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Copper-catalyzed C–C bond cleavage and intramolecular cyclization: an approach toward acridones†

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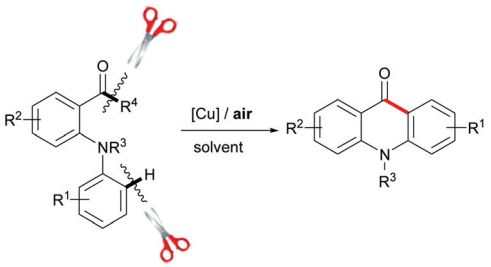
A copper-catalyzed approach for the synthesis of acridones *via* C–C bond cleavage and intramolecular cyclization using air as the oxidant under neutral conditions is described. This transformation offers an alternative method to prepare medicinally important acridones and a new strategy for C–C bond cleavage.

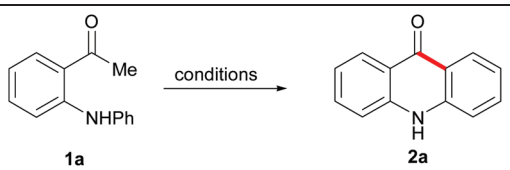
Because of its potential applications in organic synthesis and industry, transition-metal-catalyzed C–C and C–H bond cleavage has recently emerged as an active research topic in organic chemistry.[1,2] Although the cleavage of C–C bonds is a challenging task, some elegant methods involved in employing the catalyst of noble metals, such as Rh,[3] Ru,[4] Pd,[5] Pt,[6] and others,[7] have been developed. However, there are a limited number of strategies using the catalyst of cheap metals such as Cu[8] and Fe.[9] In the mid-1960s, Brackman and Volger reported the conversion of aliphatic aldehydes to aldehydes of one less carbon atom *via* a radical process.[10] Later, Sayre and co-workers studied the mechanism of oxygenation α to carbonyl groups.[11] To date, there are only a few reports employing the copper/O_2 catalytic system for C–C bond cleavage.[12] Recently, we reported a copper-catalyzed intramolecular direct amination of the sp^2 C–H bond for the synthesis of *N*-aryl acridones.[13] As part of our ongoing research, herein, we disclose an efficient copper-catalyzed approach for the synthesis of acridones *via* C–C bond cleavage and intramolecular cyclization using air as an oxidant under neutral conditions (Scheme 1).

Our initial studies focused on identifying the optimal conditions. 1-(2-(Phenylamino)phenyl)ethanone (**1a**) could be smoothly converted to the desired acridone **2a** in 80% yield with 20 mol% CuI in dimethyl sulfoxide (DMSO) under O_2 (1 atm) at 140 °C for 12 h (Table 1, entry 1). Carrying out the reaction under N_2 or without CuI led to almost quantitative



Scheme 1 New route to synthesize acridones.

Table 1 Optimization of reaction conditions[a]



1a **2a**

Entry	Cat. (20 mol%)	Oxidant (1 atm)	Solvent	1 (h)	Yield[b] (%)
1	CuI	O_2	DMSO	12	80
2[c]	CuI	None	DMSO	12	Trace
3	None	O_2	DMSO	12	Trace
4	CuI	O_2	NMP	12	79
5	CuI	O_2	DMA	12	58
6	CuI	O_2	DMF	12	55
7	CuI	O_2	*p*-Xylene	12	0
8	CuI	Air	DMSO	36	85
9[d]	CuI	Air	DMSO	36	17
10[e]	CuI	Air	DMSO	36	75
11[f]	CuI	Air	DMSO	36	17
12	CuBr	Air	DMSO	36	58
13	$CuBr_2$	Air	DMSO	36	70
14	CuCl	Air	DMSO	36	48
15	$Cu(OAc)_2$	Air	DMSO	36	17
16	$Cu(NO_3)_2 3H_2O$	Air	DMSO	36	19
17	$Pd(OAc)_2$	Air	DMSO	36	58
18[g]	CuI	Air	DMSO/PhCl	48	90

[a] Reaction conditions: **1a** (0.3 mmol), catalyst, and solvent (1.6 mL) were stirred at 140 °C. [b] Isolated yield. [c] The reaction was carried out under N_2. [d] The reaction was carried out at 100 °C. [e] The reaction was carried out at 120 °C. [f] CuI (10 mol%) was used. [g] Mixed solvent (v_{DMSO}/v_{PhCl} = 1 : 1) was used.

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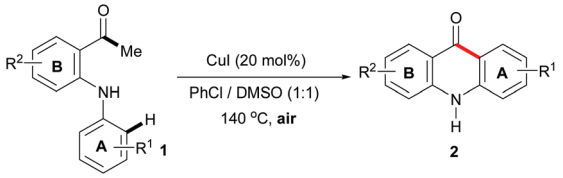
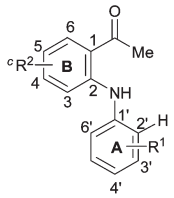
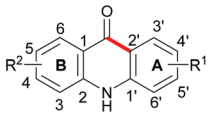
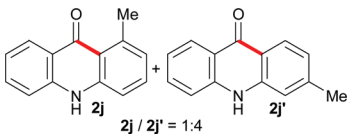
†Electronic supplementary information (ESI) available. See DOI: 10.1039/c2gc36502b

Table 2 The effect of substituents on the aromatic moiety[a]



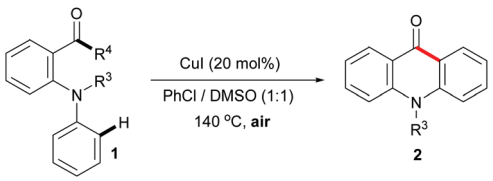
Entry	Substrate			Product		Yield[b] (%)
		R^1	R^2			
1		H	H	**1a**		**2a** 90
2		4′-Me	H	**1b**		**2b** 91
3[c]		6′-Me	H	**1c**		**2c** 56
4		4′-OMe	H	**1d**		**2d** 89
5		4′-NHAc	H	**1e**		**2e** 86
6		4′-Ph	H	**1f**		**2f** 85
7		4′-COOEt	H	**1g**		**2g** 90
8		4′-F	H	**1h**		**2h** 92
9		4′-Cl	H	**1i**		**2i** 50
10[d]		3′-Me(**1j**)	H		 2j / 2j' = 1:4	84
11		H	3-Me	**1k**		**2c** 38
12		H	5-Me	**1l**		**2b** 65
13		H	5-OMe	**1m**		**2d** 65
14		H	5-OCF_3	**1n**		**2k** 84
15		H	5-F	**1o**		**2h** 83
16		H	5-Cl	**1p**		**2i** 84
17		4′-F	5-F	**1q**		**2l** 69
18		4′-Me	5-OCF_3	**1r**		**2m** 70
19		4′-OMe	5-Cl	**1s**		**2n** 53

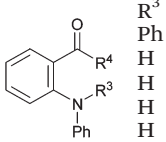
[a] Reaction conditions: **1** (0.30 mmol), CuI (20 mol%) in solvent (v_{DMSO}/v_{PhCl} = 1/1, 1.6 mL) were stirred at 140 °C under air (1 atm) for 48 h. [b] Isolated yield. [c] CuI (40 mol%) was used. [d] Determined by ^{1}H NMR.

recovery of **1a**, suggesting that the presence of oxygen and CuI are essential (Table 1, entries 2 and 3). Then, we began to screen solvents under O_2, finding that polar solvents, such as *N*-methyl-2-pyrrolidone (NMP), *N*,*N*-dimethylacetamide (DMA), and *N*,*N*-dimethylformamide (DMF), gave products in lower yields (entries 4–6). Notably, none of **2a** but unreacted **1a** was detected in the presence of *p*-xylene as a solvent (entry 7). Gratifyingly, the desired acridone could be obtained in 85% yield under air by prolonging the reaction time (36 h, entry 8). Lower temperature or catalyst loading has a significant effect on the yield (entries 9–11). Other copper catalysts, such as CuBr, CuCl, $CuBr_2$, $Cu(OAc)_2$ and $Cu(NO_3)_2{\cdot}3H_2O$, showed sluggish catalytic activity (entries 12–16). Moreover, $Pd(OAc)_2$ was not a suitable catalyst for this transformation (entry 17). On the basis of these observations, we tried to investigate the substrate scope under the reaction conditions as entry 8 listed (Table 1). However, the unsatisfying results spurred us to explore more conditions (ESI, Tables S1 and S2†). Finally, a mixed solvent furnished the best result unexpectedly (entry 18).

Based on the optimized conditions, the substrate scope was observed. The effect of different substituents on the aromatic rings **A** and **B** is listed in Table 2. Substrates bearing electron-donating substituents on the aromatic ring **A** could be successfully transformed into the desired products in high yields, such as 4′-Me (entry 2), 4′-OMe (entry 4) and 4′-NHAc (entry 5), but on the aromatic ring **B** in relatively low yields,

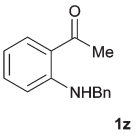
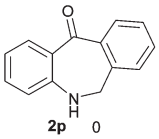
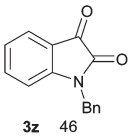
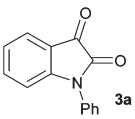
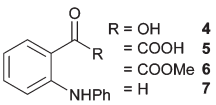
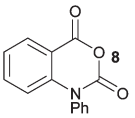
Table 3 The effect of substituents on the nitrogen and ketone moiety[a]



Entry	Substrate			Product		Yield[b] (%)
		R^3	R^4			
1		Ph	Me	**1t**	**2o**	82
2		H	Et	**1u**	**2a**	80
3		H	^{t}Bu	**1v**	**2a**	7
4		H	4-Methylbenzyl	**1w**	**2a**	60
5		H	4-Methoxybenzyl	**1x**	**2a**	65
6		H	Styryl	**1y**	**2a**	19

[a] Reaction conditions: **1** (0.30 mmol), CuI (20 mol%) in solvent (v_{DMSO}/v_{PhCl} = 1/1, 1.6 mL) were stirred at 140 °C under air (1 atm) for 48 h. [b] Isolated yield.

Table 4 Mechanism probing experiments[a]

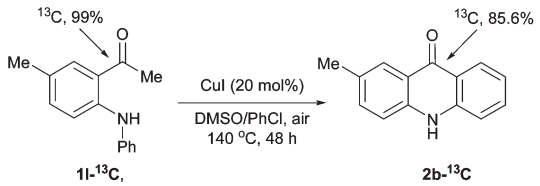
Entry	Substrate	Product[b] (%)	Others[b] (%)
1	 **1z**	 **2p** 0	 **3z** 46
2[c]	 **3a**	**2a** Trace	**3a** 66
3		**2a** 79	**3a** 0
4[d]		**2a** 17	**3a** 60
5[d,e]		**2a** 65	**3a** 35
6	 R = OH **4**, = COOH **5**, = COOMe **6**, = H **7**	**2a** Trace	
7		**2a** 17	
8		**2a** Trace	
9		**2a** 92	
10	 **8**	**2a** 0	

[a] Reaction conditions: substrate (0.15 mmol), CuI (20 mol%) in solvent (v_{DMSO}/v_{PhCl} = 1/1, 0.8 mL) stirred at 140 °C under air (1 atm) for 48 h. [b] Isolated yield. [c] The reaction was carried out without CuI. [d] The reaction was carried out under N_2. [e] $CuBr_2$ was used instead of CuI.

such as 5-Me (entry 12) and 5-OMe (entry 13). The product with the phenyl substituent could be obtained in high yield (entry 6). It is worth noting that 3′-Me substituted substrate **1j** led to a mixture of 3′-Me and 5′-Me products in 84% yield with the ratio of 1 : 4 (**2j**/**2j′**, entry 10). Electron-withdrawing functional groups, such as 4′-COOEt (entry 7) and 4′-F (entry 8), on the aromatic ring **A** or 5-OCF_3 (entry 14) and 5-F (entry 15) on the aromatic ring **B** could be well-tolerated, giving products in good to excellent yields. Moreover, the reaction scope could be expanded to the substrates with substituents on both rings **A** and **B** at the same time (Table 2, entries 17–19).

In addition, a series of substrates with different substituents on both the nitrogen atom and the ketone were examined (Table 3). The substituting group R^3 could be phenyl (Table 3, entry 1). R^4 could be alkyl (entries 2–5) or alkenyl (entry 6). Notably, the substrate with *tert*-butyl only gave the product in 7% yield (entry 3). Moreover, we could detect *p*-methyl and *p*-methoxyl benzaldehydes as by-products when **1w** and **1x** were employed respectively (Table 3, entries 4 and 5).

When 1-(2-(benzylamino)phenyl)ethanone (**1z**) was employed, we could only observe *N*-benzyl-indoline-2,3-dione (**3z**) as the product (Table 4, entry 1). Meanwhile, similar species could be detected by GC-MS analysis when **1a** was used (ESI, Fig. S1†). To probe the reaction mechanism, indoline-2,3-dione **3a** was synthesized and subjected to control experiments, giving **2a** in 79% yield under the optimized conditions (Table 4, entry 3). When CuI or $CuBr_2$ was used as the catalyst under N_2, acridone **2a** was obtained in 17% and 65% yields respectively (Table 4, entries 4 and 5). Furthermore, other possible intermediates also have been investigated (Table 4, entries 6–10). Although *N*-arylanthranilic aldehyde **7** could be successfully converted into the desired product in excellent yield (Table 4, entry 9), further studies ruled out the possibility of compound **7** working as a key intermediate in this transformation (see ESI, Table S3† for details). Moreover, radical mechanism studies indicate that a radical pathway may be not involved in this reaction (see ESI, Table S4† for details).



Scheme 2 ^{13}C labeling experiments.

Intermolecular kinetic isotope effects (k_H/k_D = 1.23) and intramolecular kinetic isotope effects (k_H/k_D = 1.69) indicate that aromatic C–H bond cleavage may be not turnover-limiting and does not occur *via* a chelation-assisted, SEAr or a free radical mechanism (see ESI† for details).[14,15] Interestingly, ^{13}C labeling experiments unveil that only about 86% of carbonyl carbon in the product originate from the carbonyl carbon of the substrate (Scheme 2).

On the basis of these preliminary results, we still can not speculate on a reasonable mechanistic pathway.[16] Multiple pathways may be involved in this transformation. A thorough mechanistic study is needed to unravel the mechanistic intricacies of this process.

In conclusion, we have demonstrated a copper-catalyzed approach for the synthesis of acridones *via* C–C bond cleavage and intramolecular cyclization using air as the oxidant under neutral conditions. This reaction not only provides an efficient

method for constructing medicinally important acridones, but also offers a new strategy for C–C bond cleavage.

Acknowledgements

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16 At the beginning, we speculated that oxygenation α to the carbonyl group of 1-(2-(arylamino)phenyl)ethanone **1** gave α-keto aldehyde **A**, which undergoes a copper-catalyzed intramolecular Friedel–Crafts type reaction to give product **2**. However, we disfavor this pathway because (1) the electron-deficient aromatic ring gave good or better results, clearly contradictory to this Friedel–Crafts type pathway. If the reaction does work in this manner, ester **6** should give product **2a** under the optimized conditions more likely (Table 4, entry 8); (2) it contradicts with the result of the ^{13}C labeling experiment (Scheme 2).