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Ruthenium on carbon catalysed carbon-carbon cleavage of aryl alkyl ketones and aliphatic aldehydes in aqueous media

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Abstract. A new ruthenium on carbon-catalysed carbon–carbon (C–C) cleavage reaction of aryl alkyl ketone derivatives in water in the presence of CaO under atmospheric oxygen conditions has been developed. Corresponding benzoic acid derivatives were produced from various aryl alkyl ketones in excellent yields. CaO acts as an adsorbent of CO and CO_2 to maintain a sufficient concentration of oxygen around the catalyst required for effective progress of the reaction. It was also revealed that aliphatic aldehydes were generated from the alkyl moiety of aryl alkyl ketones over the course of the reaction. The aliphatic aldehyde derivatives undergo either an oxidation to the corresponding aliphatic carboxylic acids or a further continuous C-C cleavage reaction to form aliphatic aldehydes with loss of one carbon along with the formation of CO and CO_2.

Keywords: C-C activation; Cleavage reactions; Heterogeneous catalysis; Oxidation; Ruthenium

Carbon–carbon (C–C) bond cleavage reactions of molecules have attracted increasing interest in synthetic organic chemistry because of their application in industry and laboratories.[1] In particular, C–C bond cleavage reactions between a carbonyl carbon and the α-carbon of aryl alkyl ketones have been reported to produce aryl carboxylic acids,[2] which could be useful as various building blocks in the synthesis of natural products, pharmaceuticals, agricultural chemicals, and dyes.[3] Some such reactions require the addition of strong acid,[2a] peroxide,[2b] or CBr_4,[2c] which should be avoided owing to their environmental impacts. Others use metal catalysts under mild but homogeneous conditions,[2d,e] where the residual metal in the products would pose a serious problem. Heterogeneous transition-metal catalysts are attractive because of their stability under atmospheric conditions, easy handling, recoverability, reusability and so on, but they have not been applied as C–C bond cleavage catalysts for phenyl alkyl ketones. We have developed an additive-dependent regioselective control method for Pd/C-catalysed C–C cleavage reactions of cinnamaldehyde derivatives.[4] The development of a novel and easy C–C bond cleavage reaction of various compounds has enormous significance because of the direct route to new synthetic strategies for the reconstruction of the chemical structure of molecules.

Herein, we have established a heterogeneous Ru/C-catalysed C–C bond cleavage reaction of aryl alkyl ketones in water in the presence of molecular oxygen as an environmentally friendly solvent and oxidizing reagent. Moreover, inexpensive CaO was found to play the role of an adsorbent of CO_2 and CO, significantly increasing the reaction efficiency. Since the formation of carboxylic acids and alkyl aldehydes bearing different lengths of alkyl chains were observed, we focused on the sequentially repeating C–C bond cleavage reactions of the alkyl aldehydes derived from aryl alkyl ketones. The proposed mechanism of the C–C bond cleavage reaction is described in detail.

Initially, we examined the catalyst activities of various carbon-supported transition metals (each 5 mol%) for the C–C bond cleavage reaction of valerophenone in water in an O_2 atmosphere (Table 1). Catalysts were evaluated by the comparison of the material ratio of the recovered valerophenone to benzoic acid after the reaction (100 °C, 24 h). As a result, 10% Ru/C was found to be effective and 5% Ru/C further improved the catalyst activity (Entries 6 and 7), while 10% Pd/C, 10% Pt/C, 10% Rh/C, 10% Ir/C, and 10% Au/C showed relatively poor catalyst activities (Entries 1–5).

Table 1. Catalyst activity

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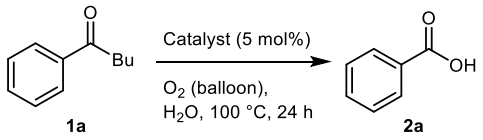
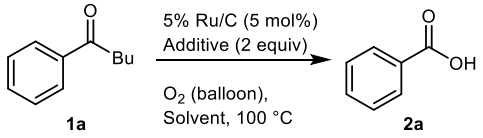


Entry	Catalyst	Ratio (Substrate : Product)[a]
1	10% Pd/C	91 : 9
2	10% Pt/C	91 : 9
3	10% Rh/C	90 : 10
4	10% Ir/C	83 : 17
5	10% Au/C	100 : 0
6	10% Ru/C	66 : 34
7	5% Ru/C	48 : 52

[a] Determined by ^{1}H NMR.

The choice of solvent was important for the present reaction (Table 2). While toluene and alcoholic solvents, such as MeOH and *i*-PrOH were inappropriate (Entries 1–3), the reaction proceeded in dimethyl sulfoxide (DMSO) and H_2O (Entries 4 and 5). H_2O was particularly effective. Consequently, a variety of additives were screened in H_2O as the solvent. Although the addition of acids decreased the reaction efficiency (Entries 6 and 7), the reaction was promoted by bases, such as Na_2CO_3, NaOH, CaO, and $Ca(OH)_2$ (Entries 8–11). CaO and $Ca(OH)_2$ led to more than 90% conversion of valerophenone after 12 h (Entries 14 and 15), and the reaction was nearly completed in 12 h on increasing the amount of CaO or $Ca(OH)_2$ from 2 equiv to 4 equiv (Entries 16 and 17). The addition of $CaCO_3$ as another Ca salt resulted in moderate conversion (Entry 18). Finally, CaO was selected as the appropriate base because of its general versatility.

Table 2. Effect of additive and solvent

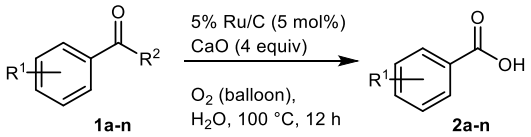


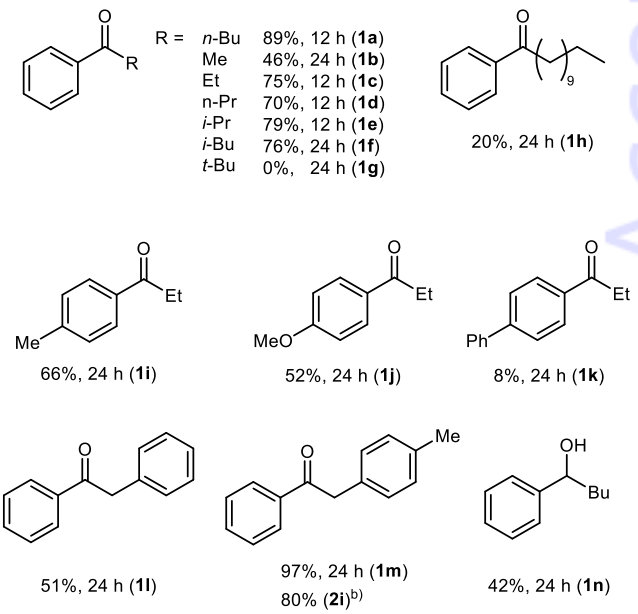
Entry	Additive	Solvent	Time (h)	Ratio (Substrate : Product)[a]
1	–	MeOH	24	100 : 0
2	–	*i*-PrOH	24	100 : 0
3	–	Toluene	24	100 : 0
4	–	DMSO	24	81 : 19
5	–	H_2O	24	48 : 52
6	AcOH	H_2O	24	74 : 26
7	TFA	H_2O	24	58 : 42
8	Na_2CO_3	H_2O	24	trace : >99
9	NaOH	H_2O	24	trace : >99
10	CaO	H_2O	24	trace : >99
11	$Ca(OH)_2$	H_2O	24	trace : >99
12	Na_2CO_3	H_2O	12	16 : 84
13	NaOH	H_2O	12	15 : 85
14	CaO	H_2O	12	10 : 90
15	$Ca(OH)_2$	H_2O	12	6 : 94
16[b]	CaO	H_2O	12	trace : >99
17[b]	$Ca(OH)_2$	H_2O	12	2 : 98
18[b]	$CaCO_3$	H_2O	12	38 : 62

[a] Determined by ^{1}H NMR. [b] 4 equiv of a additives were used.

Encouraged by these results, we applied the optimal conditions to the C–C bond cleavage of various aryl alkyl ketones (Table 3). Benzoic acid (**2a**) was obtained in good yields from phenyl alkyl ketones irrespective of the length of the alkyl moiety (**1a–f**). Although the C–C bond cleavage reaction of 2,2-dimethylpropiophenone (**1g**) did not proceed significantly, monosubstitution of a methyl group at the α- or β-position of the carbonyl group of isobutyrophenone (**1e**) and isovalerophenone (**1f**) had a negligible influence on the yields. The propiophenone bearing an electron-donating methyl or methoxy group on the benzene ring (**1i** and **1j**) could be converted to the corresponding benzoic acid derivatives, while the lipophilic substrates **1h** and **1k** did not react well under the present aqueous reaction conditions.[5] Moreover, benzyl phenyl ketone derivatives were also good substrates, and the desired corresponding carboxylic acid derived from the benzoyl moiety could be obtained together with theoretically equimolar benzoic acids originating from the corresponding benzyl moiety of the substrates (**1l** and **1m**). Benzoic acid was also generated from fenipentol (**1n**), which has a hydroxy group at the benzyl position of alkyl group instead of a carbonyl group.[6]

Table 3. Scope of substrate[a]





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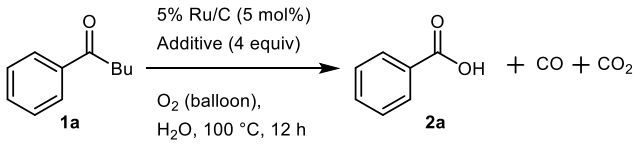
[a] Determined by ^{1}H NMR. [b] Obtained from the 4-tolylmethyl moiety of **1m**.

We examined the internal gas composition in the reaction vessel after the cleavage reaction of valerophenone using gas chromatography (GC/TCD) (Table 4). While 1.5 v/v% of CO and 4.8 v/v% of CO_2 were detected in the absence of CaO (Table 4, Entry 1), CO and CO_2 were hardly detected on the addition of CaO (Entry 2). In addition, CO underwent Ru/C-catalysed oxidation to CO_2 under an O_2 atmosphere.[7] Based on these results, it can be suggested that CaO functioned not only as a neutralizer of the resulting acids but also as an adsorbent of CO_2, which suppressed the reaction progress due to the interference of the smooth contact between the 5% Ru/C-substrate complex and oxygen in the reaction vessel by CO_2 possessing a comparatively heavy specific gravity.

Table 4. GC analysis of CO and CO_2

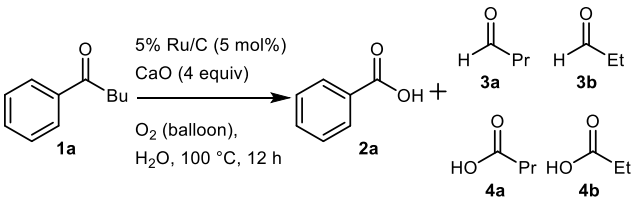


Entry	Additive	CO v/v(%)	CO_2 v/v(%)
1	–	1.5	4.8
2	CaO	1.0	trace

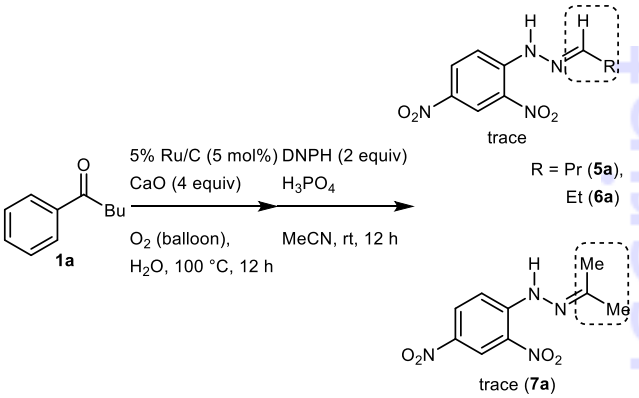
The formation of aliphatic aldehydes **3a** and **3b** and aliphatic carboxylic acids **4a** and **4b** was also confirmed by GC along with benzoic acid (**2a**) (Scheme 1), suggesting that butanal (**3a**), generated by Ru/C-catalysed C–C cleavage of valerophenone (**1a**), would undergo either oxidation or a further C–C bond cleavage reaction of **3a** to produce butanoic acid (**4a**) or propanal (**3b**), respectively. Furthermore, 2,4-dinitrophenyl hydrazine (DNPH) and H_3PO_4 in MeOH was added to the reaction mixture at room temperature after the Ru/C-catalysed C–C bond cleavage of valerophenone in H_2O for 12 h in the presence of CaO under an O_2 atmosphere, and then the corresponding hydrazones derived from butanal (**5a**), propanal (**6a**), and acetone (**7a**) could be obtained (Scheme 2).

Although C–C bond cleavage reactions based on the oxidative decarbonylation of **3a** and subsequent further oxidation catalysed by a homogeneous rhodium,[8] manganese,[9] or iridium-catalyst[10] to give propanoic acid, acetic acid, and formic acid have been reported, the related reaction mechanisms have never been proposed in these reports.

Scheme 1. GC analysis of aldehydes and carboxylic acids



Scheme 2. DNPH derivatization



To clarify the mechanism of the C–C cleavage reaction of aliphatic aldehydes, we conducted several experiments using heptanal and heptanoic acid as substrates. Heptanal was smoothly oxidized to heptanoic acid in water at 100 °C under an O_2 atmosphere in the absence of 5% Ru/C and CaO (Scheme 3, Eq. 1). Since heptanoic acid was totally tolerant toward the Ru/C-catalysed C–C cleavage reaction conditions (Eq. 2), CO_2 was not generated by the decarboxylation of aliphatic carboxylic acids. On the basis of the similar and continuous 5% Ru/C-catalysed C–C bond cleavage reaction of heptanal, several smaller aliphatic aldehydes possessing different lengths of alkyl chains were detected by GC (Eq. 3). Therefore, valerophenone (**1a**) was initially converted to benzoic acid (**2a**) and butanal (**3a**), which partially underwent further oxidation to the corresponding butanoic acid (**4a**), and a sequential C–C cleavage reaction of butanal (**3a**) occurred to form propanal (**3b**) and smaller acetaldehyde and formaldehyde (undetected), and the corresponding propionic acid (**4b**) and smaller acetic acid and formic acid (undetected).

Scheme 3. Cleavage reaction of aliphatic aldehyde and carboxylic acid

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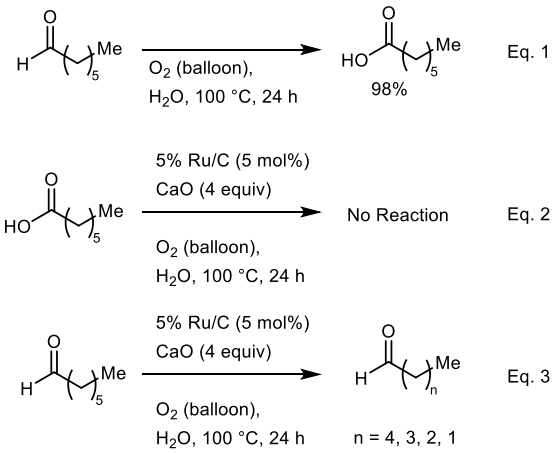
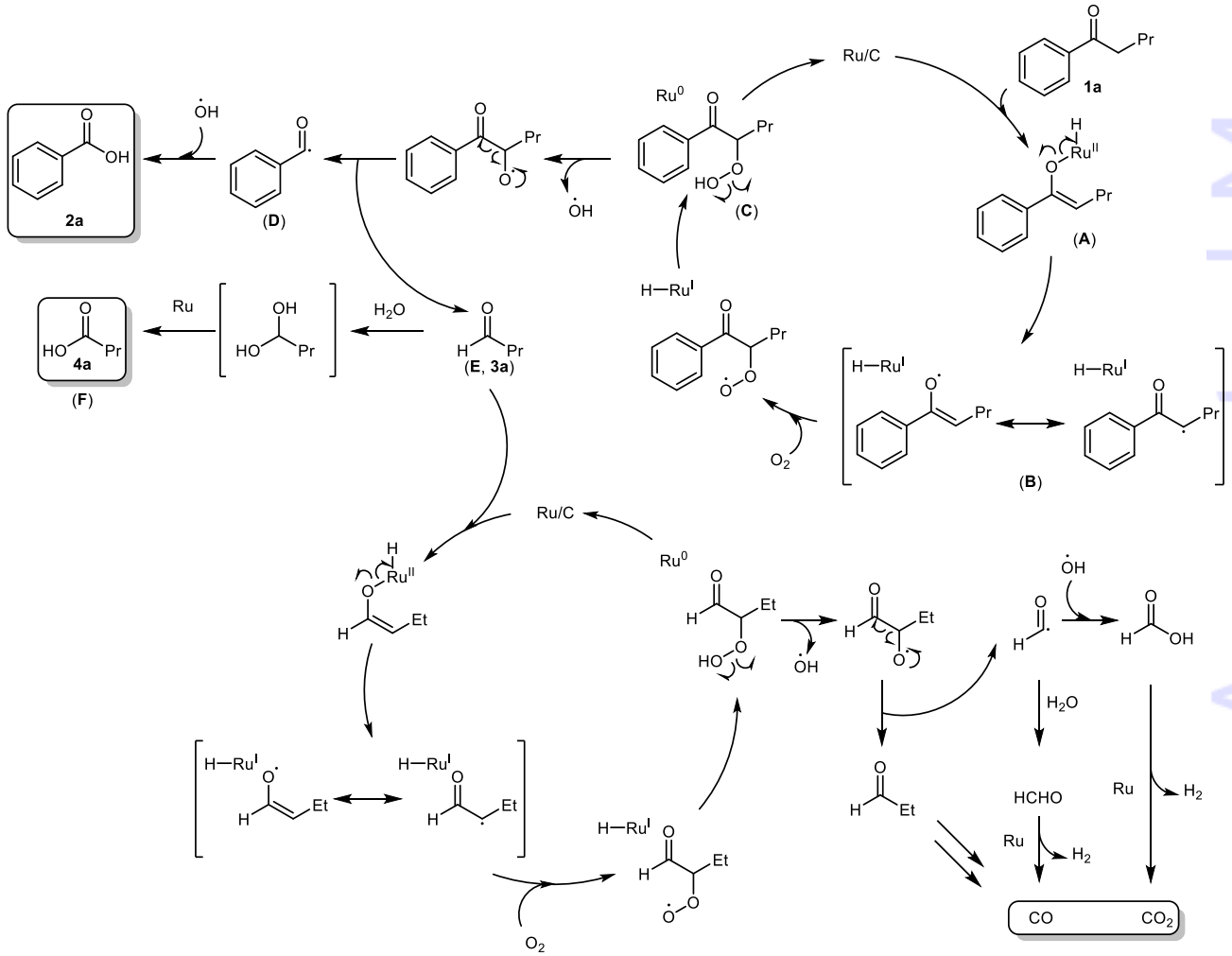


The plausible mechanism of the oxidative C–C bond cleavage reaction is illustrated in Scheme 4.[11]

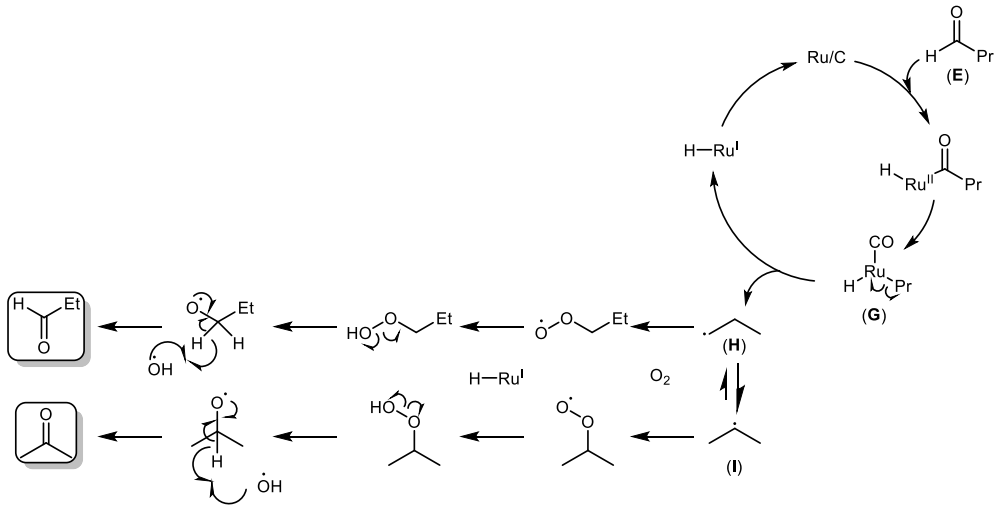
According to the mechanism, Ru(0) on Ru/C would be oxidatively inserted into the O-H bond of the enol form of valerophenone (**1a**) to form ruthenium(II) enolate **A**. Then, the phenacyl radical **B**,[12] produced by homolysis of the O-Ru bond of **A**, reacts with molecular oxygen to give the hydroperoxide intermediate **C** and Ru(0). Subsequent homolytic cleavage of the O–O and C–C bonds of **C** affords acyl radical **D** and butanal (**E**) together with the hydroxyl radical, and then benzoic acid could be obtained from **D** and the hydroxyl radical. Although butanal (**E**) is certainly oxidized to the corresponding butyric acid (**F**, **1a**),[13] **E** also undergoes Ru/C-catalysed C–C bond cleavage in a similar manner. Finally, CO and CO_2 would be discharged via Ru/C-catalysed dehydrogenation of formaldehyde and formic acid, respectively.

Scheme 4. Proposed mechanism 1



It is difficult to explain the formation of the DNPH derivative **7a** derived from acetone as shown in Scheme 2 by the mechanism depicted in Scheme 4. Therefore, we propose an additional possible pathway in Scheme 5. The oxidative addition of the C(O)–H bond of butanal (**E**) to Ru(0) and subsequent Ru-migration would form a Ru(II) hydride complex **G**.[4] The homolysis of the C–Ru bond of **G** would afford a primary aliphatic radical intermediate **H**, which is transformed to propanal via oxidation by molecular oxygen. On the other hand, **H** could migrate to a more stable secondary radical **I**, and subsequent oxidation easily provides acetone.

Scheme 5. Proposed mechanism 2



In conclusion, we have demonstrated a novel Ru-catalysed aqueous oxidative C–C cleavage reaction of aryl alkyl ketones and aliphatic aldehydes. The reaction provides a practical and mild synthetic approach to benzoic acid derivatives, because of the use of molecular oxygen as an oxidant, heterogeneous Ru/C as the catalyst, and inexpensive CaO as a base. Although the reaction seems simple, it includes complicated reaction pathways centred around Ru/C-catalysed oxidative C–C cleavage reactions. A plausible radical process is proposed on the basis of mechanistic studies.

Experimental Section

General procedure for benzoic acids derivatives synthesis (Table 3)

A mixture of 5% Ru/C (25.3 mg, 12.5 μmol), aryl alkyl ketone derivative (250 μmol), and CaO (56.1 mg, 1 mmol) in H_2O (2 mL) in a 17-mL test tube was stirred using a personal organic synthesizer ChemistPlaza™ (Shibata Scientific Technology, Ltd., Tokyo) at 100 °C under an O_2 atmosphere for 12 h. The mixture was passed through a membrane filter (Millipore Corp., Billerica, MA; Millex-LH, 0.45 μm) to remove the insoluble catalyst, and the filtered residue was washed with AcOEt (30 mL). The combined filtrate was washed with H_2O (3 ×20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane : Et_2O : MeOH = 2 : 1 : 0.01) to afford the corresponding benzoic acid derivative.

Acknowledgements

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[5] The addition of a small amount of *i*-PrOH (500 μL) or cyclohexane (500 μL) in H_2O (2 mL) for the reaction of **1k** (250 μmol) indicated a negligible impact on the reaction progress. Therefore, the low yield might not be simply attributed to the solubility of **1k**.

[6] The C–C cleavage reactions of 2-acetylnaphthalene, 4-acetylpyridine, and 2-acetyl-5-methylfuran hardly proceeded.

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[12] The generation of phenacyl radical (**B**) during the reaction would be supported by the relatively low yield of benzoic acid from acetophenone (**1b**) in Table 3 due to the less stability of the corresponding primary radical rather than secondary and tertiary radicals.

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