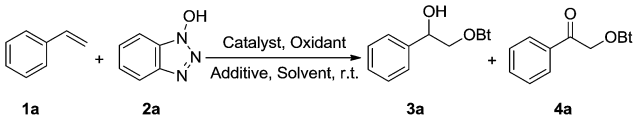
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c6ra16266e

Table 1 Optimization of the reaction conditions[a]



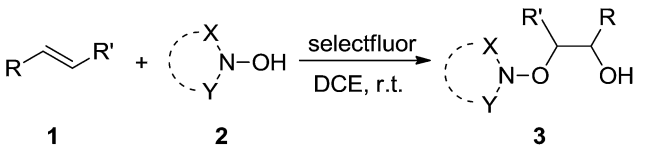
Entry	Oxidant	Catalyst	Additive	Solvent	Yield[b] (%) 3a	4a
1	Selectfluor	$FeCl_2$	—	CH_3CN	47	36
2	Selectfluor	$FeCl_2$	—	DCE	85	Trace
3	Selectfluor	$FeCl_2$	—	DMF	26	15
4	Selectfluor	$FeCl_2$	—	CH_2Cl_2	10	Trace
5	**Selectfluor**	**—**	**—**	**DCE**	**93**	**0**
6	—	$FeCl_2$	—	DCE	0	0
7	TBHP[c]	—	—	DCE	Trace	Trace
8	H_2O_2[d]	—	—	DCE	Trace	Trace
9	$Na_2S_2O_8$	—	—	DCE	Trace	Trace
10	Selectfluor	$FeCl_3$	—	CH_3CN	41	20
11	Selectfluor	$Fe(NO_3)_3$	—	CH_3CN	34	27
12	Selectfluor	—	$Mn(OAc)_3$	CH_3CN	21	36
13[e]	**Selectfluor**	**—**	**PCC**	**CH_3CN**	**Trace**	**70**

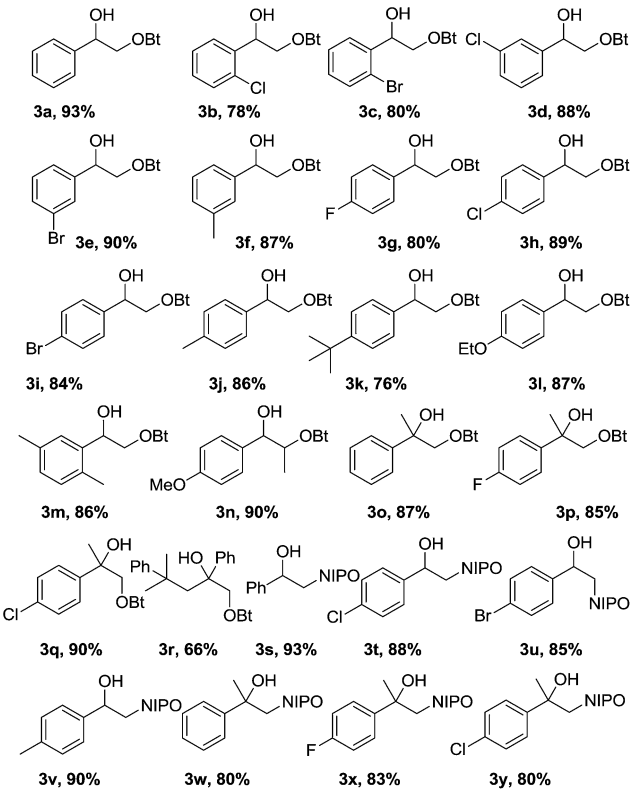
[a] Reaction conditions: **1a** (0.36 mmol), **2a** (0.3 mmol), oxidant (0.3 mmol), catalyst (0.03 mmol), additive (0.3 mmol), solvent (3.0 mL), at room temperature, in air, 12 h. [b] Yield of the isolated product. [c] TBHP (70% in water). [d] H_2O_2 30% in water. [e] 3 h.

regioselectivity as well as absolute chemoselectivity (Table 1, entry 5). Notably, an example of a direct transformation from **1a** and **2a** to **3a** has not been reported until this work. Neither **3a** nor **4a** was observed when selectfluor was absent (Table 1, entry 6). Selectfluor was the most effective oxidant in the process. Other oxidants such as *tert*-butylhydroperoxide (TBHP), 30% H_2O_2 and $Na_2S_2O_8$ did not perform well (Table 1, entries 7–9). To maximize the yields of **4a**, different catalysts and additives were also tested. Instead of $FeCl_2$, the use of some other iron catalysts such as $FeCl_3$ and $Fe(NO_3)_3$ decreased the yields of **4a** dramatically (Table 1, entries 10 and 11). Then several additives were screened, such as $Mn(OAc)_3$ and pyridinium chlorochromate (PCC), and PCC gave a better result (70%; Table 1, entries 12 and 13).

With the optimized reaction conditions in hand, the scope of this highly selective method was investigated. As described in Table 2, styrenes **1** with different substituents on the aromatic ring, including electron-donating and electron-withdrawing groups, can be transformed into the corresponding products **3** in moderate to excellent yields (**3a–r**). Halo-substituted styrenes (**1b–e**, **1g–i**) were tolerated in the dioxygenation reaction, and could be very useful for further transformations. Notably, *trans*-anethole was amenable to this protocol as well and afforded the desired product **3n** in 90% yield. 1,1-Disubstituted alkenes such as **1o–r** were also effective to provide **3o–r** in 66–90% yields. With the role of HOBt established in the dioxygenation, we sought to explore other hydroxylamines that would effect similar oxidations. The dioxygenation of styrenes using NHPI also produced β-oxo alcohols in 80–93% yields (**3s–y**). In all cases, the reactions proceeded smoothly at room temperature

Table 2 Selective synthesis of β-oxo alcohols **3**[a,b]





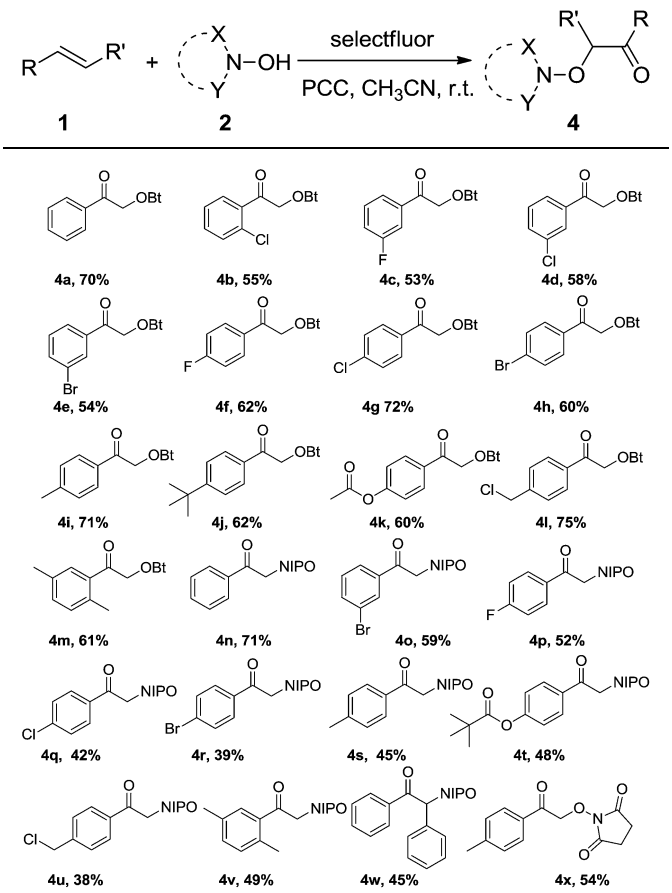
[a] Standard reaction conditions: **1** (0.36 mmol), **2** (0.3 mmol), selectfluor (0.3 mmol), DCE (3.0 mL), at room temperature, in air, 12 h. [b] Yield of the isolated products.

under very mild reaction conditions, and the desired β-oxo alcohols (**3a–y**) were consistently obtained in moderate to excellent yields with high regioselectivity and excellent chemoselectivity (Table 3).

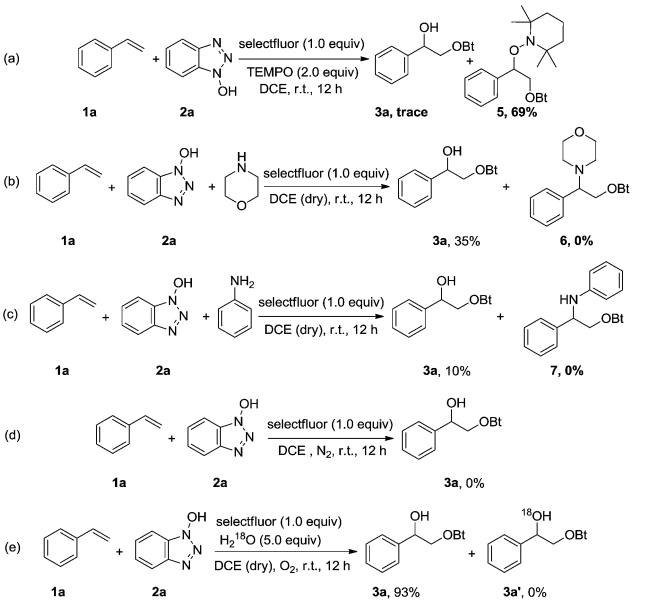
The success of dioxygenation of alkenes encouraged us to further explore the scope of this protocol. When PCC was used as additive, a series of α-oxy ketones were obtained in moderate to good yields (Scheme 3). Halosubstituted styrenes were also tolerated in this transformation, forming the corresponding α-oxy ketones **4b–h**, **4l**, **4o–r** and **4u** in 38–75% yields. (*E*)-1,2-Diphenylethene can produce the desired **4w** in 45% yield. In addition, starting from NHSI, the corresponding product **4x** could be obtained in 54% yields.

Several control experiments were performed to probe the reaction mechanism. When the radical scavenger 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO, 2.0 equiv.) was added to the reaction of styrene **1a** under the optimal condition, after 12 h, a TEMPO-captured product **5** was isolated (69%) and only a trace amount of **3a** was detected (Scheme 2a). In addition,

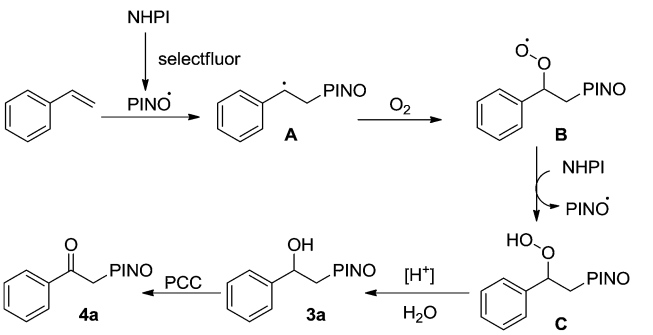
Table 3 Selective synthesis of α-oxy ketones 4[a,b]



[a] Standard reaction conditions: **1** (0.36 mmol), **2** (0.3 mmol), selectfluor (0.3 mmol), PCC (0.3 mmol), CH_3CN (3.0 mL), at room temperature, in air, 3 h. [b] Yield of the isolated products.



Scheme 2 Mechanistic experiments.



Scheme 3 Proposed mechanism.

adding a radical inhibitor 2,6-ditert-butyl-4-methylphenol (BHT) to the reaction system, the formation of the dioxygenation product was also suppressed. The results indicates that a radical addition mechanism was involved in this transformation. Furthermore, the reaction of **1a**, **2a** and morpholine did not result in the formation of **6** (Scheme 2b). When aniline was introduced into the model reaction mixture, no oxoamination product **7** was observed (Scheme 2c). The above results indicate that the benzylic carbocation was not involved in this dioxygenation process. It is notable that no reaction occurred under N_2 and the substrates **1a** and **2a** were completely recovered (Scheme 2d). To gain insight in the reaction pathway, the model reaction between **1a** and **2a** using $H_2{}^{18}O$ was conducted and no ^{18}O-labeled product **3a′** was generated, indicating the oxygen source may be O_2 and not H_2O (Scheme 2e).

Based on the experimental results and literature precedent,[7–10,12] a possible mechanism was proposed in Scheme 3. Initially, selectfluor reacts with NHPI to generate NIPO radical. Then, radical addition of NIPO radical to styrene affords carbon-centered radical **A**, which would further react quickly with dioxygen and be transformed into peroxyl radical **B**.[13] Subsequently, an intermolecular hydrogen abstraction process occurs between NHPI and **B**, delivering NIPO radical and intermediate **C**. Finally, the intermediate **C** can be further transformed into the desired product **3a** under acid conditions.[14] When PCC was used as additive, the β-oxo alcohols **3a** can be further oxidized to give the α-oxy ketones **4a** (see ESI†).

In summary, we have reported a novel selectfluor mediated operationally simple method for selective radical dioxygenation of alkenes. Various styrenes and a diverse range of hydroxylamines such as NHPI, HOBt and NHSI were efficient. The mild reaction conditions, broad substrate scope and high chemoselectivity and regioselectivity would make this process attractive. Further investigations to gain a detailed mechanistic understanding of this reaction and apply this strategy in other difunctionalization reactions of alkenes are currently in progress.

Acknowledgements

We gratefully acknowledge the Science & Technology Foundation of Henan Province, the Foundation of Henan Educational

Committee (15A150029), the open project of Jilin Province Key Laboratory of Organic Functional Molecular Design & Synthesis (130028651) and AYNU-KP-A04 for financial support.

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