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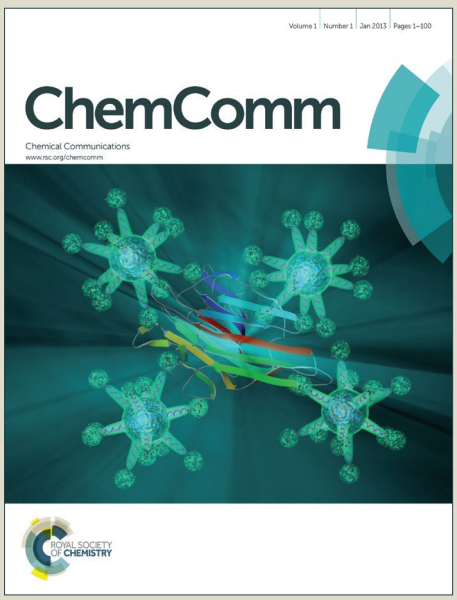

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Iron-Catalyzed Aerobic Oxidative Cleavage of C–C σ-Bond Using Air as Oxidant: Chemoselectively to Carbon Chain-Shortened Aldehydes, Ketones and 1,2-Dicarbonyl Compounds

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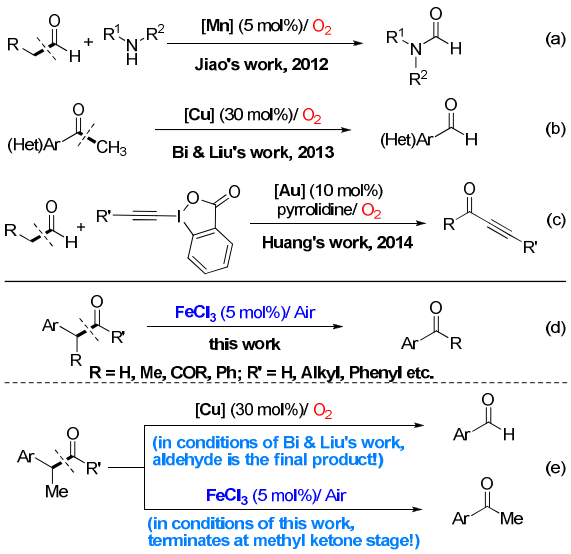
A simple iron-catalyzed aerobic oxidative C–C σ-bond cleavage of ketones has been developed. Readily available and environmently benign air is used as the oxidant. This reaction prevents the use of noble metal catalysts or specialized oxidants, chemoselectively yielding carbon chain-shortened aldehydes, ketones and 1,2-dicarbonyl compounds without overoxidation.

In recent years, catalytic unstrained C–C bond cleavage, similar to the emerging C–H bond functionalization, has attracted much attention due to its fundamental scientific appeal and potential application in organic synthesis.[1] Up to now, transition-metal-assisted approach to activate the inert C–C bond has proved to be the most promising tool for this purpose.[2] Although the direct C–C bond cleavage has been significantly developed in the past decades, transition-metal involved oxidative C–C σ-bond cleavage is still a challenging task. In order to achieve this goal, noble metal catalysts and stoichiometric oxidants, such as peroxides have traditionally been required. Therefore, the development of milder and greener process for oxidative C–C bond cleavage is highly desirable.

Air is considered to be an ideal oxidant due to its easy availability and environmentally benign character. Recently, a few elegant examples of aerobic oxidative C–C σ-bond cleavage have been developed for the synthesis of esters, amides, ketones, aldehydes etc.[3] For example, Jiao and co-workers developed a Mn-promoted oxidative C–C bond cleavage of aldehydes under oxygen atmosphere for formamide synthesis (Scheme 1a). Later, the same group reported a copper-catalyzed aerobic oxidative C(CO)–C(alkyl) bond cleavage of aryl alkyl ketones and C–N bond formation to amides. The group of Bi and Liu reported a copper catalyzed oxidative C(CO)–C(methyl) bond cleavage of ketones to aldehydes with molecular oxygen as the oxidant (Scheme 1b). Huang and co-workers reported gold-catalyzed oxidative C–C



Scheme 1. Transition-metal-catalyzed oxidative C–C σ-bond cleavage

bond cleavage of aldehydes for synthesis of ynones under aerobic conditions (Scheme 1c). Despite the progress achieved in aerobic oxidative C–C bond cleavage, iron/air catalytic system promoted unstrained C–C single bond cleavages are quite rare.[4] As we know, iron, as an inexpensive, abundant and non-toxic metal, offers a wide range of oxidation and spin states.[5] These features render it a potential catalyst for oxidative C–C bond cleavage by means of single electron catalysis. Herein, we reported an iron-catalyzed aerobic oxidative cleavage of C–C σ-bond under air atmosphere. Various phenylacetone derivatives with different alkyl chain, 3-aryl-substituted 2,4-dicarbonyl compounds, 1,1-diphenylpropan-2-one and cyclic β-carbonyl ketone were all suitable for this

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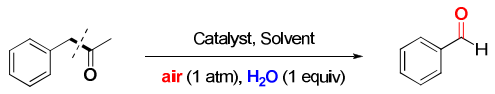
reaction, chemoselectively providing carbon chain-shortened aldehydes, ketones and 1,2-dicarbonyl compounds in good yields (Scheme 1d). Particularly, this method terminated at methyl ketone when 1-methyl-1-aryl-2-propanone derivatives were used as the substrates. Whereas, in the work of Bi and Liu, methyl ketones were liable to undergo further C–C bond cleavage to aldehydes under oxidative conditions (Scheme 1e). In addition, this method can be applied to the preparation of 2-acetylamino-benzaldehydes from *o*-(*N*-acylamino)aryl ketones. The latter could be synthesized efficiently from *ortho*-iodoanline and 1,3-diones *via* C–C bond cleavage.[6] As reported, 2-acetylamino-benzaldehydes are reactive intermediates for quinolin-2(1 *H*)-one skeletons construction.[7]

Table 1. Optimization of the reaction conditions.

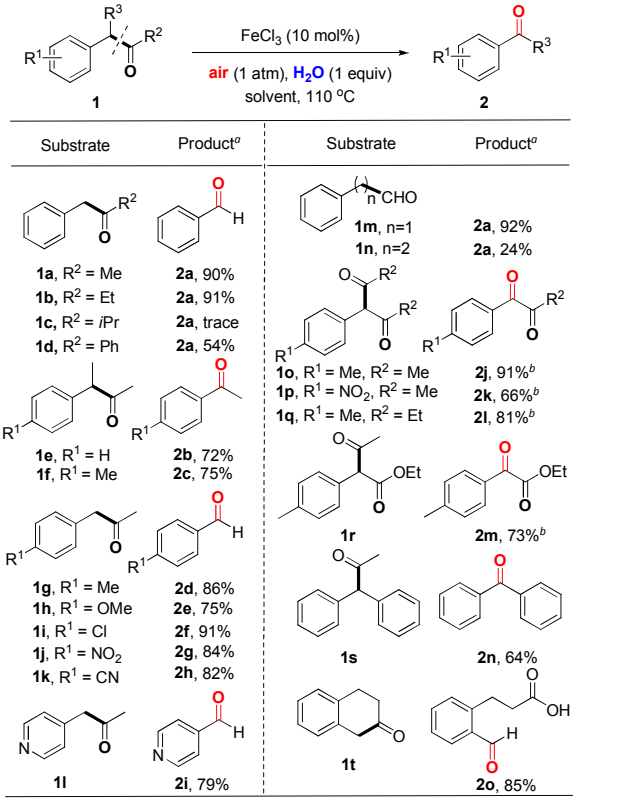


1a 2a

Entry	Solvent	Catalyst	T (°C)	Yield (%)[a]
1	DMSO	$FeCl_3$	90	77
2	DMSO	----	90	n.r.
3[b]	DMSO	$FeCl_3$	90	64
4	1,4-dioxane	$FeCl_3$	90	44
5	CH_3CN	$FeCl_3$	90	29
6	DMF	$FeCl_3$	90	54
7	DMSO	$FeCl_3$	110	83
8	DMSO	$FeCl_2$	110	47
9	DMSO	$Fe(OTf)_3$	110	49
10	DMSO	CuI	110	78
11[c]	DMSO	HCl	110	Trace
12[d]	DMSO	$FeCl_3$	110	90
13[e]	DMSO	$FeCl_3$	110	Trace

[a]Reaction conditions: **1a** (0.5 mmol), H_2O (0.5 mmol), 10.0 mol % of metal catalyst, air (1 atm), solvent (2 mL), 110 °C, 12 h. Isolated yield. [b]O_2 (1 atm) was inflated instead of air. [c]HCl (30 mol %). [d]20 h. [e]The reaction was conducted in the glove box and no air was inflated.

We commenced our study with Fe-catalyzed aerobic oxidation of 1-phenylpropan-2-one **1a** (Table 1). Initially, the aimed product benzaldehyde **2a** was obtained in 77% yield with $FeCl_3$ as the catalyst (entry 1). The reaction did not work in the absence of Fe catalyst (entry 2). What's more, when 1 atm O_2 was used instead of air, a lower yield of **2a** was obtained along with benzoic acid as the main byproduct, which probably resulted from further oxidation of **2a** under O_2 (entry 3). Then we screened other solvents (1,4-dioxane, CH_3CN, DMF), but no better results were obtained (entries 4-6). Increasing the temperature to 110 °C led to an improved yield (83%) (entry 7). In addition, other Fe catalyst such as $FeCl_2$ and $Fe(OTf)_3$ could also catalyze this reaction, but the efficiency was much lower than $FeCl_3$ (entries 8 and 9). As reported, CuI is widely used to catalyze oxidative C–C bond cleavage. Under the same reaction conditions, CuI is as efficient as $FeCl_3$ (entry 10). The Brønsted acid HCl was also tested, however, only trace of the desired products was obtained (entry 11). Prolonging the reaction time to 20 h gave **2a** in 90% yield (entry 12). As expected, the reaction hardly proceeded in the absence of air (entry 13).



Scheme 2. C–C bond cleavage of different β-carbonyl compounds. Conditions: [a]**1** (0.5 mmol), $FeCl_3$ (10 mol%), DMSO (2 mL), H_2O (0.5 mmol), air (1 atm), 110 °C, 20 h. [b]CH_3CN (2 mL) was used as the solvent, 90 °C.

With the optimized conditions in hand, we further investigate the substrate scope toward this oxidaitve C–C bond cleavage (Scheme 2). Firstly, our efforts were directed to propiophenone derivatives with different alkyl substituents. Reactions with benzyl methyl ketone **1a** and benzyl ethyl ketone **1b** proceeded smoothly, giving benzaldehyde **2a** in excellent yields. However, for benzyl isopropyl ketone **1c**, only trace amount of **2a** was obtained and most of **1c** was preserved, possibly due to the larger steric hindrance. To our delight, 1,2-diphenylethanone **1d** was also suitable for the C–C bond cleavage reaction with a modest yield. Fortunately, substrates **1e** and **1f** bearing methyl group on the benzyl carbon atom were also compatible with the standard reaction conditions, providing acetophenone **2b** and **2c** in 72% and 75% yield, respectively. Subsequently, we investigated substrates with different substituents on the aryl ring. The results showed that electron-donating (-Me, -OMe), electron-withdrawing (-NO_2, -CN) and halogen groups were all well tolerated under the standard conditions, giving the corresponding aldehyde in 75%-91% yields. Moreover, heteroaryl ketone such as **1l** also underwent the reaction successfully to furnish the corresponding product in good yield. Interestingly, the standard conditions were also compatible with benzenacetaldehyde **1m**

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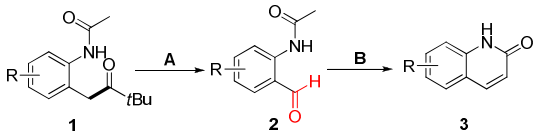
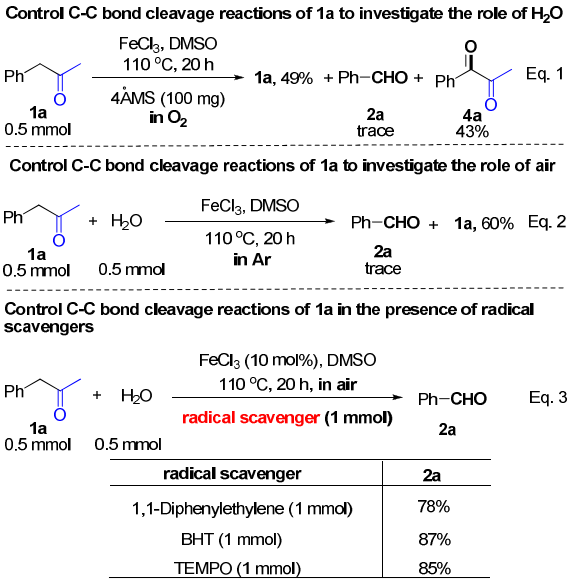
with benzaldehyde as the final product in 92% yield. However, in contrast to **1m**, **1n** showed a much lower reactivity providing **2a** in 24% yield and 66% of **1n** was recovered. It's probably due to a stepwise C–C bond cleavage reaction, in which $PhCH_2CH_2CHO$ was firstly converted into $PhCH_2CHO$ followed by a second C–C cleavage from $PhCH_2CHO$ to PhCHO.[9] In this process, the conversion from $PhCH_2CH_2CHO$ to $PhCH_2CHO$ is probably the rate-determining step in view of the facile transformation from **1m** to **2a**. Notably, 3-aryl-substituted 2,4-dicarbonyl compounds **1o** to **1r** could also be used in this reaction, giving the corresponding 1,2-dicarbonyl compounds **2j** to **2m** in good yields. In addition, 1,1-diphenylpropan-2-one **1s** was also a suitable substrate to provide benzophenone **2n** in 64% yield. Fortunately, cyclic β-carbonyl ketone **1t** could also undergo this reaction smoothly, giving ring-opening product 3-(2-formylphenyl)propanoic acid **2o** in 85% yield. It's worth to note that the aromatic ring of substrates is required for this reaction and only trace amount of an alternative carboxylic acid and formaldehyde were observed. Taking the reaction of **1a** for example, benzaldehyde was the main product while only trace amount of benzoic acid was detected by GC-MS. As shown in Scheme 5, enolate **I** formed on the side which is close to the aromatic ring is more stable due to conjugation action. Subsequent reaction of **I** with O_2 provides benzaldehyde as the major product.



R	1	2[a]	3
R = H	**1u**	**2p**, 82%	**3a**, 79%
R = 4-Cl	**1v**	**2q**, 65%[b]	**3b**, 84%
R = 4-Me	**1w**	**2r**, 84%	**3c**, 70%
R = 4, 6-di-Me	**1x**	**2s**, 87%	**3d**, 64%

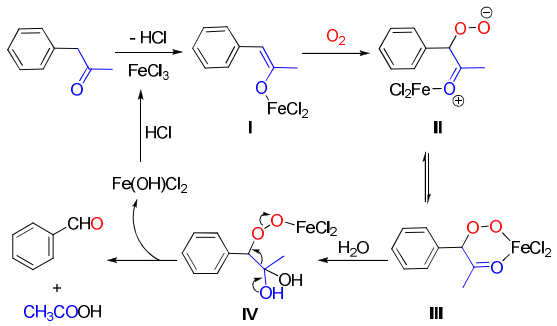
Scheme 3. C–C bond cleavage of *o*-(*N*-acylamino)aryl ketones and further transformation to quinolin-2(1 *H*)-one. Condition **A**: [a]**1** (0.25 mmol), $FeCl_3$ (10 mol%), CH_3CN (1 mL), H_2O (0.25 mmol), air (1 atm), 90 °C, 20 h, isolated yield. [b]110 °C. Condition **B**: **2** (0.125 mmol), Cs_2CO_3 (0.625 mmol), DMF (1 mL), 60 °C, 12 h, isolated yield based on **2**.

In our previous work, *o*-(*N*-acylamino)aryl ketones could be synthesized efficiently from *ortho*-iodoanline and 1,3-diones *via* C–C bond cleavage.[6] To our delight, through iron catalyzed aerobic oxidative C–C bond cleavage, these products could also be converted to the corresponding aldehydes in good yields. Taking *N*-(2-(3,3-dimethyl-2-oxobutyl)phenyl)acetamide and its derivatives (**1u** to **1x**) for example, they could be converted into 2-acetylamino-benzaldehydes (**2p** to **2s**) efficiently *via* iron-catalyzed C–C bond cleavage with the acetyl amino group remained. Further more, in the presence of base, 2-acetylamino-benzaldehydes underwent further cyclization to form quinolin-2(1 *H*)-one and its derivatives (**3a** to **3d**) (Scheme 3).[7] Quinolin-2(1 *H*)-one skeleton is frequently found in many pharmacologically useful compounds, such as antitumor, antiplatelet, antiviral agents, and various types of receptor antagonists.[8] Our method provides a useful alternative pathway for the synthesis of quinolin-2(1 *H*)-ones.



Scheme 4. Control C–C bond cleavage of **1a**.

We performed some control experiments to explore the reaction mechanism (Scheme 4). In the absence of H_2O, 49% of **1a** was recovered and only trace amount of **2a** was observed. Meanwhile, 43% yield of 1-phenylpropane-1,2-dione **4a** was obtained (Eq. 1). This result confirmed the essential role of H_2O in this C–C bond cleavage reaction. Then we placed **4a** under the optimized conditions for C–C cleavage, but no reaction occured, which suggested that **4a** was not the intermediate for this reaction (SEq. 6 in the Electronic Supplementary Information). It's noteworthy that experiment of Eq. 1 was carried out under O_2 in order to avoid the interference of H_2O in air. When the reaction was conducted under Ar, only trace amount of the desired product was detected (Eq. 2). So the presence of air (or O_2) is also essential for the present reaction. In addition, the reaction proceeded well in the presence of radical scavengers such as 1,1-diphenylethylene, butylated hydroxytoluene (BHT) and 1,1,5,5-tetramethylpentamethylene nitroxide (TEMPO), providing the desired product **2a** in 78% to 87% yields (Eq. 3). These reactions indicate that a radical process might not be involved in the present transformation.



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Scheme 5. Plausible mechanism for C–C bond cleavage.

Based on the results above, a proposed mechanism for this oxidative C–C bond cleavage reaction is drawn in Scheme 5. First, with the catalysis of Fe(III), propiophenone is converted into the iron enolate **I**, which is attacked by molecular oxygen to yield a peroxide (**II** or **III**) coordinated by iron.[9] Then this peroxide suffers nucleophilic attack of H_2O to form intermediate **IV**. Subsequently, C–C bond cleavage delivers the benzaldehyde along with one equivalent of acetic acid.

In conclusion, we have developed an iron-catalyzed aerobic oxidative C–C bond cleavage of ketones under air, which chemoselectively provides carbon chain-shortened aldehydes, ketones and 1,2-dicarbonyl compounds as the final products without overoxidation. In this transformation, environmently benign air and naturally abundant iron salt were used as the oxidant and catalyst, respectively. In addition, this method could be applied to the synthesis of 2-acetylamino-benzaldehyde and its derivatives, which are facile synthetic precursors of quinolin-2(1 *H*)-ones.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Detailed experimental procedures and spectral data for all compounds, including scanned images of ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/b000000x/

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