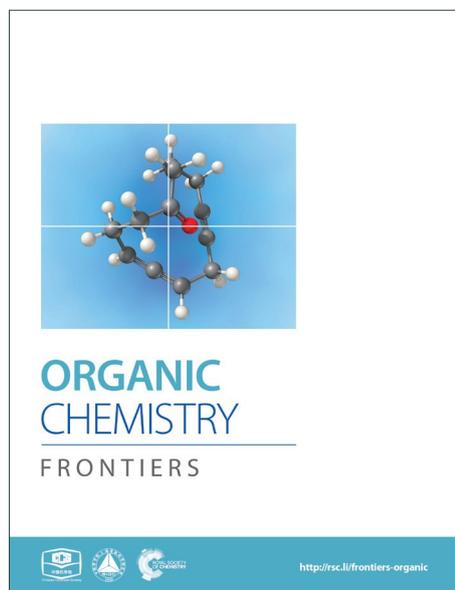
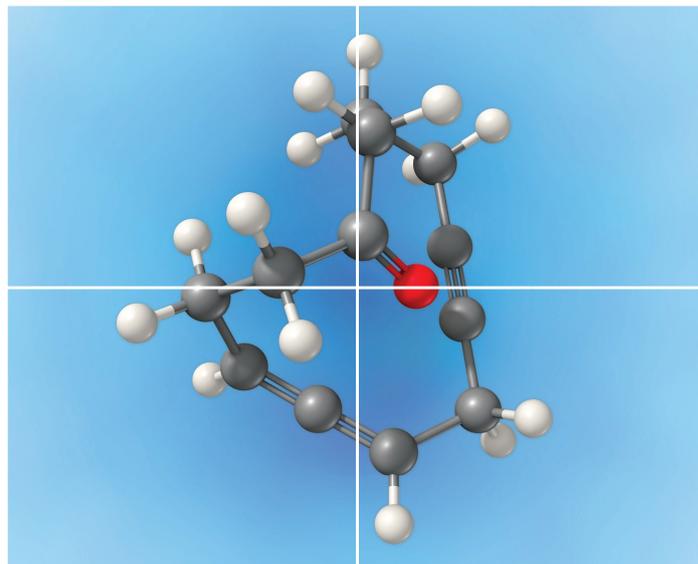


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RESEARCH ARTICLE

Dearomative C–C and C–N Bond Cleavage of 2-Arylindoles: Transition-Metal-Free Access to 2-Aminoarylphenones

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

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DOI: 10.1039/x0xx00000x

A transition-metal-free conversion of 2-arylindoles to 2-aminoarylphenones, using environmentally benign O₂ as the sole oxidant, has been developed. This novel oxidative dearomatization process involves cleavage of both C-C and C-N bonds followed by new C-C and C-O bonds formation. The C2 carbon of indole scaffold was released in a form of CO₂.

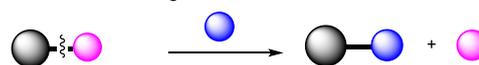
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In recent years, much attention has been paid to chemoselective C-C bond cleavage followed by new C-C and/or C-heteroatom bond formation; since it enables a great number of readily available substances in chemical transformations.¹ In general, certain class of molecules such as carbonyl derivatives, restrained small rings, alkenes, or alkynes, etc., in combination with transition-metal catalysts are applied in this process due to the relatively higher energy barrier for C-C bond dissociation.² Meanwhile, dearomatization of aromatic compounds is also a thermodynamically unfavourable transformation in which transition-metal catalysts or hypervalent iodine reagents are normally required.³ Notably, in most of the reported dearomatization reactions, the frameworks of starting material are maintained in the dearomatized products. Merging the two important classes of reactions together, that is cleavage of C-C bond(s) inbuilt in an aromatic system to lead to dearomatized products, is scarce in literature.

One major class of C-C bond cleavage reaction proceeds through one C-C bond activation followed by introducing a new group from another reactant (a, Scheme 1).^{2h-j} Thus, the part excised is unavoidably wasted. Another form of the reaction involves two bonds cleavage including at least one C-C bond, and then two of the three resulting parts are reconnected. That is, a small portion of the substrate is extruded from the parent molecule (b, Scheme 1). For example, transition-metal-catalyzed decarboxylation and decarbonylation reactions are the representatives of this class, in which carbon dioxide and carbon monoxide are extruded from substrates, respectively (c, Scheme 1).⁴ However, extrusion reaction involving a non-carbonyl substrate is rare, especially under transition-metal-free conditions. In a relative study, we reported an uncommon hypervalent iodine(III)-promoted tandem demethylenation/C-H cycloamination process of *N*-benzyl-2-aminopyridines via C-C and C-N bonds cleavage.⁵ Recently, Laha et al. developed a novel conversion of 10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]-diazepines to phenazines through transition-metal-

free tandem oxidative extrusion of the benzylic methylene group.⁶ Cui et al. reported a metal-free synthesis of diaryl-1,2-diketones by extrusion of a carbon atom of alkynes.⁷ Herein, we present a transformation of 2-arylindoles to unexpected products, which was identified to be 2-aminoarylphenones, through dearomative C-C and C-N bonds cleavage using environmentally benign oxygen as the sole oxidant (d, Scheme 1). In this process, three chemical bonds (2 C-C and 1 C-N) are cleaved and one new C-C bond and one C-O bond are generated in one step. It is well known that 2-aminoarylphenones are unique precursors for heterocyclic synthesis,⁸ and traditional methods for its syntheses including Friedel-Crafts acylation,⁹ palladium-catalyzed carbonylation reactions,¹⁰ and addition reactions of Grignard reagents to nitriles.¹¹ However, all of these present procedures have some disadvantages, including lack of regio-selectivity, use of transition metals or poor functional groups tolerance. The development of an efficient and general synthetic route is highly desirable.

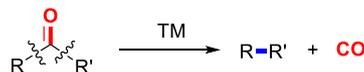
(a) Classical C-C cleavage



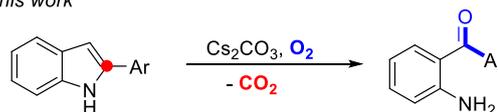
(b) Extrusion reaction



(c) Transition-metal-catalyzed decarboxylation and decarbonylation



(d) This work



+ 3 bonds cleavage + 2 bonds formation
+ transition-metal free + O₂ as the oxidant

Scheme 1 C-C Bond Cleavage Reactions.

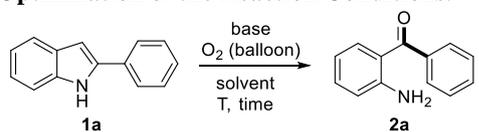
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*Electronic Supplementary Information (ESI) available: Experimental details see DOI: 10.1039/x0xx00000x

Initially, treatment of 2-phenylindole **1a** in the presence of 2.0 equiv of Cs₂CO₃ in DMSO (used as received) under an O₂ (1 atm) atmosphere at 120 °C afforded an unexpected product which was identified as 2-aminobenzophenone **2a** (51% yield, entry 1, Table 1). When the reaction was performed in toluene, dioxane, DCE or acetonitrile, **1a** was completely recovered (entries 2-5). However, **1a** was decomposed in NMP and **2a** could be obtained in only 10-20% yields in DMF or DMA, which indicated the crucial role played by DMSO (entries 6-8). Screening of bases demonstrated that Cs₂CO₃ was the most effective in promoting the reaction (entries 9-12). It was worth noting that the yield of **2a** decreased significantly in anhydrous DMSO. The importance H₂O was further proven by adding 10 equiv of H₂O to anhydrous DMSO, which gave comparable yield of **2a** (see ESI for details). Shortening the reaction time from 18 h to 16 h was beneficial (56%, entry 14). It was intriguing that when the reaction tube was sealed in air and then equipped with an oxygen balloon rather than in pure O₂, **2a** was isolated in an improved 69% yield (entry 15). Changing the reaction tube to a smaller one (10 mL) under the same procedure described in entry 15, the isolated yield of **2a** was finally improved to 73% (entry 16).

Table 1 Optimization of the Reaction Conditions.^a



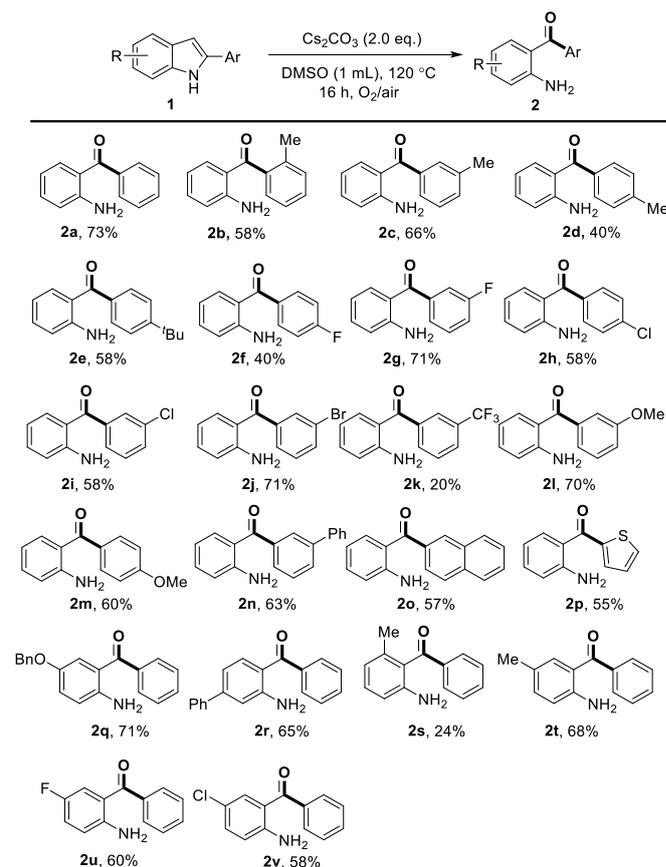
Entry	Solvent	Base (2.0 eq.)	Yield (%) ^b
1	DMSO	Cs ₂ CO ₃	51
2	toluene	Cs ₂ CO ₃	nr
3	dioxane	Cs ₂ CO ₃	nr
4	DCE	Cs ₂ CO ₃	nr
5	MeCN	Cs ₂ CO ₃	nr
6	NMP	Cs ₂ CO ₃	0
7	DMF	Cs ₂ CO ₃	20
8	DMA	Cs ₂ CO ₃	10
9	DMSO	K ₂ CO ₃	0
10	DMSO	Na ₂ CO ₃	nr
11	DMSO	CsOAc	nr
12	DMSO	LiOH	9
13 ^c	DMSO	Cs ₂ CO ₃	38
14 ^d	DMSO	Cs ₂ CO ₃	56
15 ^{d,e}	DMSO	Cs ₂ CO ₃	73 (69)
16 ^{d,e,f}	DMSO	Cs ₂ CO ₃	78 (73)

^a Reaction conditions: **1a** (0.2 mmol), solvent (1 mL), base (2.0 equiv), degassed with O₂, 120 °C, 18 h, O₂ balloon, in a 50 mL Schlenk tube. ^b NMR yields with CH₂Br₂ as an internal standard. Numbers in the parentheses are isolated yields. ^c Anhydrous DMSO with 100 mg of 4Å MS. ^d 16 h. ^e Without degassing with O₂. ^f Reaction was run in a 10 mL Schlenk tube.

With the optimal reaction conditions in hand, the substrate scope was then investigated as summarized in Scheme 2. Substrates with various substituents on the 2-phenyl group, regardless of their electron-donating (Me, ^tBu and OMe) or electron-withdrawing (F, Cl, Br and phenyl) properties, could undergo the transformation in moderate to good yields. In general, 2-arylindoles with *meta* substituents gave high yields than the same group in the *para* position (e.g., 71% for **2g** and 40% for **2f**, 70% for **2l** and 60% for **2m**). However, 2-arylindole bearing a strong electron-withdrawing CF₃ group (**2k**) was less compatible with reaction conditions. Substrate with an *ortho* Me group on the phenyl ring delivered **2b** in 58% yield. Moreover, naphthyl and thienyl substituents were also tolerated

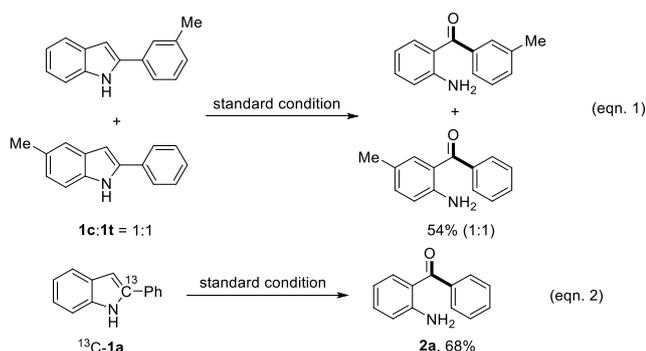
in this oxidative condition and provided the desired products in 57% and 55% yields, respectively (**2o** and **2p**). Unfortunately, no product was observed when 2-alkylindoles or 2-alkenylindoles were subjected to the reaction.

Then, substrates with different functional groups on the indole ring were also investigated. The corresponding products were obtained in moderate to good yields irrespective of the electronic nature of the substituents on 5- or 6- position of the indole ring (**2q**, **2r**, **2t**, **2u** and **2v**). However, a low yield of 24% was obtained when a methyl group was located at the 4-position of the indole ring, probably due to the steric hindrance (**2s**). The structures of products **2r** and **2s** clearly showed that the anilinic carbon linked to the carbonyl moiety was the one originally connected to C3 of indole.

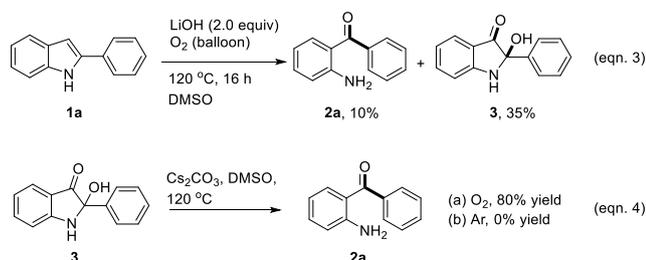


Scheme 2. Substrate scope. Reaction conditions: **1** (0.2 mmol), Cs₂CO₃ (0.4 mmol), DMSO (used as received, 1.0 mL), 10 mL Schlenk tube, sealed in air, O₂ balloon, 120 °C, 16 h.

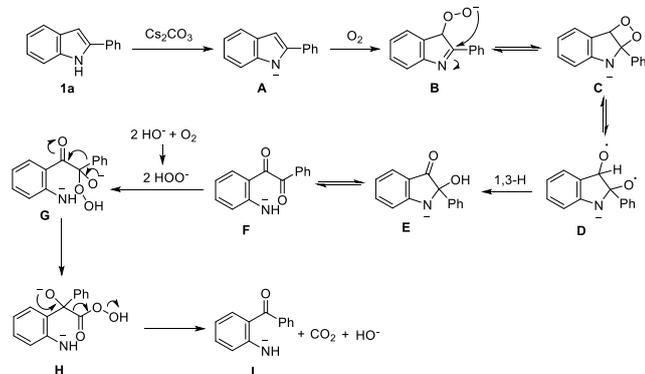
To gain more insight to the reaction mechanism, a crossover experiment using a 1:1 mixture of 2-(*m*-tolyl)-1*H*-indole (**1c**) and 5-methyl-2-phenyl-1*H*-indole (**1t**) was conducted under the standard conditions. No crossover product was detected by NMR analysis of the reaction products, which indicated that an intramolecular pathway was involved (eqn. 1). To confirm which carbon atom (C2 or C3) was extruded during the reaction, 2-phenyl-2-[¹³C]indole (¹³C-**1a**) was prepared and subjected to the standard conditions. No ¹³C enriched **2a** was isolated, demonstrating undoubtedly that the indole C2 carbon was extruded during the process (eqn. 2).



During the optimization of the reaction conditions, we found that when LiOH was used as a base, the desired product **2a** was isolated in low yield (10%) along with a byproduct **3** (35% yield, eqn. 3). Subjecting compound **3** to the standard reaction led to the desired product **2a** in 80% yield, which suggested that compound **3** might be a reaction intermediate (eqn. 4(a)). It was interesting to find out that compound **3** was stable in the absence of O₂ (eqn. 4(b)). In addition, CO₂ was proved to be generated by passing the gas in the reaction tube to a clear limewater which turned cloudy during the test (see ESI for details).⁷



Based on the results obtained, a plausible mechanistic pathway was proposed for this uncommon oxidative cleavage reaction (Scheme 3). A peroxy anion **B** is formed by the deprotonated substrate in the presence of base and oxygen. Then intramolecular nucleophilic attack to the C-N double bond results in a four-membered ring **C**. Subsequently, intermediate **D** is formed by a homolytic cleavage of the peroxy bond, followed by 1,3-H shift to give intermediate **E**, which can be protonated to afford **3**. Then, C-N bond cleavage in the aminoacetal moiety of **E** generates a diaryl-1,2-diketone **F**, which undergoes nucleophilic attack by the in-situ-formed peroxy anion to afford intermediate **G**. Finally, aryl group migration and subsequent elimination of carbon dioxide to give intermediate **I**, which is protonated to afford the final product.



Scheme 3 Proposed reaction mechanism.

In summary, we have developed an unexpected, novel and environmentally benign method for the conversion of 2-arylidole to 2-aminoarylphenones under transition-metal-free conditions using oxygen as the sole oxidant. The reaction proceeds through cleavage of two C-C bonds and one C-N bond followed by a new C-C and a C-O bond formation. Reaction using ¹³C labbed 2-arylidole revealed that the C2 carbon of indole scaffold was released in a form of CO₂.

Acknowledgements

We are grateful for financial support of this work by National Science Foundation of China (21202167, 21402203, 21472190, and 21532009).

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