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COMMUNICATION

Tert-butyl nitrite: a metal-free radical initiator for aerobic cleavage of benzylic C=C bonds in compressed carbon dioxide†

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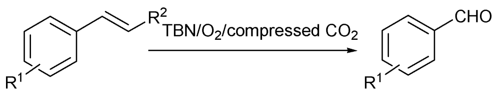
***Tert*-butyl nitrite easily releasing alkoxyl radical and NO in combination with compressed CO_2 under metal free condition was applied to efficiently and selectively initiate aerobic cleavage of benzylic C=C bonds. Notably, compressed CO_2 in this study not only provides a safe reaction environment but also tunes the selectivity.**

Carbon dioxide as either an abundant and readily available carbon resource or a reaction medium has attracted great attention.[1] In particular, compressed CO_2 appears to be an ideal solvent for use in oxidation and free-radical reactions. Unlike almost any other organic solvent, CO_2 can not be oxidized further, and hence the use of CO_2 as a reaction medium eliminates byproducts originating from solvents. At the same time, with its excellent mass- and heat-transfer properties compressed CO_2 provides a safe reaction environment for aerobic oxidations. Consequently, novel chemistry aimed at enhancing the selectivity towards desired products as well as improving reactivity and ease of product separation can be established if compressed CO_2 is utilized smartly.

Nowadays, oxidative cleavage of carbon–carbon double bonds to give the corresponding carbonyl compounds as one of the promising methodologies for the formation of carbonyl compounds has drawn much attention.[2] Conventionally, the following two ways have been used: (1) transformation of olefins into 1, 2-diols followed by cleavage with an oxidant like $NaIO_4$;[3] (2) direct cleavage of olefins by ozonolysis.[4] As for direct oxidative cleavage of olefins with ozonolysis, safety would become the major concern. Therefore, a number of studies on direct cleavage of olefins were focused on using relatively safe metal reagents and oxidants, such as OsO_4-oxone,[5] OsO_4-$NaIO_4$,[6] Au(I)-TBHP (*tert*-butyl hydrogen peroxide),[7] Ru(II)-H_2O_2,[8] $PdCl_2$ in supercritical CO_2 ($scCO_2$)/polyethylene glycol (PEG)/O_2,[9] or PEG-$PdCl_2$ in water.[10] Although much progress has been made in this field, expensive and toxic heavy metals are often used.

Recently, the development of a metal-free process for the cleavage of olefins has become an interesting research field from the viewpoint of green chemistry. Kroutil *et al.*[11] described a simple biocatalytic alkene cleavage to yield aldehydes by using the most innocuous oxidant, namely oxygen. Aerobic photo-oxidative cleavage of the C=C bond of α- or β-substituted styrenes was also found by using CBr_4 as the catalyst.[12] Very recently, we developed free-radical chemistry of PEG for C=C bond cleavage in $scCO_2$.[13] This system (PEG/$scCO_2$/O_2) does not require any catalyst or additional radical initiator. In our continuing effort towards developing green methodologies for the oxidative cleavage of C=C bonds, we want to introduce a more efficient metal-free radical process in $scCO_2$.

As is known, *tert*-butyl nitrite can react with *N*-hydroxyphthalimide to directly produce nitrosocycloalkanes or cycloalkanone oximes.[14] In addition, nitrosoalkyl derivatives could also be used in the Barton reaction.[15] This is understandable given that *tert*-butyl nitrite can release NO and an alkoxyl radical of great interest under high temperature.[16] On the other hand, nitrogen monoxide reacts with olefins, often leading to nitryl-substituted compounds and oximes.[16,17] We envisioned that the alkoxyl radical originating from TBN could serve as an initiator to induce cleavage of C=C bonds (Scheme 1) and selectivity could be tuned by compressed CO_2.



Scheme 1 Aerobic oxidation of benzylic C=C double bonds.

We chose styrene as the model substrate to test the cleavage reaction by employing this protocol.‡ The results are summarized in Table 1. It was found that oxygen and TBN are indispensable for the reaction (Table 1, entries 1, 2, 3). However, selectivity of benzaldehyde was poor in the absence of CO_2 (entry 3). Accordingly, the influence of CO_2 pressure on the reaction was examined. Notably, there was great improvement in the selectivity when the total pressure reached 13 MPa (entries 3–7).

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† Electronic supplementary information (ESI) available: General information, representative procedure for aerobic cleavage of benzylic C=C bonds, ^1H NMR and ^{13}C NMR charts for product identification and the GPC investigation of the oligomer of styrene. See DOI: 10.1039/c0gc00676a

Table 1 TBN-initiated aerobic oxidative cleavage of styrene[a]

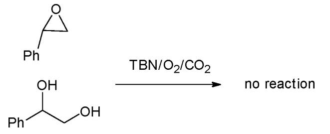
				Yield[b] (%)	
Entry	P_{O_2}/MPa	$P_{O_2+CO_2}$/MPa	Conv.[b] (%)	Aldehyde	Acid
1	0	0	2	1	0
2[c]	1	1	26	6	0
3	1	1	100	49	21
4	1	4	100	37	9
5	1	7	100	44	7
6	1	10	80	53	6
7	1	13	45	40	0
8	1	16	2	2	0
9[d]	1	13	3	2	0
10[e]	1	13	98	36	18
11[f]	1	13	88	72	5
12[g]	1	1	3	0.5	0

[a] Reaction conditions: styrene (0.5 mL, 4.35 mmol), TBN (11 μL, 2 mmol%), 80 °C, 12 h. [b] Determined by GC using biphenyl as an internal standard. [c] Without TBN. [d] $T = 60$ °C. [e] $T = 120$ °C. [f] $t = 18$ h. [g] 2 mmol% TEMPO (2,2,6,6-tetramethyl-piperdine-1-oxy) was added.

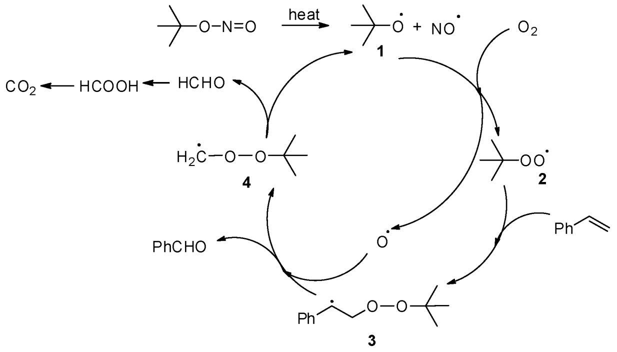
To our delight, the yield of benzaldehyde reached 72% after prolonging the reaction time to 18 h (entry 11). CO_2 pressure could play a crucial role in boosting the desired reaction as well as noticeably improving the selectivity towards aldehyde, and thus could allow this approach to be much more practically viable in organic synthesis. Compressed CO_2 could dissolve oxidized products and small molecules like oxygen, alkoxy radicals and NO, and thus prevent overoxidization/oligomerization.[13,18] On the other hand, higher oxygen concentrations favor deeper oxidation, resulting in a significant increase in the yield of benzoic acid (entries 3–7). However, too much CO_2 could dilute the reaction species over 16 MPa of total pressure, and thus result in slowing of the reaction (entry 8). Consequently, the optimal pressure was found to be *ca.* 13 MPa. It is also worth mentioning that there is often a white viscous solid, this being oligomers of styrene generated in the range of 1–10 MPa (see ESI†). In addition, high O_2 pressure facilitates the reaction with increasing yield of acid (entries 14, 15, Table S1, ESI†). On the other hand, the reaction did not occur below 80 °C, while the selectivity would become poor with further raising of the temperature (entries 7, 9, 10). Therefore, an appropriate temperature would be 80 °C. Furthermore, the amount of TBN does not affect the reaction (entries 7, 11, 12, Table S1, ESI†). This is understandable because TBN is assumed to serve as a radical initiator.

The utility and generality of this metal-free process for the aerobic cleavage of C=C bonds were further examined. As shown in Table 2, a series of aromatic olefins can be transformed into the corresponding carbonyl compounds. Obviously, terminal benzylic olefins showed good activity (entries 1–6). The *p*-substituted styrene gave better results than styrene (entries 2, 3 *vs.* 1), whereas *o*- or *m*-substituted styrene showed slightly lower activity (entries 4, 5). Notably, α-methyl styrene afforded the ketone instead of the aldehyde as the predominant product in a comparable yield after prolonging the reaction time to 24 h (entry 6). On the other hand, internal benzylic olefins gave poor results. The reaction almost returned only starting material at 80 °C in the case of methyl cinnamate (entry 7). The activity was still not good even at 120 °C (entry 8). In addition, cinnamyl alcohol could be transformed to benzyl aldehyde and cinnamyl aldehyde (entry 9). Unfortunately, aliphatic olefins did not work using this protocol (entries 10–11), probably due to instability of the radical intermediate derived from aliphatic olefins.

In the conventional two-step process, the cleavage of the C=C bond often involves the "diol or epoxide" intermediate[3] and subsequent oxidation to products. However, styrene oxide or 1,2-dihydroxyethylbenzene remained intact under the reaction conditions (Scheme 2).[19] Accordingly, the reaction pathway involving the "diol or epoxide" intermediate could be excluded. On the other hand, the TBN-induced C=C cleavage of styrene was completely inhibited by adding TEMPO (entry 12, Table 1), presumably indicating that the oxidation goes through a free-radical pathway. Based on the previous reports and our aforementioned results, a possible mechanism was proposed as delineated in Scheme 3. As is well known, TBN can release NO and the alkoxyl radical **1** under reaction temperature, and nitrogen monoxide can subsequently react with an olefin to give the nitryl-substituted compounds and oximes.[16,17] As a result, cleavage reaction of the C=C bond with $TBN/O_2/CO_2$ system probably could be initiated by the alkoxyl radical generated *in situ* from TBN. The reaction of the radical **1** and molecular oxygen affords the peroxide radical **2**, which subsequently reacts with an olefin like styrene to furnish the radical **3**, followed by its arrangement in combination with an oxygen radical to give the carbonyl product and the radical **4**. Furthermore, the primary radical **1** can be regenerated from radical **4**.



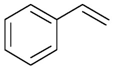
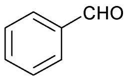
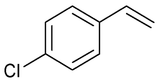
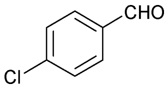
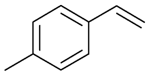
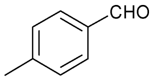
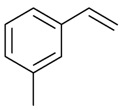
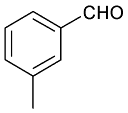
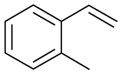
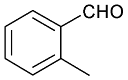
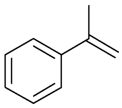
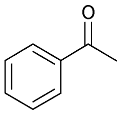
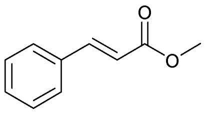
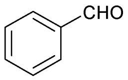
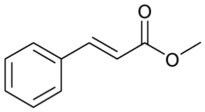
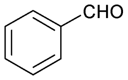
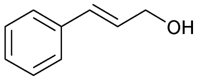
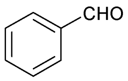
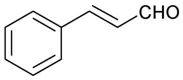
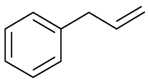
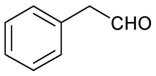
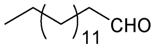
Scheme 2 Oxidation reaction of epoxide or 1,2-diol with $TBN/O_2/CO_2$.



Scheme 3 Proposed mechanism.

In summary, we developed a metal-free system comprising *tert*-butyl nitrite, oxygen and compressed CO_2 for aerobic cleavage of benzylic C=C bonds to carbonyl compounds. Compressed CO_2 could play a crucial role in boosting the desired reaction as well as noticeably improving the selectivity towards aldehyde, and thus could allow this approach to be much more practically viable in organic synthesis. Furthermore, the alkoxyl radical resulting from TBN is assumed to initiate the reaction.

Table 2 Aerobic oxidative cleavage of olefins[a]

Entry	Substrate	Product	t/h	Conv.[b] (%)	Yield[b] (%)		
					Aldehyde or ketone	Acid	Others
1			18	88	72	5	9
2			12	100	80	12	6
3			18	94	73	12	1
4			18	79	61	3	10
5			18	74	59	5	11
6			24	90	81	0	4
7			24	8	2	0	0
8[c]			24	39	11	0	0
9		 and 	24	74	32 19	0	16
10			24	0	0	0	0
11			24	0	0	0	0

[a] Reaction conditions: olefin (4.35 mmol), TBN (11 μL, 2 mmol%), T = 80 °C, P_{O_2} = 1 MPa, $P_{CO_2} + P_{O_2}$ = 13 MPa. [b] Determined by GC. [c] TBN (28 μL, 5 mmol%), T = 120 °C.

Acknowledgements

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Notes and references

‡ **Caution**. Experiments with large amounts of compressed gases, especially molecular oxygen and supercritical fluids, are potentially hazardous and must only be carried out using the appropriate equipment and rigorous safety precautions. In particular, oxygen should be introduced into the substrate-loaded reactor after CO_2. Moreover, the

oxygen content should not exceed 14 vol% when CO_2 is used as a reaction medium.

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19 Reaction conditions: styrene oxide or 1,2-dihydroxyethylbenzene (4.35 mmol), TBN (11 μL, 2 mmol%), $T = 80$ °C, $t = 18$ h, $P_{O_2} = 1$ MPa, $P_{CO_2} + P_{O_2} = 13$ MPa.