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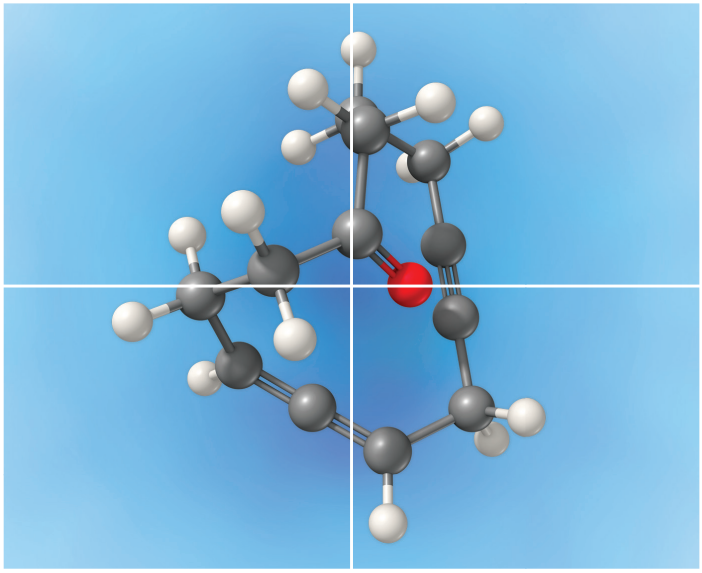

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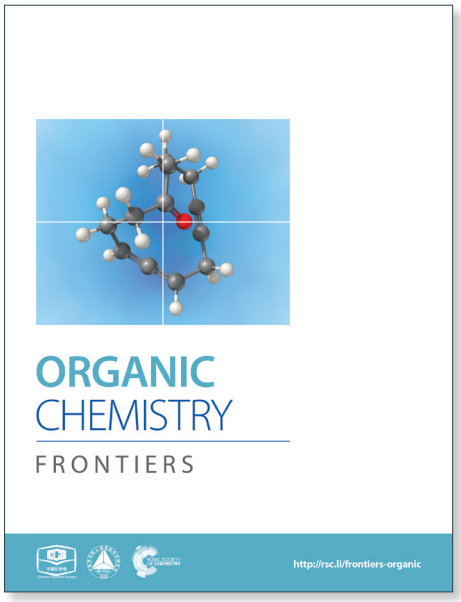

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COMMUNICATION

Cu-Catalyzed Aerobic Oxidative Amidation of Aryl Alkyl Ketones with Azoles to Afford Tertiary Amides via Selective C-C Bond Cleavage

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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Chemoselective cleavage of C(CO)-C(alkyl) bond in aryl ketones leading to azole amides is disclosed with a broad substrate scope. Aryl ketones with a variety of long-chain alkyl groups have been demonstrated to be active substrates and mechanism studies suggested that molecular oxygen serves both as oxidant and reactant in this strategy.

Selective cleavage of carbon–carbon bonds is a long standing theme and a holy grail in synthetic organic chemistry and has attracted great attention over the past few decades.[1] Among them, selective cleavage of C-C single bond is more challenging due to the following reasons: (1) C-C single bonds are more stable, thus are inert to most reaction conditions,[2] (2) C-C single bonds are less polar,[3] (3) C-C single bonds has weaker coordination with metal catalysts, making them difficult to be activated,[4] (4) C-C single bonds widely existed in one molecule, making the selective cleavage difficult.[5] Currently there are three strategies to cleave the C-C single bonds: (1) design special substrates, such as employ strained structure scaffold like three- and four-membered rings, to lower the C-C single bond stability;[6] (2) prefunctionalize substrates to increase C-C single bond reactivities, such as preinstall some activating group adjacent to the C-C single bonds,[7] (3) develop suitable catalytic systems to activate C-C single bonds by decreasing its activation energy.[8] Although the great advances have been achieved in cleavage of C-C single bonds, the harsh reaction conditions, expensive and toxic transition-metal catalysts, stoichiometric oxidants (especially peroxides) and limited substrate scopes make it highly desirable to develop more efficient and sustainable protocols to cleave unstained C-C single bonds.

Aryl ketones are one of ubiquitous structural motif in organic compounds and the direct manipulation of ketones is one of most versatile transformations in organic synthesis.[9] In very recent times, a few elegant examples of aerobic oxidative C(CO)-C(alkyl) bond cleavage of ketones have been reported.[10-12] Despite significant progress in the area of aerobic oxidative C(CO)-C(alkyl) bond cleavage in aryl ketones, the direct aerobic oxidative tertiary amide formation through C(CO)-C(alkyl) single bond cleavage with molecular oxygen as oxidant has not been reported to date. Meanwhile, aryl ketones with a wide variety of long-chain groups are either inert or have not been reported in the above reported (CO)-C(alkyl) single bond cleavage reactions yet, therefore, activation of such aryl ketones under dioxygen is a big challenge and a fascinating area in synthetic community.

Azoles, particular benzimidazoles are prevalent scaffolds in a broad spectrum of bioactive natural products and pharmaceutically active molecules.[13] Therefore, it is highly desirable to develop novel and practical methods for the construction of functionalized azoles. Traditionally, acylation of azoles either were made from free carboxylic acids or made from acyl chloride.[14] In the former process, preactivation of the free carboxylic acids are always required with stoichiometric activating reagents, and in the latter reaction, corrosive byproducts are often generated during the reaction. Recently, a metal-free N-acylation of azole was reported from aldehydes and azoles.[15] However, excess amount of peroxides was required for the success of the transformation. Molecular oxygen is an ideal oxidant owing to its well-known sustainable properties.[16] Acylation of azoles via aerobic oxidative C(CO)-C single bonds cleavage with aryl ketones has not been reported thus far. As part of our ongoing interest on copper catalyzed aerobic oxidative C-C bond activation reaction,[17] herein we would like to report a copper-catalyzed aerobic oxidative amidation between aryl alkyl ketones and azoles. Azole tertiary amides were found to be formed with molecular oxygen as the sole terminal oxidant in good yields with a broad substrate scope. Notably, numerous aryl ketones with a wide variety of long-chain groups have been demonstrated to be active substrates in this novel strategy, thus greatly broaden the substrate scope.

At the outset, acetophenone (**1**) and benzimidazole (**2**) were selected as substrates in model reactions. As we can see, copper salts demonstrated good activities on this novel transformation (details see the Supporting Information) and 76% of desired product was obtained with the superb CuBr with pyridine (3 equiv) at 130 ^{o}C in 1 mL of p-xylene under O_2 in a sealed tube (Table 1, entry 2). When the solvent was changed into DMSO, DMF or toluene, the yield of the desired product was dramatically decreased to 33% with toluene (entry 3) and no desired product was detected with DMSO and DMF.[18] Ligand screening indicated that pyridine is the superior choice to 2-phenyl-pyridine, 2-methyl-pyridine, 2-amino-pyridine, Et_3N and DMEDA.[18] When temperature was decreased to

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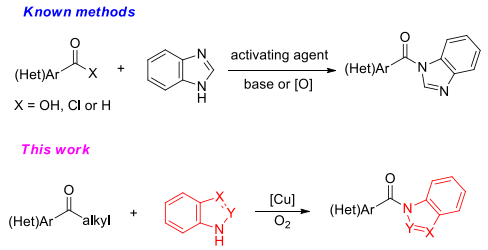
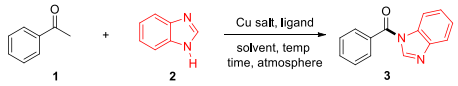
120 °C and 110 °C, the yields of desired product **3** was dropped to 22% and 4% correspondingly (entries 6-7). Copper salt, pyridine and dioxygen were all essential to this transformation, which have been indicated by entries 8-11: without CuBr, no desired product was ever detected (entry 8); without pyridine, the yield of desired product was reduced to 33% with other unknown compounds generated (entry 9); If the reaction was conducted under N_2 atmosphere or in air, only trace or small amount product was detected (entries 10-11). Further ligand and catalyst loading fine tuning (entries 12-15) revealed that the optimal reaction condition for **3** was: acetophenone **1** (0.25 mmol), benzimidazole **2** (0.5 mmol), CuBr (10 mol%), pyridine (3 equivalent), p-xylene (1 mL) at 130 °C under oxygen (entry 2).



Scheme 1. Azole amide formation from various starting substrates

Table 1. Optimization of the reaction conditions.[a]

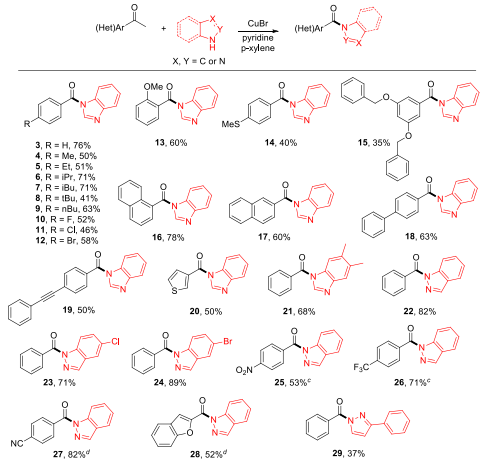


entry	catalyst (mol %)	atmosphere	ligand (equiv)	temperature	solvent	yield of **3** (%)[b]
1	CuCl (10)	O_2	pyridine (3)	130 °C	*p*-Xylene	16
2	CuBr (10)	O_2	pyridine (3)	130 °C	*p*-Xylene	76[c]
3	CuBr (10)	O_2	pyridine (3)	130 °C	Toluene	38
4	CuBr (10)	O_2	2-Methyl-py (3)	130 °C	*p*-Xylene	33
5	CuBr (10)	O_2	pyridine (0.5)	130 °C	*p*-Xylene	trace
6	CuBr (10)	O_2	pyridine (3)	120 °C	*p*-Xylene	22
7	CuBr (10)	O_2	pyridine (3)	110 °C	*p*-Xylene	4
8	-	O_2	pyridine (3)	130 °C	*p*-Xylene	no product
9	CuBr (10)	O_2	-	130 °C	*p*-Xylene	33
10	CuBr (10)	N_2	pyridine (3)	130 °C	*p*-Xylene	no product
11	CuBr (10)	air	pyridine (3)	130 °C	*p*-Xylene	11
12	CuBr (10)	O_2	pyridine (2)	130 °C	*p*-Xylene	74
13	CuBr (10)	O_2	pyridine (4)	130 °C	*p*-Xylene	64
14	CuBr (20)	O_2	pyridine (3)	130 °C	*p*-Xylene	4
15[d]	CuBr (10)	O_2	pyridine (3)	130 °C	*p*-Xylene	39[c]

Reaction Conditions: [a] acetophenone (**1**, 0.25 mmol), benzoimidazole (**2**, 0.5 mmol), Cu salt (10 mol %), ligand, solvent (1 mL), 16 h, temp., corresponding atmosphere. [b] GC yield. [c] Isolated yield. [d] acetophenone (**1**, 0.25 mmol), benzoimidazole (**2**, 0.25 mmol).

To explore the scope of this transformation, a variety of acetophenones and azoles were applied under the optimal conditions. As shown in Scheme 2, acetophenone derivatives with H, alkyl substituents and halo substituents in the para position performed well, giving the desired products in moderate to good yields (**3-12**) and among them, halo substituted desired products provide the feasibility for further structural manipulation (**10-12**). Electron-donating groups, like methoxy, methylthiol and bis-benzyloxyl substituents on the aromatic rings also indicated good reactivity (**13**-**15**). Polyphenylene substrates, such as 1-acetonaphthone, 2-acetonaphthone, 4-phenylacetophenone and 4-phenylethynylacetophenone were all tolerated under the standard conditions to afford the corresponding desired products in good yields (**16**-**19**). Moreover, other aromatic rings, such as 3-thiophene methyl ketone was compatible in this reaction as well (**20**). Bis-substituted benzimidazole was also found to be tolerated for this transformation to give the desired product in 68% yield (**21**). Intrigued by the above results, we further investigated the azole scope by extending benzimidazoles to other heterocycles. 3-Phenyl pyrazole and a variety of indazoles were found to show good reactivities in this transformation (**22**-**29**). Notably, indazole could react very well with acetophenones which bear strong electron-withdrawing groups on the aromatic rings to afford corresponding desired products in good to excellent yields (**25-27**). Meanwhile, heteroaromatic methyl ketone, for example, benzofuranylethanone reacted well with indazole to generate the desired product **28** in 52% yield. All above results have demonstrated that a very broad scope of (hetero)aryl methyl ketones and azoles are suitable substrates for the copper-catalyzed aerobic oxidative C(CO)-C single bond cleavage reaction, which infers our method might be an efficient and practical method to convert readily available acetophenones to an acyl synthons for a tertiary amide synthesis.

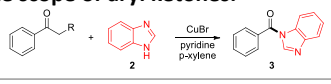
Scheme 2. Substrate scope for the formation of azole amides from aryl methyl ketones and azoles.[a, b]



[a] Reaction Conditions: acetophenone derivative (0.25 mmol), azole derivative (0.5 mmol), CuBr (10 mol %), pyridine (0.75 mmol), *p*-xylene (1 mL), 130 °C, 16 h, in O_2 in a sealed tube. [b] Isolated yield based on acetophenone derivative. [c] 135 °C, 12 h. [d] 135 °C, 18 h.

With the broad substrate scope of acetophenone derivatives established for this transformation, we were fascinated about the possibility of aryl ketones with different long-chain substituents under the standard conditions (Table 2). Delightfully, in addition to various aryl alkyl ketones (**30**, **31** and **32**), which have been demonstrated to be active substrates by Jiao and his co-workers in their primary amide formation with NaN_3,[11a] steric hindered compounds **33** (isopropyl) and **34** (benzyl) were also compatible substrates in this transformation, albeit the yields were a little bit lower than the former ones. Most attentions should be paid to compound **33** since similar compound was inert in ester formation from aryl ketone,[11b] which implies that the mechanism of this reaction is quite different from the precedent reports.

Table 2. Substrate scope of aryl ketones. [a, b]



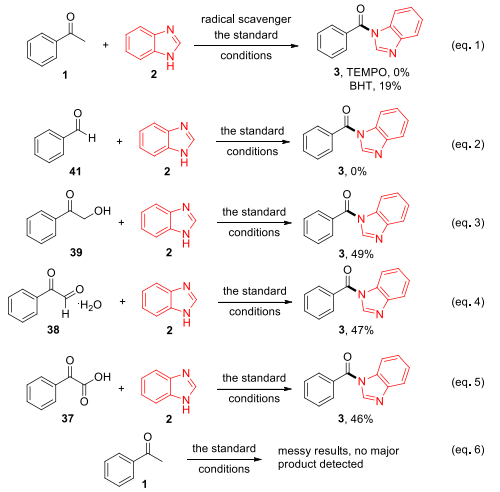
entry	ketones	yield of product (%)	entry	ketones	yield of product (%)
1	**30**	68	7	**36**	77
2	**31**	71	8	**37**	46
3	**32**	74	9	**38**	47
4	**33**	37	10	**39**	49
5	**34**	59	11	**40**	ND
6	**35**	55	12	**41**	0

[a] Reaction Conditions: aryl ketone (0.25 mmol), benzoimidazole (0.5 mmol), CuBr (10 mmol%), pyridine (0.75 mmol), *p*-xylene (1 mL), 130 °C, 16 h, in O_2 in a sealed tube. [b] Isolated yield based on aryl ketone. ND = not detected.

Gratifyingly, 1,3-dicarbonyl compounds, such as ethyl 3-oxo-3-phenylpropanoate (**35**) and 1,3-diphenylpropane-1,3-dione (**36**)

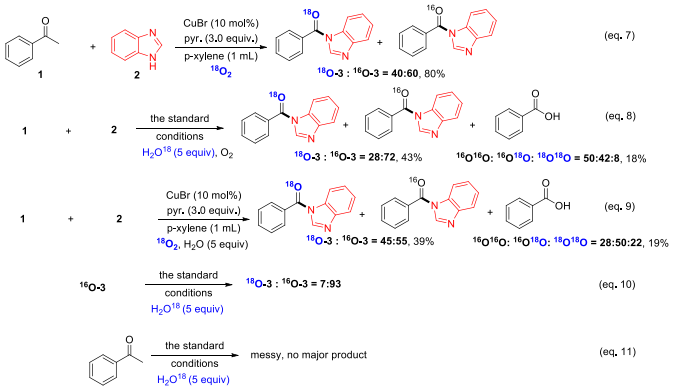
exhibit good reactivities under the standard conditions as well. Among the above aryl ketones, compounds **33**-**36** were all firstly reported active substrates in such Cu-catalyzed aerobic oxidative C(CO)-C single bond cleavage reaction, which greatly broaden the substrate scope. Meanwhile, 2-oxo-2-phenylacetic acid (**37**), 2-oxo-2-phenylacetaldehyde monohydrate (**38**) and 2-hydroxy-1-phenylethanone (**39**) were all applied under the standard conditions and moderate yields of desired products were obtained (See detailed explanation on these three compounds in Scheme 2 for control experiments). Interestingly, diethyl β-keto-phosphonate (**40**) and benzaldehyde (**41**) are inert in this transformation and no cleavage of the C(CO)-C(alkyl) single bond were ever detected.

In order to gain insight into the reaction mechanism of the novel C(CO)-C single cleavage reaction, several control experiments were carried out. As shown in Scheme 3, the reactions were almost totally inhibited by radical scavengers 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and BHT (2,6-di-tert-butyl-4-methylphenol), indicating that a radical pathway might be involved in this reaction (eq 1). No desired product **3** was obtained from benzaldehyde (**41**) and benzimidazole (**2**), suggesting benzaldehyde (**41**) is not the intermediate for this reaction (eq 2). The reactions of 2-hydroxy-1-phenylethanone (**39**), 2-oxo-2-phenylacetaldehyde monohydrate (**38**), and 2-oxo-2-phenylacetic acid (**37**) with benzimidazole (**2**) under standard conditions were also investigated and the desired products were afforded in 49%, 47% and 46% yields respectively (eqs 3, 4 and 5)，these results demonstrated that they might be the intermediates during the reaction transformation (yet compared to 76% of **3** in Table 1, entry 4, the yields were still quite lower). If only acetophenone was exposed under the standard conditions without benzimidazole, no major product was detected (eq 6).



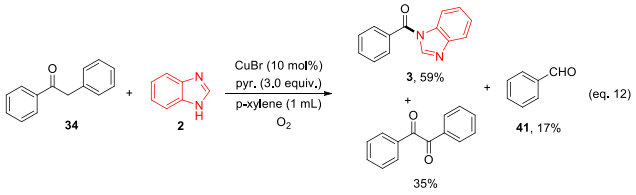
Scheme 3. Control experiments under standard conditions

As shown in Table 1, oxygen was crucial for the success of this transformation (Table 1, entries 10-11). To understand the originality of the oxygen in the product amide, the reaction was conducted firstly under $^{18}O_2$. Surprisingly, ca. 40% of **3** was labeled with ^{18}O (Scheme 4, eq 7). Further isotope labeled control experiments demonstrated that the amide product **3** could only slightly undergo oxygen exchange with water (eq 10). Moreover, when the reaction was conducted in the presence of 5.0 equiv. of $H_2{}^{18}O$ under the standard conditions (with $^{16}O_2$), product **3** was only obtained in 43% yield with 28% ^{18}O labeled, at the same time, 18% of benzoic acid was generated (eq 8) with a great amount of benzimidazole remaining; which indicated that water plays deterious effect on the reaction and slows down the entire process (competitive reaction vs azole). Yet when the reaction was performed under $^{18}O_2$ with 5.0 equiv. of H_2O, 45% ^{18}O labeled product **3** was detected (eq 9) and the total yield of **3** was only 39% with 19% of benzoic acid formed. When acetophenone (**1**) was exposed under the optimal condition with 5.0 equiv. of $H_2{}^{18}O$, it was totally decomposed and no major product was detected (eq 11); if the reaction was shortened to 6 hr, only starting material remained and no oxygen scrambling was detected. All above reactions reveal that the oxygen atom of the product amide partially originated from molecular oxygen in this novel transformation, which was consistent to the ^{18}O incorporation in byproduct benzoic acid (eqs 8 and 9) and consistent to previous report[11b] as well.



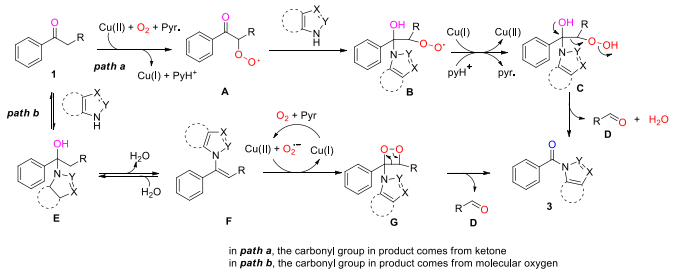
Scheme 4. Isotope labeled control experiments

Noteworthy, when compound **34** was conducted under the standard conditions (Table 2, entry 5), in addition to desired product **3** (59% yield), benzaldehyde (**41**) and benzil were obtained in 17% and 35% yield respectively (eq 12), which suggested that oxidation on the methylene group adjacent to the carbonyl group in aryl ketone might occur before the nucleophilic addition of ketone with azole and benzaldehyde (**41**) might be a byproduct in this transformation.



On the basis of the above results and the reported literature,[11, 19] a tentative mechanism was given below (Scheme 5): in path **a**, the methylene group adjacent to carbonyl group was oxidized before the nucleophilic addition of ketone with azoles in the presence of Cu salt and molecular oxygen[20] via single electron transfer (SET) process, generating superoxide intermediate **A**. Then, the nucleophilic attack of the carbonyl group with azole in intermediate **A** occurred, leading to intermediate **B**. Subsequently, the SET reduction and protonation of intermediate **B** generates hydroperoxide intermediate **C**,[21] in which the cleavage of C-C bond occurred during the rearrangement of intermediate **C**, affording amide along with aldehyde **D**.[22] In this pathway, the carbonyl group in the desired product **3** stays intact without the O atom incorporation; in path **b**, the nucleophilic addition of ketone with azole took place before the aerobic oxidation reaction, affording intermediate **E**. Dehydration of intermediate **E** generates enamine **F**. Subsequently, dioxetane intermediate **G** was formed[23] from enamine **F** under Cu(II)/oxygen system in the presence of pyridine.[24] Eventually, the C–C bond and O–O bond cleavage of dioxetane

intermediate **G** affords amide **3** and aldehyde byproduct **D**.[23]



Scheme 5. Proposed mechanism

Conclusions

In summary, a novel Cu-catalyzed aerobic oxidative amidation via C(CO)-C single bond cleavage of aryl ketones with various azoles has been demonstrated. Azole amides were obtained in moderate to good yields with a very broad range of substrate scope. This reaction has many advantages like cheap copper salt as catalyst, oxygen as the sole terminal oxidant, cheap and readily available starting materials and wide substrate scope. Meanwhile, aryl ketones with a variety of long-chain groups have been demonstrated to be active substrates in this novel strategy, and most of them are inert or have not been reported in the previous reported (CO)-C(alkyl) single bond cleavage reactions yet. Therefore, our strategy greatly widen the aryl ketone substrate scope in C(CO)-C single bond cleavage reaction and show a potential application in organic synthesis. Further investigation on new C-C single bond cleavage is under the way in our laboratory.

Acknowledgments

Financial support from the National Science Foundation of China (21202049), the Recruitment Program of Global Experts (1000 Talents Plan), Fujian Hundred Talents Program, and Program for Innovative Research Team of Huaqiao University are gratefully acknowledged.

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