

Selective Oxidative Cleavage of the C–C Bond in α,β -Epoxy Ketone into Carbonyl CompoundsBing Jiang,[†] Huai-Zhu Li,[†] Rui-Jun Li,^{*} Jianye Zhang,^{*} and Yun-Xiao Zhang^{*}Cite This: *ACS Omega* 2022, 7, 21608–21614

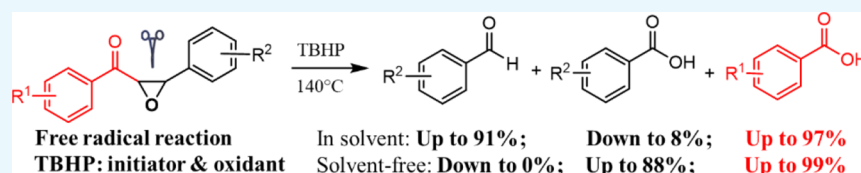
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ABSTRACT: This method afforded aromatic carbonyl compounds under TBHP via selective oxidative cleavage of the C–C bond in α,β -epoxy ketones. Aromatic acid came from the aroyl section, and aromatic aldehyde came from the other aromatic group. TBHP acted as a free radical initiator and oxidant. The reaction within the solvent went through a ring-opening addition, cleavage of the C–C bond in the ethylene oxide section, and oxidation, affording the target compounds in moderate to good yields. The HPLC yield of aromatic aldehyde was up to 91%. The HPLC yield of aromatic acid was up to 99%. The reaction under solvent-free conditions gave two kinds of aromatic acids coming from different moieties of α,β -epoxy ketone via the further oxidation of aromatic aldehyde. The substituent effect was discussed, and the reaction mechanism was proposed. This method allowed the reaction to occur in a simple system metal-free.

INTRODUCTION

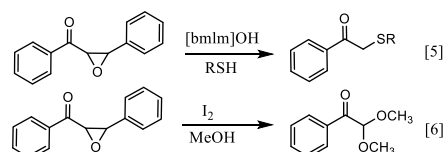
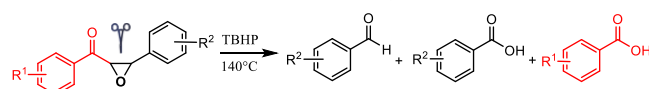
Oxidative cleavage of the C–C bond is widely presented in organic synthetic chemistry. Especially, selective oxidative cleavage has attracted many efforts in the fields of synthesis and biotechnology. Achieving efficiently selective cleavage of the C–C bond for chemical transformations remains challenging.

Epoxides, including derivatives of ethylene oxide, are an important class of building blocks. They could be converted into various functional groups. To date, much research on the transformation of α,β -epoxy ketones is generally focused on ring-opening reactions of the oxirane ring.¹ The dominant reactions of α,β -epoxy ketones involve cleavage of the C–O bond of epoxide to form 1, 2-² or 1, 3-³ dicarbonyl compounds with no change in the total number of carbon. On the other hand, the breakage of the C–O bond of α,β -epoxy ketones followed by rearrangement could form carbonyl compounds with a changed skeleton.⁴ However, the direct C–C bond cleavage of the epoxide motif is more difficult and has been less studied due to the harsh conditions required. The ionic liquid [bmIm]OH-catalyzed retro-Aldol cleavage reaction could catalyze the thiolysis of α,β -epoxy ketones to provide β -keto sulfides.⁵ Chalcone epoxides could form β -methoxy alcohols via ring-opening reaction under iodine in methanol, and then the C–C bond cleaved to form α -ketoaldehyde, followed by acetalization to give α,α -dimethoxyacetophenones.⁶ It has not been reported that cleavage of the C–C bond followed by oxidation, that is, oxidative cleavage of the C–C bond of α,β -epoxy ketone affords aromatic aldehyde and aromatic acid.

Herein, we report the selective oxidative cleavage of the C–C bond of α,β -epoxy ketones (chalcone epoxides) to form the corresponding aromatic carbonyl compounds by *tert*-butanol hydroperoxide (TBHP) as a free radical initiator and oxidant (Scheme 1).

Scheme 1. Reactions Involving the C–C Bond Cleavage in α,β -Epoxy Ketones

Previous work: Cleavage of the C–C Bond

**This work:** Selective Oxidative Cleavage of the C–C Bond

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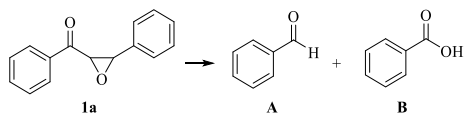
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RESULTS AND DISCUSSION

When chalcone epoxide (**1a**) was added to the TBHP system [TBHP 4.0 equiv in diethylene glycol diethyl ether (DGDE)]

Table 1. Cleavage Reaction of 1a^a



entry	T (°C)	free radical oxidant (equiv.)	solvent (10 mL)	time (min)	yield (%) ^b		conv. (%) ^b
					A	B	
1	130	TBHP (4.0)	DGDE	120	27	20	55
2	130	BPO (4.0)	DGDE	120	0	0	16
3	130	LPO (4.0)	DGDE	120	0	0	0
4	130	H ₂ O ₂ (4.0)	DGDE	120	4	5	16
5	130	<i>m</i> -CPBA (4.0)	DGDE	120	trace	trace	15
6	130	DCP (4.0)	DGDE	120	trace	trace	48
7	130	DTBP (4.0)	DGDE	120	trace	trace	28
8	130	CHP (4.0)	DGDE	120	trace	trace	5
9	130	TBHP (4.0)	DMSO	120	trace	trace	>99
10	130	TBHP (4.0)	PG	120	4	6	89
11	130	TBHP (4.0)	ODCB	120	trace	25	29
12	130	TBHP (4.0)	NMP	120	3	3	25
13	130	TBHP (2.0)	DGDE	120	3	2	13
14	130	TBHP (8.0)	DGDE	120	65	51	82
15	130	TBHP (10)	DGDE	120	76	64	94
16	130	TBHP (12)	DGDE	120	77	97	>99
17	130	TBHP (14)	DGDE	120	77	113	>99
18	130	TBHP (18)	DGDE	120	76	118	>99
19	130	TBHP (20)	DGDE	120	70	126	>99
20	90	TBHP (4.0)	DGDE	120	0	0	0
21	110	TBHP (4.0)	DGDE	120	11	3	20
22	140	TBHP (4.0)	DGDE	120	32	16	65
23	150	TBHP (4.0)	DGDE	120	22	13	47
24	160	TBHP (4.0)	DGDE	120	25	12	50
25	140	TBHP (12)	DGDE	60	81	65	88
26	140	TBHP (12)	DGDE	75	84	79	94
27	140	TBHP (12)	DGDE	90	85	94	98
28	140	TBHP (12)	DGDE	95	87	95	>99
29	140	TBHP (12)	DGDE	105	83	97	>99

^aReaction conditions: 0.5 mmol compound **1a**. ^bDetermined by HPLC with biphenyl as an internal standard. ^cIsolated yield.

at 130 °C for 2 h, the reaction led to the two expected products, which were benzaldehyde (**A**) and benzoic acid (**B**) in 27% and 20% yield, respectively (Table 1, entry 1). At first, various free radical oxidants (4.0 equiv) were screened at 130 °C for 2 h, such as TBHP, benzoyl peroxide (BPO), lauroyl peroxide (LPO), H₂O₂, *m*-chloroperbenzoic acid (*m*-CPBA),

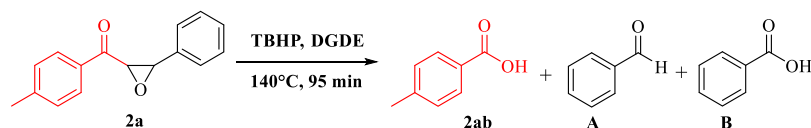
dicumyl peroxide (DCP), di-*tert*-butyl peroxide (DTBP), and cumyl hydroperoxide (CHP). The results showed that TBHP was more suitable for the reaction as a free radical initiator and oxidant (Table 1, entries 1–8). Second, several protic, aprotic, polar, or nonpolar solvents with higher boiling points were screened, such as DGDE, propylene glycol (PG), *o*-dichlorobenzene (ODCB), and *N*-methyl pyrrolidone (NMP). DGDE gave a better result (Table 1, entries 1 and 9–12). Although the conversion rates were high in DMSO and PG, only trace or small amounts of the target compounds (**A** and **B**) were produced (Table 1, entries 9 and 10).

Next, the conversion rate of **1a**, as expected, enhanced with the increase of TBHP at 130 °C. The yields of **A** and **B** also increased simultaneously. When TBHP reached 12 equivalents, **1a** completely converted, giving the 77% yield of **A** (Table 1, entries 1 and 13–19). Interestingly, as shown in entries 1 and 13–15, the yield of **A** was usually greater than that of **B**. This trend continued until TBHP was over 10 equivalents. It means that the formation rate of **A** might be higher than that of **B** (Scheme 3). On the other hand, the situation reversed when TBHP exceeded 12 equivalents and the yield of **B** exceeded **A** and persistently enhanced with the increase of TBHP. Increasing TBHP to 18 equivalents, the reaction only showed a 1% drop of **A**, but 20 equivalents of TBHP resulted in a 7% drop. That was due to further oxidation of benzaldehyde (**A**) into benzoic acid (**B**) by surplus TBHP (Scheme 3), usually occurring in the final stage. It was an undesired result because too much aldehyde was oxidized unless we did not wish to get aldehyde.

To further figure out how much equivalents of TBHP would result in the excessive oxidation of aromatic aldehyde, the substituted chalcone epoxide (**2a**) was carried on the free radical oxidative cleavage reaction under the optimized conditions mentioned above. Entry 3 in Table 2 showed that oxidation of **A** had begun when TBHP closed to 10 equivalents. Now the reaction was not done yet, the conversion rate of **2a** was only 76%, and the yield of **2ab** was also low (69%). **2ab** gradually increased with the increase of TBHP, and oxidation of **A** increased accordingly (Table 2, entries 4–6). However, TBHP over 20 equivalents was unable to further improve the yield of **2ab**, instead of causing much oxidation of **A** (Table 2, entry 7), indicating that the high yield of **2ab** was inevitably accompanied by the excessive oxidation of aromatic aldehyde.

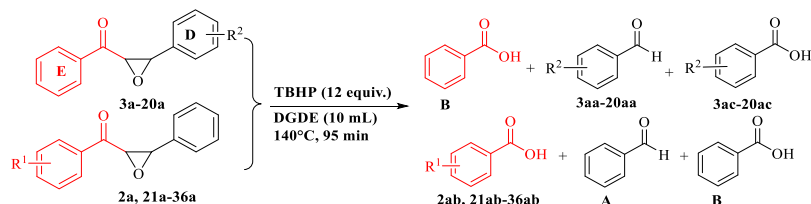
What follows is the expansion of substrates under the optimized conditions. Substrates, all in the *cis* configuration, were prepared according to the reported method⁷ (see Supporting Information). Table 3 shows that the substituents had profound effects on the C–C cleavage reaction, whether on the phenyl D-ring (black) adjacent to the epoxide or the phenyl E-ring (red) connected to the carbonyl.

For D-ring, *para*-substituents with electron-donating (ED) or weak electron-withdrawing (EW) effects, such as CH₃-, CH₃O-, F-, Cl-, and Br- (substrates **3a**–**7a**), gave the medium to high yields of benzoic acid (**B**) and the corresponding aromatic aldehydes (**3aa**–**7aa**). However, the NO₂-substituted substrate did not react (substrate **8a**). Interestingly, the stronger ED group CH₃O- could result in heavy deep oxidation of aldehyde (**4ac** reached 26% for substrate **4a**), indicating that the aromatic aldehyde with high electronic density could be oxidized easily. Surprisingly, these substituents, whether at *ortho*- or *meta*-, showed serious inhibitory effects toward the cleavage reaction (substrates **9a**–**20a**),

Table 2. Cleavage Reaction of 2a^a

entry	TBHP (equiv.)	DGDE (mL)	yield (%) ^b			conv. ^b (%)
			A	B	2ab	
1	4.0	10	11	trace	8	14
2	8.0	10	59	trace	40	66
3	10	10	66	7	69	76
4	12	10	69	14	78	>99
5	14	10	61	23	86	>99
6	18	10	56	31	88	>99
7	20	10	50	40	88	>99
8	10	0	0	74	70	93
9	15	0	0	81	65	>99
10	20	0	0	84	69	>99

^aReaction conditions: 0.5 mmol compound 2. ^bDetermined by HPLC with biphenyl as an internal standard.

Table 3. Scope of α,β -Epoxy Ketones^a

substrate	R ²	product and yield (%) ^b			substrate	R ¹	product and yield (%)		
3a	4-CH ₃	3aa (89)	3ac (7)	B (93)	2a	4-CH ₃	A (69)	B (14)	2ab (78)
4a	4-OCH ₃	4aa (74)	4ac (26)	B (88)	21a	4-OCH ₃	A (78)	B (18)	21ab (76)
5a	4-F	5aa (91)	5ac (8)	B (87)	22a	4-F	A (72)	B (16)	22ab (85)
6a	4-Cl	6aa (64)	6ac (14)	B (73)	23a	4-Cl	A (74)	B (14)	23ab (87)
7a	4-Br	7aa (65)	7ac (14)	B (67)	24a	4-Br	A (76)	B (16)	24ab (91)
8a	4-NO ₂	8aa (trace)	8ac (trace)	B (trace)	25a	4-NO ₂	A (trace)	B (trace)	25ab (trace)
9a	2-CH ₃	9aa (88)	9ac (11)	B (>99)	26a	2-CH ₃	A (64)	B (17)	26ab (75)
10a	2-OCH ₃	10aa (91)	10ac (7)	B (91)	27a	2-OCH ₃	A (75)	B (18)	27ab (89)
11a	2-F	11aa (trace)	11ac (trace)	B (trace)	28a	2-F	A (64)	B (15)	28ab (76)
12a	2-Cl	12aa (trace)	12ac (trace)	B (trace)	29a	2-Cl	A (61)	B (16)	29ab (75)
13a	2-Br	13aa (trace)	13ac (trace)	B (trace)	30a	2-Br	A (57)	B (14)	30ab (57)
14a	2-CF ₃	14aa (trace)	14ac (trace)	B (trace)	31a	3-CH ₃	A (78)	B (20)	31ab (90)
15a	3-CH ₃	15aa (73)	15ac (13)	B (84)	32a	3-OCH ₃	A (75)	B (18)	32ab (8)
16a	3-OCH ₃	16aa (66)	16ac (15)	B (97)	33a	3-F	A (74)	B (17)	33ab (90)
17a	3-F	17aa (trace)	17ac (trace)	B (trace)	34a	3-Br	A (75)	B (16)	34ab (78)
18a	3-Cl	18aa (trace)	18ac (trace)	B (trace)	35a	3-NO ₂	A (trace)	B (trace)	35ab (trace)
19a	3-Br	19aa (trace)	19ac (trace)	B (trace)	36a	Benzo[c]3,4	A (48)	B (11)	36ab (63)
20a	3-NO ₂	20aa (trace)	20ac (trace)	B (trace)					

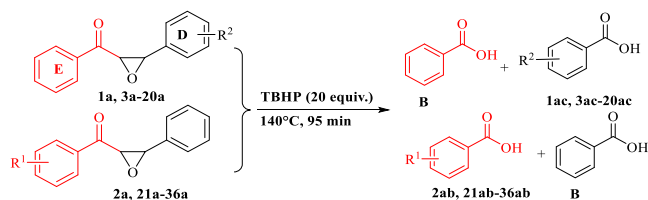
^aReaction Conditions: 0.5 mmol of each substrate. ^bDetermined by HPLC with biphenyl as an internal standard.

except CH₃- and CH₃O- (substrates 9a, 10a, 15a, and 16a). It seems like the higher electron density on D-ring could be conducive to the cleavage reaction, but not exactly (e.g., *m*-CH₃O- with EW effect).

On the E-ring, whether the substituents (except NO₂-) were at *para*-, *ortho*-, or *meta*-, the cleavage reaction gave good results (substrates 2a and 21a–36a). For *para*-substituents, CH₃O- and CH₃- (with the ED effect) gave the lower yields than that of halogen- (with EW) (substrates 21a–24a), indicating that the lower electron density on the E-ring may be conducive to the cleavage reaction, but excessive low electron density (e.g., NO₂- with strong EW) would not trigger

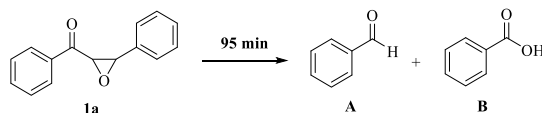
the reaction. There may be a threshold value of electron density that triggers the reaction. Moreover, the *ortho*- and *meta*-substituents did not present relatively large differences and regularity (substrates 26a–34a), except the substrate 35a with NO₂-. As to the E-ring replaced by naphthalene, the yield of 36ab reduced may be due to the steric hindrance.

We also tried to use the aliphatic-substituted α,β -epoxy ketone, or the aliphatic-substituted epoxy as substrates, such as 2-phenyl-1-oxaspiro[2,5]octan-4-one, or 2-(phenoxymethyl) oxirane; unfortunately, no corresponding products formed (see Supporting Information).

Table 4. Scope of α,β -Epoxy Ketones with Solvent-Free^a

substrate	R ²	product and yield (%) ^b		substrate	R ¹	product and yield (%)	
1a	H	1ac (B)	B (>99) (88) ^c	2a	4-CH ₃	B (84)	2ab (69)
3a	4-CH ₃	3ac (55)	B (95)	21a	4-OCH ₃	B (82)	21ab (88)
4a	4-OCH ₃	4ac (30)	B (89)	22a	4-F	B (81)	22ab (90)
5a	4-F	5ac (78)	B (89)	23a	4-Cl	B (88)	23ab (>99)
6a	4-Cl	6ac (87)	B (94)	24a	4-Br	B (80)	24ab (93)
7a	4-Br	7ac (78)	B (89)	26a	2-CH ₃	B (82)	26ab (88)
9a	2-CH ₃	9ac (48)	B (>99)	28a	2-F	B (83)	28ab (60)
10a	2-OCH ₃	10ac (10)	B (66)	29a	2-Cl	B (71)	29ab (77)
11a	2-F	11ac (78)	B (89)	30a	2-Br	B (87)	30ab (90)
12a	2-Cl	12ac (70)	B (90)	31a	3-CH ₃	B (83)	31ab (67)
13a	2-Br	13ac (72)	B (94)	32a	3-OCH ₃	B (80)	32ab (84)
14a	2-CF ₃	14ac (trace)	B (trace)	33a	3-F	B (82)	33ab (88)
15a	3-CH ₃	15ac (62)	B (90)	34a	3-Br	B (81)	34ab (87)
16a	3-OCH ₃	16ac (74)	B (94)	36a	Benzo[c]3,4	B (80)	36ab (79)
17a	3-F	17ac (79)	B (97)				
18a	3-Cl	18ac (79)	B (89)				
19a	3-Br	19ac (73)	B (87)				
20a	3-NO ₂	20ac (trace)	B (trace)				

^aReaction Conditions: 0.5 mmol of each substrate. ^bDetermined by HPLC with biphenyl as an internal standard. ^cIsolated yield.

Table 5. Control Experiment^a

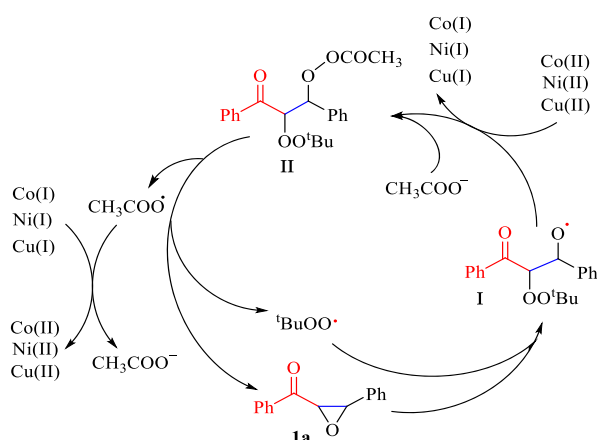
entry	DGDE (mL)	additive (mol %, equiv., atm)	TBHP (equiv.)	yield (%) ^b		conv. ^b (%)
				A	B	
1	10	Cu(CH ₃ COO) ₂ •H ₂ O 10%	4.0	trace	trace	11
2	10	Co(CH ₃ COO) ₂ •4H ₂ O 10%	4.0	trace	trace	19
3	10	Ni(CH ₃ COO) ₂ •4H ₂ O 10%	4.0	trace	trace	19
4	10	TEMPO 4.0 equiv	4.0	0	0	0
5	10	O ₂ 1.0 atm.	4.0	20	27	65
6	10	N ₂ 1.0 atm.	4.0	20	26	64
7	10	O ₂ 1.0 atm.	0	trace	trace	trace
8	2		12	30	168	>99
9	4		12	58	141	>99
10	6		12	75	121	>99
11	8		12	85	98	>99
12	10		12	87	95	>99

^aReaction Conditions: 0.5 mmol of 1a. ^bDetermined by HPLC with biphenyl as an internal standard.

It was found that with no solvent, the cleavage reaction gave only two kinds of aromatic acids from different phenyl rings, and no benzaldehyde (A) was detected. Table 2 entries 8–10 displayed the reaction results of substrate 2a under solvent-free conditions. With 20 equivalents of TBHP at 140 °C for 95 min, the reaction gave 69% 4-methylbenzoic acid (2ab) and 84% benzoic acid (B) in more than 99% conversion rate. The oxidative cleavage process with or without solvent (DGDE) should be similar: A formed first, 2ab formed slowly in multiple steps, and during this period, A was further oxidized to B by excessive TBHP (Scheme 3). Under solvent-free

conditions, aldehyde A was oxidized easily in a high concentration of TBHP. On the contrary, TBHP with a lower concentration in DGDE would decrease oxidizing ability, and more, TBHP may form a solvate, thereby weakening its oxidative activity. Table 4 shows the results of most substrates' reaction under solvent-free conditions with 20 equivalents of TBHP. The substrates of D-ring substitution gave high yields of benzoic acid (B), except the substituents NO₂- and CF₃- with a strong EW effect. The yield of B originating from the E-ring was slightly affected by electronic effects and positions of substituents on the D-ring, even F-, Cl-, and Br-, that were

Scheme 2. Proposed Effect Mechanism of Transition Metal Ions on the Free Radical Oxidative Cleavage of the C–C Bond



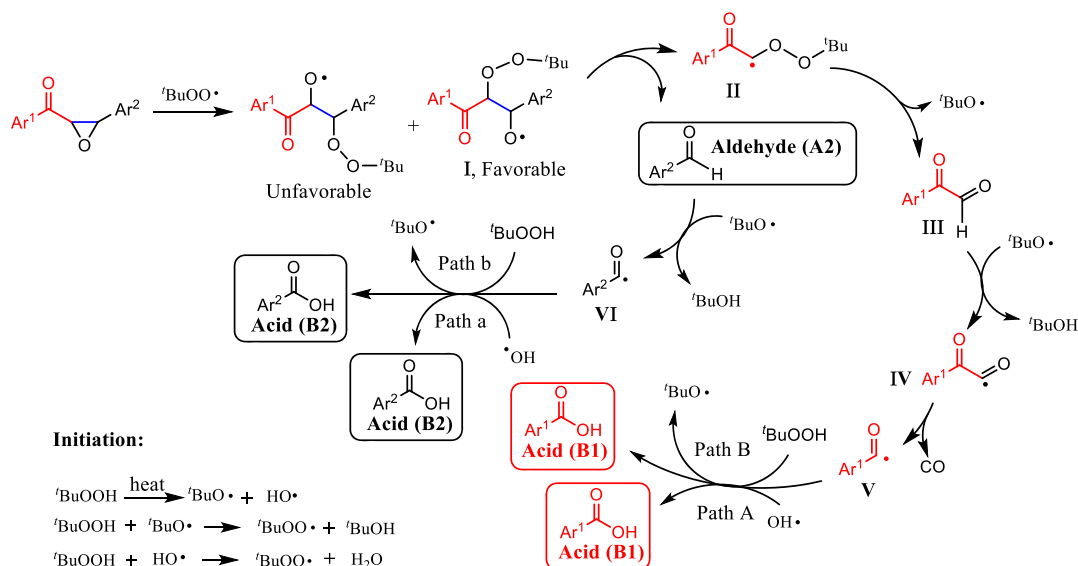
different from the reaction in DGDE (Tables 3 vs 4). However, aromatic acids yielding from the D-ring were influenced greatly by substituents. The substrates **3a**, **9a**, and **15a** with CH_3 - respectively on *para*-, *ortho*-, and *meta*- gave only medium yields (Table 4, **3ac** 55%, **9ac** 48%, and **15ac** 62%). Similarly, the substrates **4a** and **10a** with CH_3O - respectively on *para*- and *ortho*- gave low yields of aromatic acids (Table 4, **4ac** 30% and **10ac** 10%). In theory, the yields of the two aromatic acids should be close, such as shown in substrates **5a–7a**, **11a–13a**, and **16a–19a** (Table 4). Further oxidation of aromatic acid may occur to form side products due to the high electronic density on the D-ring. Especially, substrate **16a** showed a higher yield of **16ac** (74%) because of the EW effect of *meta*- OCH_3 . It means that the appropriate electronic density on the D-ring was beneficial to the selective oxidative cleavage reaction. On the other hand, with no substituents on the D-ring, the substrates gave steady yields of **B** from 71 to 87% under solvent-free conditions. The effects of substituents on the E-ring were similar to the reaction in solvent (substrates **2a**, **21a–24a**, **26a**, **28a–34a**, and **36a**).

To understand the feature of the reaction and the role of TBHP, the control experiments were carried out with different additives (Table 5). With transition metal ions (Cu^{2+} , Co^{2+} , and Ni^{2+}), the cleavage reaction presented significantly reduced conversion rates (Table 5, entries 1–3). The possible inhibitory mechanism of transition metal ions is shown in Scheme 2. The free radical ${}^t\text{BuOO}\cdot$ from TBHP reacted with substrate **1a** to form the free radical intermediate **I** via ring-opening addition, followed by oxidation by metal ions and reacted with the acetate ion (CH_3CO_2^-) to form acetate peroxide (**II**). Cleavage of the peroxy-bond resulted in re-cyclization to give the substrate **1a**. The futile circle inhibited the oxidative cleavage of the C–C bond.⁸ Furthermore, the reaction was completely inhibited by radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) (Table 5, entry 4). It revealed that the C–C cleavage of α,β -epoxy ketones belongs to a free radical-induced reaction, and TBHP acted as a free radical initiator.

Next, the reaction could occur in O_2 or N_2 (Table 5, entries 5–6). However, in O_2 without TBHP, the reaction could not happen. It means that TBHP acted not only as a free radical initiator but also as an oxidant in the cleavage reaction. Moreover, entries 7–11 showed that as the amount of DGDE increased from 2 to 10 mL, the concentration of TBHP gradually decreased, the yield of **A** gradually increased, and **B** gradually decreased, indicating the concentration of TBHP and solvate greatly affected its oxidize ability.

Based on the results mentioned above, this work proposed the mechanism of the free radical selective oxidative cleavage of the C–C bond of α,β -epoxy ketone (Scheme 3). At first, TBHP generated *t*-butyl peroxy radicals at a high temperature, followed by reacting with the substrate to form the two free radical intermediates via ring-opening addition. The free radical intermediates belong to the classical O-class radicals, and **I** was the favorable form with the ED substituent,⁹ resulting in the higher electron density on the D-ring could be conducive to the cleavage reaction. The free radical α -cleavage of **I** yielded one target product--Aldehyde (**A2**), and an intermediate **II**, which converted to α -carbonyl aldehyde **III** by homolytic cleavage.⁶ The α -carbonyl aldehyde **III**

Scheme 3. Proposed Mechanism of the Free Radical Selective Oxidative Cleavage of the C–C Bond in α,β -Epoxy Ketone



generated a new free radical intermediate **IV**, which decomposed into **V**.¹⁰ The benzaldehyde radical **V** was further oxidized into acid (**B1**) by TBHP via path a or b. Second, the product **A2** was further oxidized into **B2** through a path similar to **III**. It is worth noting that α -carbonyl aldehyde **III** had the advantage in competition with **A2** for being oxidized into acids because of its higher activity than that of **A2**. Therefore, only at the later stages of the reaction, **A2** was further oxidized into **B2** with the increase of TBHP. The high yield of **B1** may inevitably bring about the increased **B2**.

In summary, this work has developed an effective way of chemically selective oxidative C–C cleavage of α,β -epoxy ketones by TBHP, thereby converting a variety of α,β -epoxy ketones into carbonyl compounds (aromatic aldehydes and aromatic acids). This reaction system is simple, metal-free, and suitable for obtaining various aromatic carbonyls from the corresponding α,β -epoxy ketones.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.2c01464>.

Preparation of substrates and their NMR data, general procedure of the oxidative cleavage of the C–C bond in α,β -epoxy ketones, reaction result analysis with HPLC, separation of benzoic acid, and NMR spectra of substrates (PDF)

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Notes

The authors declare no competing financial interest.

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