



Copper-Catalyzed Aerobic Oxidative C–C Bond Cleavage for C–N Bond Formation: From Ketones to Amides**

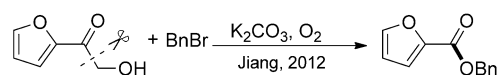
Conghui Tang and Ning Jiao*

Abstract: A novel copper-catalyzed aerobic oxidative C(CO)–C(alkyl) bond cleavage reaction of aryl alkyl ketones for C–N bond formation is described. A series of acetophenone derivatives as well as more challenging aryl ketones with long-chain alkyl substituents could be selectively cleaved and converted into the corresponding amides, which are frequently found in biologically active compounds and pharmaceuticals.

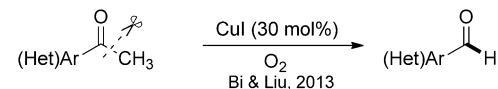
Carbon–carbon bonds are ubiquitous in organic compounds. Compared to the highly developed C–C bond forming reactions, the chemoselective cleavage of C–C bonds has always been on the cutting edge in organic chemistry, biodegradation, and industrial applications.^[1] Among them, the cleavage of C–C single bonds is the most challenging issue because of their thermodynamic stability and uncontrollable selectivity.^[1] Chemists have always been pursuing new methods to solve these challenges. Employing strained skeletons^[2] (three- and four-membered rings) or strategies that make use of chelation assistance^[3] are representative methods to promote C–C cleavage. To cleave unstrained inert C–C bonds, harsh conditions with stoichiometric oxidants, such as peroxides and toxic metal salts, have traditionally been required. Therefore, there is an urgent need for chemists to find milder and greener processes. To achieve this goal, two main approaches have been taken into consideration: 1) The development of suitable catalytic systems to decrease the activation energy of C–C bonds, and 2) the use of air or molecular oxygen as a benign oxidant instead of peroxides and toxic metal salts.

Molecular oxygen has been considered as an ideal oxidant for organic synthesis because of its atom-economical and environmentally benign character.^[4–6] Recently, a few elegant examples of aerobic oxidative C–C bond cleavage involving

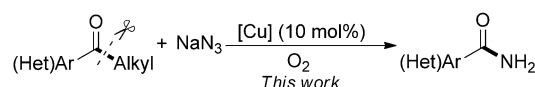
a) C–O bond formation



b) C–H bond formation



c) C–N bond formation



Scheme 1. Aerobic oxidative C–C single-bond cleavage.

carbonyl compounds have been reported. Jiang and co-workers^[7] reported a transition-metal-free aerobic oxidative C–C bond cleavage of α -hydroxyketones and subsequent esterification (Scheme 1a). The group of Bi and Liu^[8] reported a copper-catalyzed C(CO)–C(methyl) bond cleavage reaction under oxygen atmosphere, which terminates at the aldehyde stage without overoxidation (Scheme 1b). Despite significant progress in the area of aerobic oxidative C–O and C–H bond formation through C–C bond cleavage, the direct aerobic oxidative C–N bond formation through C–C single-bond cleavage has not been reported to date. Furthermore, aryl ketones with long-chain alkyl groups do not work in either of the reactions described above, and transformations of such inactive substrates also represent a challenge.

Herein, we report a novel copper-catalyzed aerobic oxidative C–C bond cleavage reaction for C–N bond formation,^[9,10] which enables the direct transformation of aryl alkyl ketones into benzamides with high efficiency (Scheme 1c). To the best of our knowledge, the aerobic oxidative C–C single-bond cleavage for the formation of C–N bonds employing molecular oxygen as the oxidant has not been disclosed thus far. Environmentally benign molecular oxygen is employed as the sole oxidant for this simple copper-catalyzed reaction.^[11] Furthermore, this method was used to realize the first aerobic oxidative C–C single-bond cleavage of aryl ketones with long-chain alkyl substituents.

Owing to our continuing interest in the construction of C–N bonds,^[12] we wished to accomplish this goal by using azide as the nitrogen source. In the beginning, we chose 4'-phenylacetophenone (**1a**) as the model substrate. To our delight, when **1a** and sodium azide were treated with a catalytic system consisting of CuI, TEMPO, and O₂ in DMF at 90 °C, 4-phenylbenzamide (**2a**) was obtained in 56 % yield (Table 1, entry 1). 4-Methoxy-TEMPO and 4-oxo-

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

Entry	[Cu] (mol %)	Additive (mol %)	H ₂ O (equiv)	T [°C]	Yield ^[b] [%]
1	CuI (10)	TEMPO (20)	H ₂ O (20)	90	56
2	CuI (10)	4-MeO-TEMPO (20)	H ₂ O (20)	90	42
3	CuI (10)	4-oxo-TEMPO (20)	H ₂ O (20)	90	37
4	CuI (10)	TEMPO (20)	H ₂ O (30)	90	59
5	CuI (10)	TEMPO (20)	H ₂ O (30)	110	70
6	CuCl (10)	TEMPO (20)	H ₂ O (30)	110	79
7	CuBr (10)	TEMPO (20)	H ₂ O (30)	110	79
8	CuBr ₂ (10)	TEMPO (20)	H ₂ O (30)	110	78
9	CuCl ₂ (10)	TEMPO (20)	H ₂ O (30)	110	82
10	CuCl₂ (10)	TEMPO (20)	H₂O (30)	120	84
11 ^[c]	CuCl ₂ (10)	TEMPO (20)	H ₂ O (30)	120	0
12	–	TEMPO (20)	H ₂ O (30)	120	0
13	CuCl ₂ (10)	–	H ₂ O (30)	120	70
14	CuCl ₂ (10)	TEMPO (20)	–	120	47

[a] Reaction conditions: **1a** (0.4 mmol), NaN₃ (1.2 mmol), copper precursor (0.04 mmol), DMF (2 mL), under O₂ (1 atm) for 16 h. [b] Yields of isolated products.

[c] The reaction was carried out under argon atmosphere. DMF = *N,N*-dimethylformamide, TEMPO = 2,2,6,6-tetramethylpiperidine-1-oxyl.

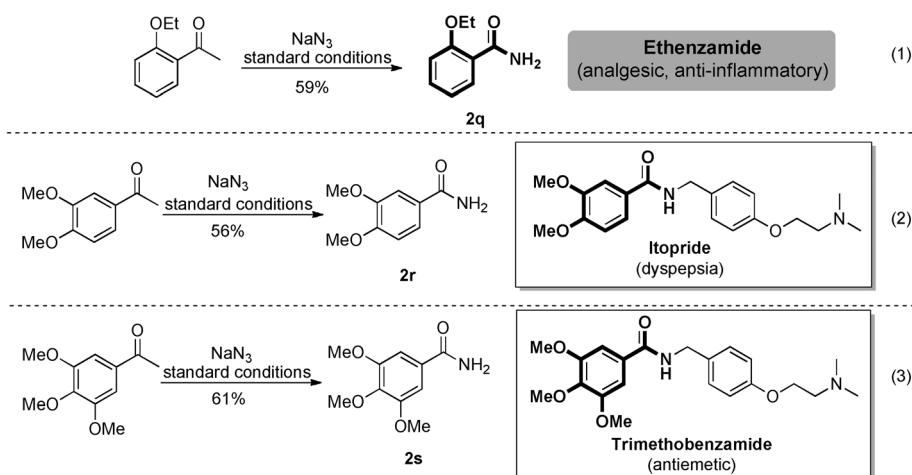
TEMPO were less efficient than TEMPO (entries 2 and 3). Elevating the reaction temperature from 90 to 110°C led to an increase in yield to 70% (entry 5). Different copper catalysts were screened, and CuCl₂ turned out to be the most effective catalyst (entries 6–9). When the temperature was further raised to 120°C, the highest yield was achieved (84%; entry 10). This reaction did not proceed in the absence of molecular oxygen or copper catalyst (entries 11 and 12). The yield decreased in the absence of TEMPO or H₂O (entries 13 and 14).

Next, the scope of this copper-catalyzed C–C bond cleavage reaction was examined in detail under the optimized reaction conditions (Scheme 2). Acetophenone (**1b**) reacted smoothly to yield benzamide (**2b**) in 66% yield. Acetophenone derivatives with alkyl substituents in the *para* position performed well, giving the desired products in moderate to excellent yields (**2c–2f**). This transformation could tolerate aryl ketones with electron-donating as well as electron-withdrawing substituents on the aryl ring. 4-Methoxy and 4-fluorobenzamide were obtained in 67% and 58% yield, respectively (**2g** and **2h**). As previously described, the coupling of aryl halides with sodium azide can easily afford aryl azide products,^[13] especially under copper catalysis in polar solvents. However, it is interesting that halogen substituents were tolerated in the present C–C cleavage process to produce the corresponding halogen-substituted

benzamides in moderate yields (**2i**, **2j**). Then, a series of disubstituted acetophenone derivatives were tested, which were compatible with the reaction conditions (**2k**, **2l**). 1-Acetonaphthone and 2-acetonaphthone also afforded the desired products in good yields (**2m**, **2n**). Furthermore, heteroaryl ketones were also suitable substrates for this transformation (**2o**, **2p**).

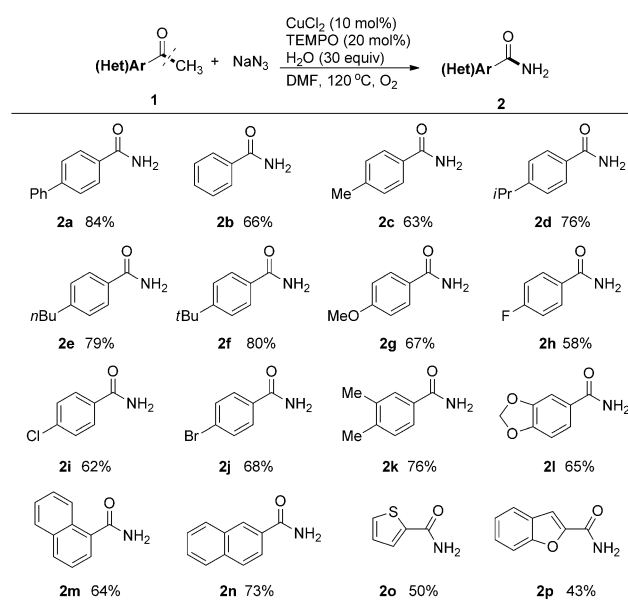
Moreover, 2-ethoxybenzamide (**2q**), which is an analgesic and an anti-inflammatory drug named Ethenzamide, was obtained in 59% yield [Eq. (1)]. Besides, 3,4-dimethoxybenzamide (**2r**) and 3,4,5-trimethoxybenzamide (**2s**) could be synthesized from the corresponding ketones using the present method; these two products are potential precursors of the dyspepsia drug Itopride and the antiemetic drug Trimethobenzamide, respectively [Eq. (2) and (3)].

Having established the broad substrate scope of this transformation, we investigated more challenging substrates under the standard conditions (Scheme 3). To our delight, various aryl alkyl ketones performed well, and the corresponding benzamides were obtained in moderate yields. Chemoselective cleavage of the C(CO)–C(alkyl) bond

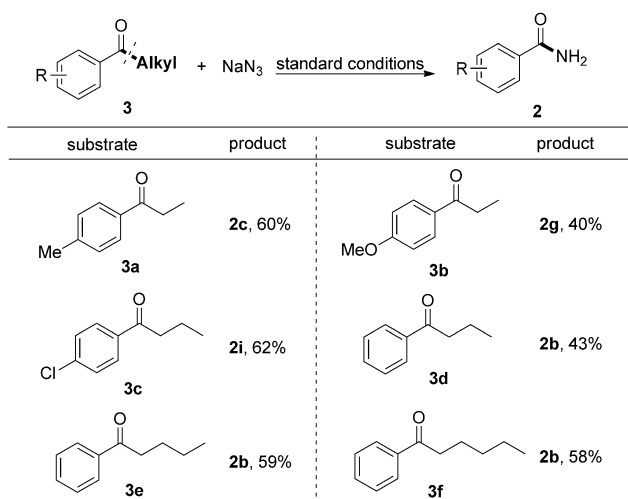


was achieved with this method. Halogen substituents such as a chloride were also tolerated by this catalytic system (**2i**). These aryl alkyl ketones were inactive under the conditions of the aldehyde syntheses described by the group of Bi and Liu,^[8] suggesting that our transformation may proceed through a different pathway.

To elucidate the mechanism of this reaction, some potential intermediates were prepared and tested under the standard conditions. However, benzaldehyde (**4**), 2-hydroxy-1-phenylethanone (**5**), 2-oxo-2-phenylacetaldehyde (**6**), and 2-oxo-2-phenylacetic acid (**7**) could not afford benzamide (**2b**) under the standard reaction conditions [Eq. (4)–(7)]. These control experiments indicate that the ketone substrate possibly first reacts with the azide nucleophile and then undergoes oxidation processes catalyzed by the Cu/O₂ system.



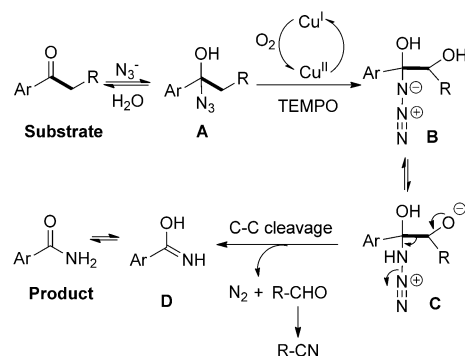
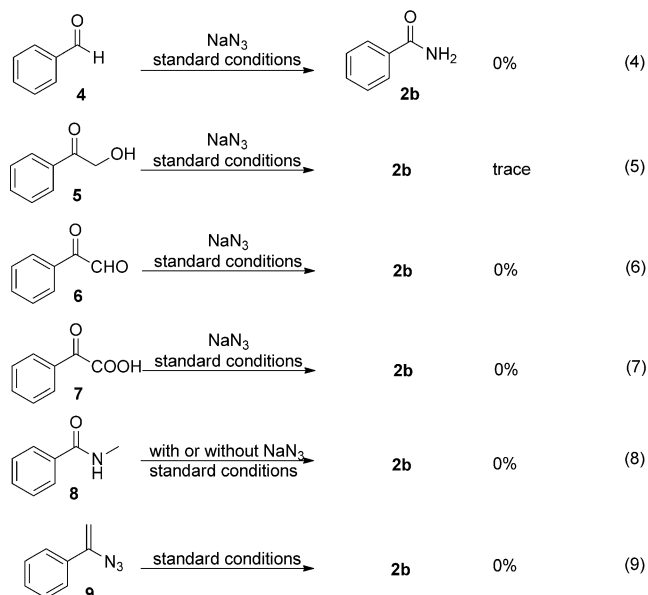
Scheme 2. Transformation of aryl methyl ketones. Standard reaction conditions: **1** (0.5 mmol), NaN₃ (1.5 mmol), CuCl₂ (0.05 mmol), TEMPO (0.1 mmol), H₂O (15 mmol), DMF (2 mL) at 120 °C under O₂ (1 atm) for 16 h. Yields of isolated products are given.



Scheme 3. Transformation of aryl alkyl ketones. Standard reaction conditions: **3** (0.5 mmol), NaN₃ (1.5 mmol), CuCl₂ (0.05 mmol), TEMPO (0.1 mmol), H₂O (15 mmol), DMF (2 mL), at 120 °C under O₂ (1 atm) for 16 h. Yields of isolated products are given.

Furthermore, *N*-methylbenzamide (**8**) did not react under the standard conditions, implying that a Schmidt reaction of acetophenone and sodium azide did not occur under the present conditions [Eq. (8)].^[14] Furthermore, (1-azidovinyl)-benzene (**9**) was completely unreactive under the standard reaction conditions [Eq. (9)].

Based on the above results, a plausible mechanism of this copper-catalyzed C–C bond cleavage of aryl alkyl ketones leading to amides was proposed (Scheme 4). The substrate is initially attacked by the azide nucleophile to form unstable



Scheme 4. Proposed mechanism.

intermediate **A** in a potentially reversible process. Subsequent aerobic oxidation of intermediate **A** generates α -hydroxylated intermediate **B** in the presence of the Cu/O₂ oxidative system.^[8,15,16] Subsequent rearrangement of intermediate **B** via its resonance structure **C** produces intermediate **D** through C–C bond cleavage with release of molecular nitrogen and an aldehyde as the byproducts.^[17] In some cases, the aldehydes undergo a Schmidt reaction to produce the corresponding nitriles, which could be detected by GC-MS (see the Supporting Information for details). Finally, tautomerization of **D** affords the desired amide.

In conclusion, the aerobic oxidative C(CO)–C(alkyl) cleavage of aryl alkyl ketones for C–N bond formation proceeded with high chemoselectivity. An inexpensive copper catalyst and molecular oxygen as the oxidant are the key features of this method with promising synthetic applications. A series of acetophenone derivatives as well as more challenging aryl ketones with long-chain alkyl substituents could be efficiently cleaved and converted into the corresponding amides, which are frequently found in biologically active compounds and pharmaceuticals. Preliminary mecha-

nistic insights have been disclosed, and further investigations of the mechanism are underway.

Experimental Section

Substrate 1-[(1,1'-biphenyl)-4-yl]ethanone **1a** (80.9 mg, 0.4 mmol), NaN_3 (75.6 mg, 1.2 mmol), CuCl_2 (5.4 mg, 0.04 mmol), and TEMPO (12.8 mg, 0.08 mmol) were added to a 20 mL Schlenk tube under O_2 atmosphere, followed by addition of H_2O (216 μL , 12 mmol) and anhydrous DMF (2.0 mL). This mixture was stirred at 120 °C under O_2 (1 atm) for 15 h as monitored by TLC. Upon completion of the reaction, the solution was extracted with ethyl acetate and brine, then purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether = 1:1) to afford product **2a** (66.4 mg; 84 %). **2a**: yellow solid; ^1H NMR (400 MHz, $[\text{D}_6]\text{DMSO}$): δ = 8.04 (s, 1H), 7.98 (d, J = 8.0 Hz, 2H), 7.80–7.70 (m, 4H), 7.48 (t, J = 7.6 Hz, 2H), 7.42–7.38 ppm (m, 2H); ^{13}C NMR (100 MHz, $[\text{D}_6]\text{DMSO}$): δ = 167.6, 142.8, 139.2, 133.1, 129.0, 128.2, 128.0, 126.8, 126.4 ppm; MS (EI) m/z 197.1 (100) $[M]^+$.

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