C–C Bond Cleavage

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Chemoselective Oxidative C(CO)–C(methyl) Bond Cleavage of Methyl Ketones to Aldehydes Catalyzed by CuI with Molecular Oxygen**

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The cleavage of carbon–carbon bonds is a critical issue in both academic research and industrial applications.[1] The inert nature of the C–C σ bond has led to a considerable amount of research on the exploration of strategies that could assist in readily breaking these bonds. Although significant progress has been achieved in the development of methods to cleave C–C single,[2] double,[3] and triple bonds,[4] the selective oxidative cleavage of C–C σ bonds still remains one of the most challenging issues in chemistry and biology. Aldehydes are an important class of compounds and widely used in all areas of chemistry; therefore, the development of new retrosynthetic disconnections of aldehydes is highly desirable.[5] The chemoselective C(CO)–C(α) bond cleavage of ketones is a fundamental reaction that has been extensively studied, and has been used for transformations into acids,[6] esters,[7] amides,[8] ketones,[9] and acyl-metal complexes[10] (Figure 1). Very recently, Jiang and co-workers described an

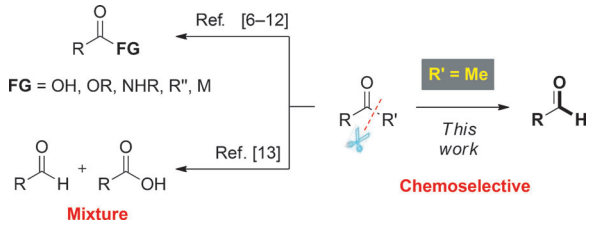
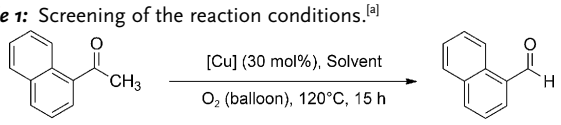


Figure 1. The C(CO)–C(α) bond cleavage of ketones.

interesting oxidative cleavage and esterification of the C–C bonds of α-hydroxy ketones under metal-free conditions.[11] Berreau and co-workers reported the regioselective C–C bond cleavage of acireductones to acids by a model system of iron-containing acireductone dioxygenase.[12] However, to the best of our knowledge, an oxidative C(CO)–C(α) bond cleavage of ketones that completely terminates at the aldehyde stage has not been described, this is probably due to easy overoxidation to the carboxylic acids.[13] As part of our ongoing efforts to develop transition-metal-catalyzed organic reactions,[14] we herein report an unprecedented copper-catalyzed aerobic C(CO)–C(methyl) bond cleavage of methyl ketones[15] that chemoselectively yields aldehydes as the sole product, along with the release of hydrogen (H_2) and carbon dioxide (CO_2). This reaction constitutes a novel transformation from methyl ketones into aldehydes.

An initial survey of the reaction parameters was performed with α-acetonaphthone (**1a**) as the model substrate, and some of the key results obtained are shown in Table 1. Cupric salts, such as $Cu(OAc)_2$ and $CuCl_2$, proved to be

Table 1: Screening of the reaction conditions.[a]



1a **2a**

Entry	[Cu]	Solvent	**2a**[b] [%]
1	$Cu(OAc)_2$	DMSO	trace
2	$CuCl_2$	DMSO	trace
3	**CuI**	**DMSO**	**92**
4	–	DMSO	n.r.
5[c]	CuI	DMSO	n.r.
6	CuCl	DMSO	90
7	CuOAc	DMSO	38
8	CuI	DMF	67
9	CuI	1,2,3-TCP	n.r.
10	CuI	CF_3Ph	n.r.

[a] Reactions were performed on a 1.0 mmol scale (0.3 M with respect to α-acetonaphthone). [b] Yields of isolated products. [c] Under nitrogen atmosphere. DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide, n.r. = no reaction, 1,2,3-TCP = 1,2,3-trichloropropane.

ineffective (entries 1 and 2), whereas cuprous salts, such as CuI, efficiently catalyzed the reaction, thus leading to α-naphthaldehyde (**2a**) in 92% yield (entry 3). Both CuI and O_2 are essential for reactivity, as verified by control experiments (entries 4 and 5). Other cuprous salts, such as CuCl and CuOAc, afforded significantly different yields of **2a**, which is indicative of the strong influence of the counteranion on the reaction (entries 6 and 7). The choice of solvent also appeared to be crucial, because, with the exception of DMF, the use of other high-boiling solvents, such as 1,2,3-trichloropropane (1,2,3-TCP) and CF_3Ph, led to no conversion. These results are in contrast to the previously docu-

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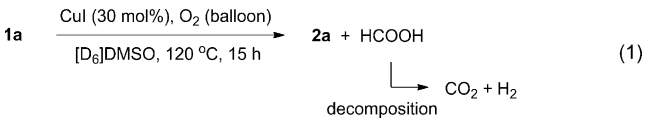
mented efficacy of these solvents in aerobic C–H bond activation reactions (entries 8–10).[14a,16] The effectiveness of DMSO may be ascribed to its metal-coordinating properties. Hence, it may stabilize the catalyst and promote the aerobic oxidation of its reduced form.[17] As a result, the reaction conditions described in entry 3 were selected as the standard conditions for further investigations.

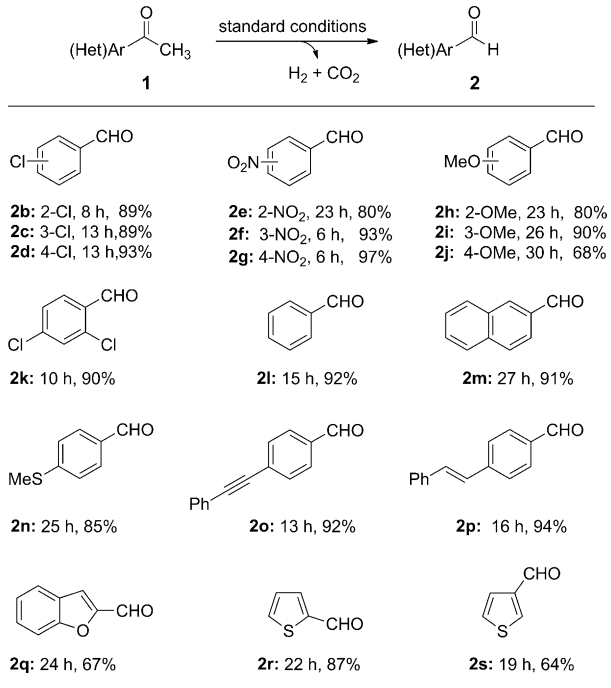
To identify other products that are generated along with α-naphthaldehyde (**2a**) in the C–C bond cleavage of α-acetonaphthone (**1a**), the reaction of **1a** was performed in deuterated dimethyl sulfoxide ([D_6]DMSO); the reaction mixture was analyzed by in situ ^{13}C NMR spectroscopy [Eq. (1)].[18] Aside from **2a**, no other compound was detected.



(1)

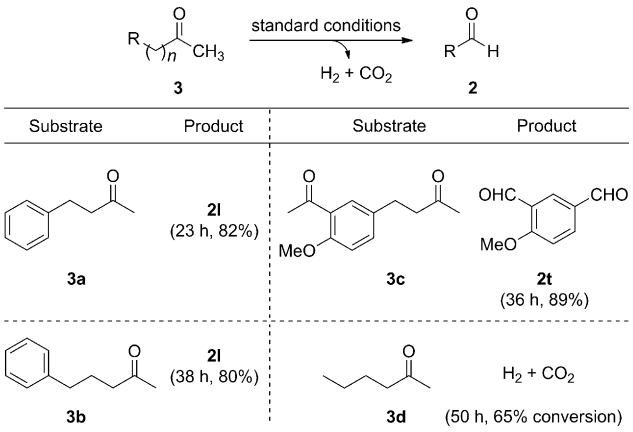
However, H_2 and CO_2, the expected by-products of the decomposition of formic acid (HCOOH), were detected with a hydrogen analyzer and by the lime-water test, respectively. In a separate experiment it could be shown that formic acid alone also generated H_2 and CO_2 under the standard conditions.[19] Therefore, the formic acid is probably generated during the degradation of α-acetonaphthone (**1a**) and decomposes to give H_2 and CO_2.

Next, the scope of the (hetero)aryl methyl ketones was examined under the standard reaction conditions (Table 1, entry 3). From the experimental data listed in Scheme 1, important conclusions include: 1) the significant influence of the electronic and/or substituent effects on the reaction (**2b**–**2m**), 2) good tolerance of a wide range of functional groups (**2b**–**2l** and **2n**–**2p**), 3) the applicability to electron-rich heteroaromatic methyl ketones (**2q**–**2s**), and 4) clean transformations that afford the aldehyde products in good to excellent yields. These results demonstrate the broad scope of (hetero)aryl methyl ketones that are suitable substrates for the copper(I)-catalyzed aerobic C–C bond cleavage reaction, which hence constitutes a practical method to make aromatic aldehydes from readily available acetophenones.[5] To date, a report by Boyer and co-workers that describes the conversion of acetophenone into benzaldehyde had been the only known example.[20,21]



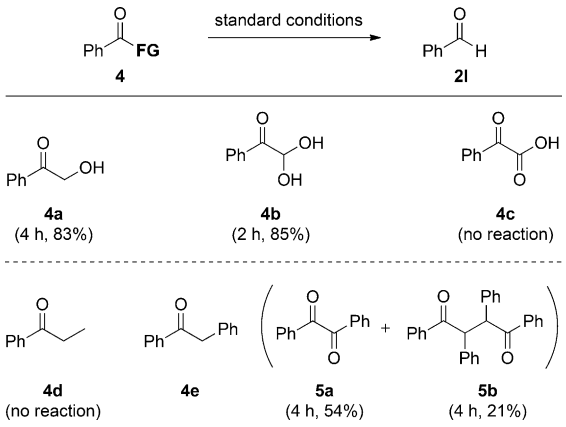
Scheme 1. Carbon–carbon bond cleavage of (hetero)aryl methyl ketones.

Efforts were also directed to reactions with aliphatic methyl ketones. Several methyl ketones, with varying alkyl chain lengths and substituents, were subjected to the standard conditions, and the results obtained are summarized in Scheme 2. To our delight, reactions with methyl ketones **3a**–**3c** proceeded smoothly to give the aldehydes **2l** and **2t** in good yields. However, in contrast to the reaction of acetophenones **1**, much longer reaction times (20–40 h), which were related to the lengths of the alkyl chain (for example, **3a** vs. **3b**), were required for efficient transformation. Notably, the complete degradation of substrate **3c**, which bears two methyl ketone units, was observed, affording 4-methoxyisophthalaldehyde (**2t**) in 89% yield within 36 h. In addition, the necessity for benzylic activation was precluded because *n*-butyl methyl ketone (hexan-2-one; **3d**), which lacks an aromatic ring at the terminal position of the alkyl chain, also underwent degradation under the standard conditions to afford H_2 and CO_2 (the conversion ratio was determined by ^{1}H NMR analysis of the reaction mixture using toluene as an internal standard). This result is extremely interesting, as it represents the first example of a complete degradation of an aliphatic ketone to H_2 and CO_2.[22,23] Collectively, the results listed in Scheme 2 demonstrate the high capability of the copper(I)-oxygen catalyst system for catalytic degradation.



Scheme 2. Carbon–carbon bond cleavage of aliphatic methyl ketones.

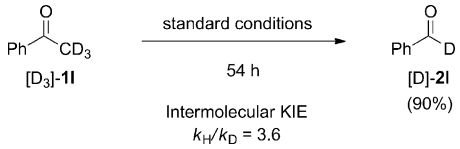
In order to explore the reaction mechanism, some representative acetophenone derivatives were selected and subjected to the standard conditions (Scheme 3). It was found that α-mono(hydroxy)acetophenone (**4a**) and α,α-bis-



Scheme 3. Reactions of acetophenone derivatives.

(hydroxy)acetophenone (**4b**) both afforded benzaldehyde (**2l**) within a very short period of time; nevertheless, the reaction was much faster for the latter than for the former (2 h vs. 4 h). These results suggest a stepwise oxygenation of the α-methyl group. In addition, the conversion of **4a** into **4b** was detected by in situ ^{1}H NMR spectroscopy.[17] The fact that phenylglyoxylic acid (**4c**) remained intact under the reaction conditions implies that no further oxidation of **4b** to **4c** occurs; hence, compound **4b** must be the precursor for the C–C bond cleavage. The tolerance of the aldehyde functional group to the CuI/O_2 catalytic oxidation system was established from the fact that compound **2l** alone remained unchanged under the standard conditions. Furthermore, it was observed that methyl ketones are preferentially oxidized in the presence of the corresponding aldehydes. For example, propiophenone (**4d**), with an ethyl group instead of the methyl group of acetophenone (**1l**), was completely unreactive under the standard conditions, whereas the reaction of α-phenylacetophenone (**4e**) yielded a mixture consisting of α-diketone **5a** (54% yield) and dimerized product **5b** (21% yield). A low yield (17.8%) of benzaldehyde was obtained by Sayre et al. from **4e** under Cu^{II} catalysis;[13a] this might indicate that a different mechanism is operating in our copper(I) catalyst system.

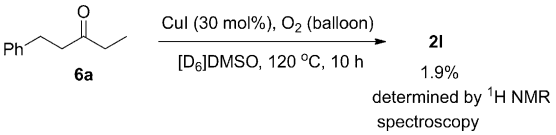
Furthermore, deuterium-labeling studies revealed a primary kinetic isotope effect (KIE) ($K_H/K_D = 3.6$) in an intermolecular competition experiment that utilized deuterated substrate [D]-**1l** [Eq. (2)].[24] This demonstrated that the



(2)

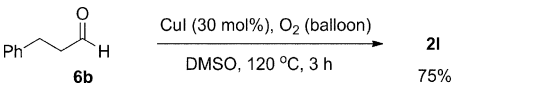
C(methyl)–H bond cleavage of acetophenone is the rate-determining step, and, more importantly, proved that the aldehydic hydrogen atom originates from the α-methyl group.

When ketone **6a**, with α-methylene substituents, was subjected to the standard conditions, extremely low conversion (1.9%) of **6a** was detected by ^{1}H NMR analysis of the reaction mixture [Eq. (3)]. Compared with our previous



(3)

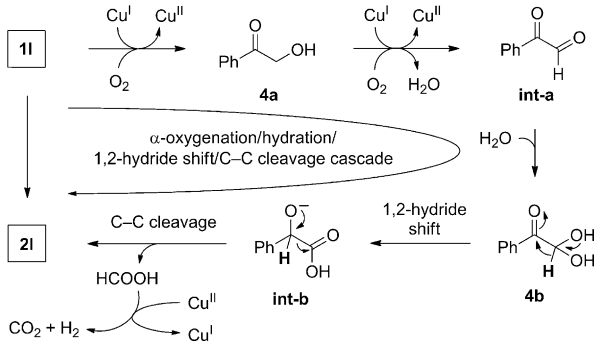
observation that propiophenone (**4d**) was left unchanged under the standard conditions, we concluded that the oxidation of a methyl substituent is more favorable than that of a methylene moiety in the initial step of the degradation of aliphatic methyl ketones **3**. However, the degradation of aliphatic aldehyde **6b** to **2l** within a shorter time (3 h) shows that aliphatic methyl ketones are initially transformed into the corresponding aldehydes, which then enter the aldehyde-degradation cycle [Eq. (4)].[25] Also, it



(4)

implies that the cleavage of the C(CO)–C(methyl) bond of methyl ketones should be the rate-limiting step in the degradation of aliphatic methyl ketones.

On the basis of these results, a reaction mechanism for the degradation of (hetero)aryl methyl ketones to aldehydes was proposed (using **1l** as a sample substrate; Scheme 4). Firstly,



Scheme 4. Mechanistic proposal.

acetophenone (**1l**) undergoes oxidation to give α-mono-(hydroxy)acetophenone (**4a**), through the activation of oxygen by the cuprous salt.[26] Compound **4a** is further oxidized to phenylglyoxal **int-a**, which quickly converts into the more-stable hydrated α,α-bis(hydroxy)acetophenone **4b** by picking up one molecule of water.[12] Following a 1,2-hydride shift in a Cannizzaro type reaction,[27] during which the methyl hydrogen atom is transferred to the carbonyl carbon, as supported by the deuterium-labeling experiment, intermediate **int-b** is produced [Eq. (2)]. Finally, C–C bond cleavage takes place, leading to product **2l**, along with the release of formic acid. The formic acid subsequently decom-

poses to liberate CO_2 and H_2, while divalent copper is reduced to the cuprous ion for the next catalytic cycle.[28]

In summary, the chemoselective oxidative cleavage of the C(CO)–C(methyl) bond of methyl ketones that yields aldehydes has been described for the first time. A wide range of aromatic and aliphatic methyl ketones can be subjected to this copper-catalyzed method under an oxygen atmosphere; the oxidation terminates at the aldehyde stage, and hydrogen (H_2) and carbon dioxide (CO_2) are released as the by-products. This reaction therefore constitutes an unprecedented dehydrogenation of saturated aliphatics. Preliminary mechanistic studies disclosed an interesting reaction sequence, involving α-oxygenation/hydration/1,2-hydride shift/C–C bond cleavage. These findings could lead to inspiring insights into copper–oxygen chemistry relevant to C–C bond cleavage. Further studies toward the elucidation of the exact reaction mechanism and the synthetic utility of this novel C–C bond cleavage reaction are currently underway.

Experimental Section

Typical procedure: A solution of 1-acetonaphthone (**1a**; 1.0 mmol, 170 mg) and CuI (0.3 mmol, 57 mg) in DMSO (3.0 mL) under oxygen (balloon) was prepared. The reaction mixture was heated to 120 °C and stirred until the starting material was consumed (monitored by TLC). Upon cooling to room temperature, the reaction mixture was diluted with dichloromethane (20 mL), and filtered through a pad of Celite. The aqueous layer was then extracted with dichloromethane (2 × 15 mL). The combined organic layers were reextracted with water (3 × 50 mL), collected, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuum, and the residue was purified by column chromatography on silica gel to afford **2a** (143 mg, 92% yield) as a pale yellow oil.

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Communications

C–C Bond Cleavage

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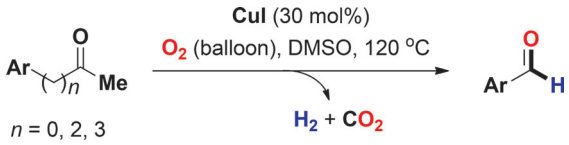

Chemoselective Oxidative C(CO)–C(methyl) Bond Cleavage of Methyl Ketones to Aldehydes Catalyzed by CuI with Molecular Oxygen

Aldehyde Termination: A novel copper-catalyzed transformation from methyl ketones into aldehydes has been accomplished. This method is applicable to a wide range of aromatic and aliphatic methyl ketones and chemoselectively produces aldehydes, accompanied by the release of hydrogen (H_2) and carbon dioxide (CO_2) as by-products.