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Transition-Metal-Free Synthesis of Acridones via Base-Mediated Intramolecular Oxidative C–H Amination

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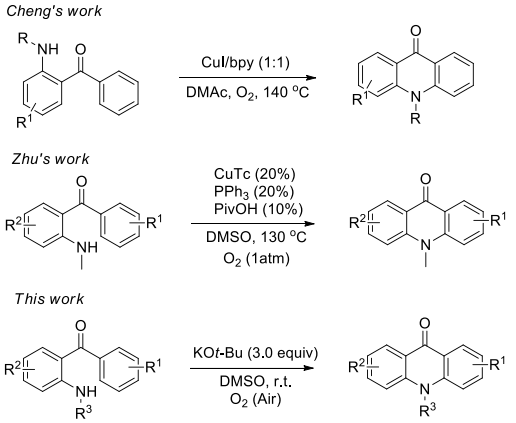
Abstract: Intramolecular oxidative C–H amination of 2-aminobenzophenones was achieved in the presence of potassium *tert*-butoxide and dimethyl sulfoxide. A series of functionalized acridones were prepared in moderate to excellent yields in a mild, efficient, and transition-metal-free manner.

Keywords: intramolecular C–H amination; acridones; 2-aminobenzophenones; potassium *tert*-butoxide; dimethyl sulfoxide.

The semi-planar structures of acridone derivatives interact specifically with different biomolecular targets, making them effective in antifungal, antiviral, antiallergic, and DNA-intercalating activities.[1] The traditional synthetic methods for acridones rely on acid-induced ring-closure of *N*-phenyl anthranilic acids,[2] oxidation of the corresponding acridinium salts by molecular oxygen,[3] and coupling reaction of 2-aminobenzoate with arynes.[4] In recent years, the transition-metal-catalyzed oxidative C–H amination has been extensively studied.[5,6] A number of heterocyclic compounds, such as carbazoles, benzimidazoles, indulines, and *N*-methoxylactams, have been synthesized.[7] Cheng et al. reported copper-catalyzed intramolecular oxidative C–H functionalization and C–N formation of 2-aminobenzophenones for the synthesis of functionalized acridones.[8] Zhu and co-workers directly constructed the acridone nucleus through intramolecular C–H amination reaction starting from readily available 2-(methylamino)benzophenones.[9] Lei described an approach to acridones through palladium/copper co-catalyzed oxidative carbonylation of diphenylamines.[10] However, transition metal catalysis was required for the above-mentioned C–H amination process to construct acridones. In 2015, Barolo successfully developed a photo-initiated $S_{RN}1$ protocol for the synthesis of substituted 9H-carbazoles using 2′-halo[1,1′-biphenyl]-2-amines under mild and transition-metal-free conditions.[11] However, the halo substitued substrates were necessary for the reaction.



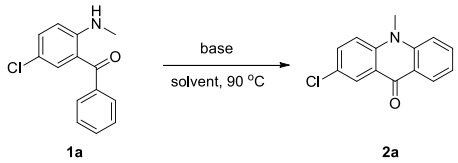
Scheme 1 Intramolecular C–H amination for synthesis of acridones

We previously reported the intramolecular cyclization of allylamines and ketones via the arrangement of α-aminoallyl radical intermediates promoted by KO*t*-Bu/DMF.[12] Recently, we observed that intramolecular oxidative C–H amination reaction could be accomplished in the presence of 2.0 equivalent KO*t*-Bu under oxygen atmosphere when *N*-allyl was replaced by *N*-methyl. The acridone nucleus can be rapidly constructed through C–N bond formation. We envisioned that other *N*-substituted 2-aminobenzophenones would also be feasible for synthesis of acridones. In this study, we report a transition-metal-free method for synthesis of acridones through intramolecular oxidative C–H amination.

We started our investigations by using **1a** as a model substrate for the study of reaction conditions, and the results are listed in Table 1. Gratifyingly, the C–N dehydrogenative coupling reaction of **1a** took

place in dimethyl sulfoxide (DMSO) with 2.0 equiv of KO*t*-Bu at 90 °C, providing the desired product **2a** in 50% yield (Table 1, entry 1). A number of bases and reaction solvents were then examined. Results showed that NaO*t*-Bu, KOMe, and KOH could also promote the reaction, but lower yields were obtained (entries 2–4). Other bases, such as K_2CO_3, Cs_2CO_3, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and NaH were proved to be inefficient. The effect of KO*t*-Bu loading was also examined. The best yield was obtained when KO*t*-Bu was increased to 3.0 equiv (entry 9). Decreasing the loading amount of KO*t*-Bu to various extent led to a remarkable loss in yields (entries 6–8).

Table 1. Intramolecular oxidative C–H amination of **1a**.[a]

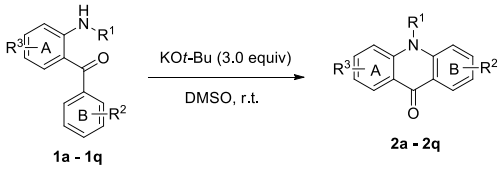


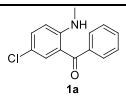
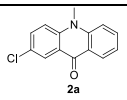
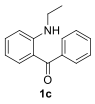
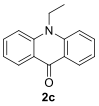
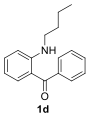
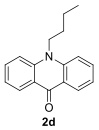
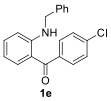
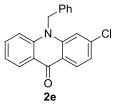
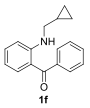
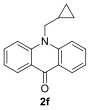
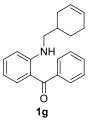
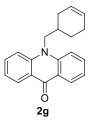
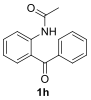
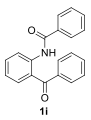
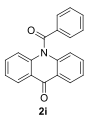
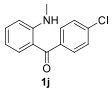
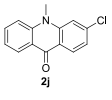
entry	base (equiv)	solvent	time (h)	yield (%)[b]
1	KO*t*-Bu (2.0)	DMSO	6	50
2	NaO*t*-Bu (2.0)	DMSO	6	45
3	KOH (2.0)	DMSO	6	40
4	KOMe (2.0)	DMSO	6	27
5	K_2CO_3 (2.0)	DMSO	10	-
6	KO*t*-Bu (1.5)	DMSO	6	40
7	KO*t*-Bu (1.0)	DMSO	6	37
8	KO*t*-Bu (0.5)	DMSO	6	23
9	KO*t*-Bu (3.0)	DMSO	6	67
10	KO*t*-Bu (3.0)	toluene	6	12
11	KO*t*-Bu (3.0)	DMF	6	63
12	KO*t*-Bu (3.0)	DMA	6	61
13[c]	KO*t*-Bu (3.0)	DMSO	12	75
14[d]	KO*t*-Bu (3.0)	DMSO	12	69
15[e]	KO*t*-Bu (3.0)	DMSO	12	64
16[f]	KO*t*-Bu (3.0)	DMSO	6	-

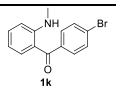
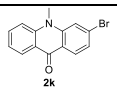
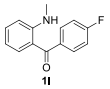
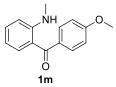
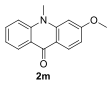
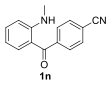
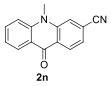
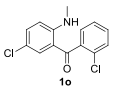
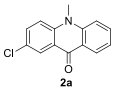
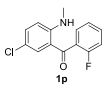
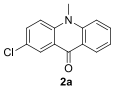
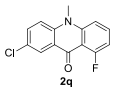
[a] *Reaction conditions*: **1a** (0.1 mmol), base, solvent (1.0 mL), and at 90 °C under air atmosphere.
[b] Isolated yields.
[c] Reaction was carried out at room temperature (r.t.).
[d] Reaction was carried out at 60 °C.
[e] Reaction was carried out at 120 °C.
[f] Reaction was carried out under nitrogen atmosphere.

The reaction solvents were also investigated. *N*,*N*-dimethylacetamide (DMA), *N*,*N*-dimethylformamide (DMF), and toluene were applicable. Good yield was obtained in DMSO (entries 11–12), but poor yield was observed in toluene (entry 10). Other solvents, such as dioxane, $ClCH_2CH_2Cl$, CH_3CN, THF, dimethoxyethane, and glycol were unsuccessful in this reaction with no desired product obtained (see Table S1, entries 9-14). The influence of reaction temperature was explored. Similar yields were obtained at 60 °C and 120 °C (entries 14 and 15, respectively), whereas good yield was obtained at room temperature by extending the reaction time to 12 h (entry 13).

Table 2. Intramolecular C–H amination of **1a**–**1q**.[a,b]



entry	substrate	product	yield (%)[b]
1			75
2			78
3			73
4			70
5			70
6			77
7			75
8			88
9			-
10			75

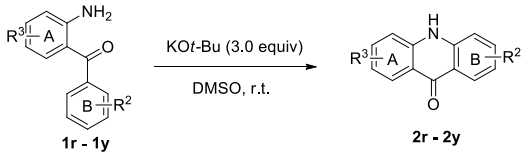
11			84
12			73
13			75
14			64
15			88
16			90
17			84

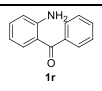
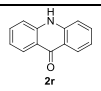
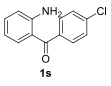
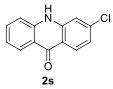
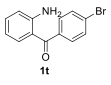
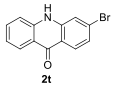
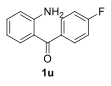
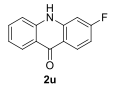
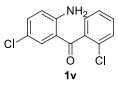
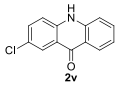
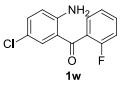
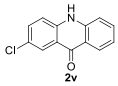
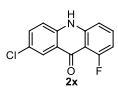
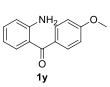
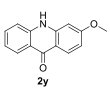
[a] *Reaction conditions*: **1a-1q** (0.2 mmol), KO*t*-Bu (0.6 mmol), DMSO (2.0 mL), at r.t. under air atmosphere, 12 h. [b] Isolated yields.

With the optimal reaction conditions in hand, various 2-aminobenzophenone derivatives **1a**–**1q** were examined, and the results are summarized in Table 2. Satisfyingly, this intramolecular oxidative C–H amination reaction displayed good functional group tolerance. When the substituent groups of R^1 were methyl, ethyl, *n*-butyl, benzyl, cyclopropylmethyl, or cyclohex-3-en-1-ylmethyl, respectively, the corresponding acridone products were obtained in good yields (Table 2, entries 2–7). It is worth noting that substrate **1h** bearing an acetyl group afforded 4-phenylquinolin-2(1H)-one **2h** in excellent yield under the standard conditions, probably owing to the presence of a more active α-H that resulted in the formation of the intramolecular dehydration product (entry 8). When the *N*-benzoylated **1i** was used as the substrate, no reaction was observed, with complete recovery of the reactant (entry 9). Reactions also did not take place when using *N*-phenyl and *N*-isopropyl substrates (data not shown); these results suggest that the steric hindrance of the *N*-substituted groups might play a role in the annulation process.

Substitutions on the B ring with 4-chloro, 4-bromo, and 4-fluoro groups caused no significant effect on the reaction. Good yields were generally achieved for substrates **1j**–**1l**. 4-Methoxyl and 4-cyano-substituted substrates **1m** and **1n** also efficiently provided the desired products (Table 2, entries 13–14). Surprisingly, results showd that the *o*-chloro- and *o*-fluoro-substituted substrates (**1o**, **1p)** exclusively provided the corresponding dehalogenation product **2a** in 88% and 90% yields, respectively (Table 2, entries 15–16). Similarly, the *o*-difluoro-substituted substrate **1q** also furnished the dehalogenation annulation product **2q** in high yield (Table 2, entry 17).[13]

Table 3. Intramolecular C–H amination of **1r**–**1y**.[a,b]



entry	substrate	product	yield (%)[b]
1			70
2			61
3			64
4			68
5			70
6			77
7			75
8			56

[a] *Reaction conditions*: **1r**–**1y** (0.2 mmol), KO*t*-Bu (0.6 mmol), DMSO (2.0 mL), at r.t. under air atmosphere, 12 h. [b] Isolated yields.

The reaction was further extended to primary aromatic amines. A variety of N–H acridone derivatives were obtained in moderate to good yields. Several functional groups, such as *p*-Cl, *p*-Br, *p*-F, and *p*-OMe on the B rings were accommodated well (Table 3, entries 2–4 and entry 8). In general, electron-deficient substrates were more reactive than electron-rich ones. The substrates of **1v**, **1w,** and **1x**

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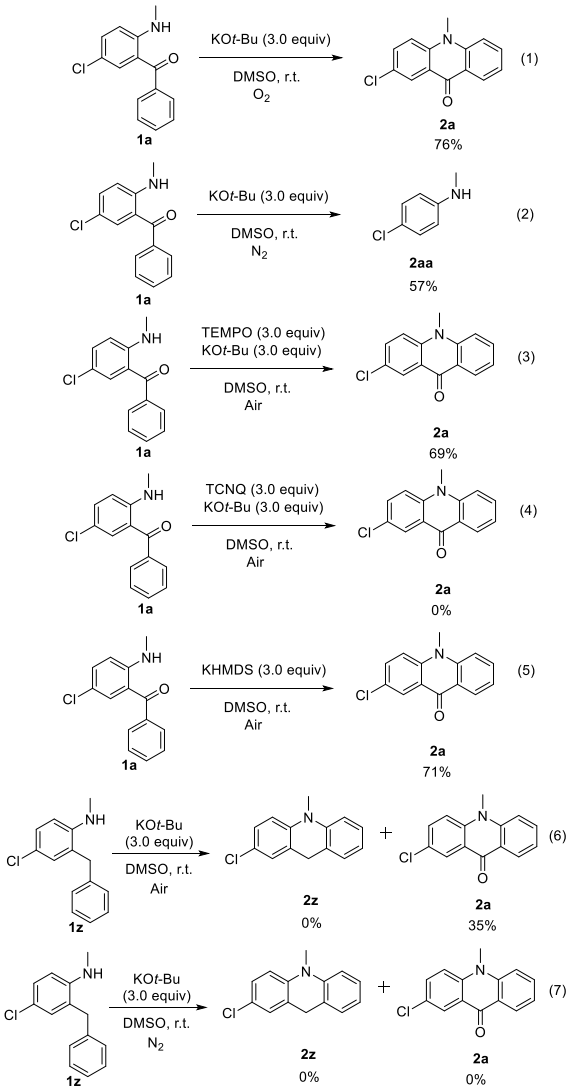
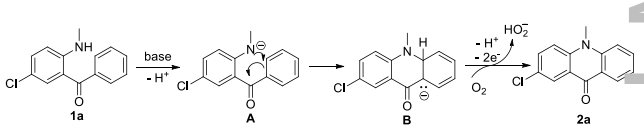
substituted in *ortho*-position with halogen were also converted to acridone derivatives smoothly through the dehalogenation C–H amination.



Scheme 2. Mechanism probing experiments.

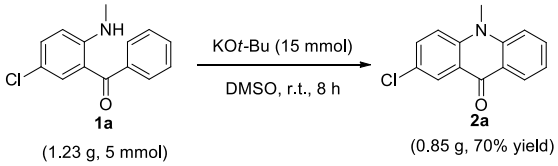
To explore the reaction mechanism, different reaction conditions were examined by using **1a** as the substrate. As expected, the product **2a** was acquired in 76% yield under oxygen atmosphere (Scheme 2, eq. 1). However, 4-chloro-*N*-methylaniline **2aa** was isolated as the single product under nitrogen atmosphere (eq. 2). We envisaged that the DMSO radical could be generated in the reaction system of KO*t*-Bu/DMSO under N_2 atmosphere.[14] The formed DMSO radical abstracted hydrogen from substrate **1a** to generate N-radical intermediate. Then, a radical 1,5-migration and Norrish type I cleavage might occur to give **2aa**. Subsequently, the radical inhibitor 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) was added, and the reaction still proceeded smoothly to afford the desired product **2a** (eq. 3). Other radical scavengers such as 1,1-diphenylethene, 2,6-di-*tert*-butyl-4-methylphenol (BHT) and galvinoxyl were also added, but no notable inhibitory effects were observed, with the desired products obtained in 65%, 61%, and 58% yield, respectively (see Scheme S1, eq. 2-4). When the single electron scavenger 7,7',8,8'-tetracyanoquinodimethane (TCNQ) was added to the mixture, the reaction was completely inhibited with no desired product obtained (eq. 4). These results indicate that a single-electron transfer process rather than a radical transfer one might be involved in this transformation.

The superbase potassium *bis*(trimethylsilyl)amide (KHMDS) was then introduced to explore whether an intramolecular nucleophilic addition took place. Result showed that **1a** could be transformed into **2a** in good yield under these conditions (eq. 5). Also worthy of mention is that when the benzhydryl substrate **1z** was employed under our optimal conditions, no corresponding product (**2z**) was detected. Instead, **2a** was obtained in 35% yield (eq. 6). We surmised that the substrate **1z** would readily generate the diaryl alkyl radical under air conditions to gave **1a** which would further be tranformed into **2a** through intramolecular oxidative C–H amination.[15] In addition, the reaction was also carried out under nitrogen atmosphere with no product was obtained (eq. 7). These experimental results displayed that the air or oxygen atmosphere was essential and electron-withdrawing carbonyl group might be benefical to this intramolecular oxidative C–H amination process.



Scheme 3. Tentative mechanism

On the basis of these control experiments and previous reports,[16] a tentative reaction mechanism is suggested in Scheme 3. The superbase would be generated in the presence of KO*t*-Bu in DMSO. Then, the *N*-anion intermediate **A** is formed through deprotonation of substrate **1a**. The subsequent intramolecular nucleophilic addition would generate the cyclohexadienone anion intermediate **B** which could then be deprotonated and transfer two single electrons to the oxygen, thus affording the intramolecular oxidative C–H amination product **2a**.



Scheme 4. Reaction of **1a** on gram-scale

The reaction of **1a** can also be carried out on gram scale (5 mmol), with the desired product **2a** obtained in 70% yield (Scheme 4).

In summary, we have reported a transition-metal-free method for synthesis of acridones through intramolecular oxidative C–H amination. A series of N–H and *N*-substituted acridone derivatives were acquired in moderate to good yields in the presence of KO*t*-Bu/DMSO.

Experimental Section

General procedure for intramolecular cyclization

A solution of **1a** (49.1 mg, 0.2 mmol), KO*t*-Bu (67.2 mg, 0.6 mmol) in DMSO (2.0 mL) was stirred at room temperature under an air atmosphere for 12 h. After the completion of the reaction as shown by TLC, the crude product was purified by flash chromatography to give **2a** as a yellow solid (36.5 mg, yield: 75%). m.p. 173–174 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.46 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.41 (d, *J* = 2.8 Hz, 1H), 7.69 (t, *J* = 7.8 Hz, 1H), 7.55 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.45 (d, *J* = 8.8 Hz, 1H), 7.38 (d, *J* = 9.2 Hz, 1H), 7.25 (t, *J* = 7.4 Hz, 1H), 3.81 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.92, 142.27, 140.79, 134.11, 133.75, 127.66, 127.15, 126.69, 123.11, 122.22, 121.61, 116.60, 114.87, 33.79. **HRMS** (ESI) calculated for $C_{14}H_{11}NOCl$ $(M+H)^+$: 244.0524, found : 244.0518.

Acknowledgements

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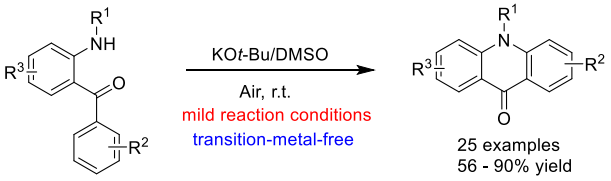
COMMUNICATION

Transition-Metal-Free Synthesis of Acridones via Base-Mediated Intramolecular Oxidative C–H Amination



Adv. Synth. Catal. **Year**, *Volume*, Page – Page

Wen-Tao Wei, Jian-Fei Sheng, Hui Miao, Xiang Luo, Xian-Heng Song, Ming Yan, and Yong Zou*