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Palladium-Catalyzed Regioselective Oxidative Annulation of Cyclohexanones and 2-Aminophenyl Ketones Using Molecular Oxygen as the Sole Oxidant

Wan-Lu Mu,[a] Meirong Wang,[b] Hui-Jing Li,[a]* Deng-Ming Huang,[a] Yi-Yun Zhang,[a] Chao-Yi Li,[a] Ying Liu,[a] and Yan-Chao Wu[a,c]*

[a] School of Marine Science and Technology, Harbin Institute of Technology, Weihai 264209, P. R. China
Phone: (+86) 631-5687230; Fax: (+86) 631-5687230; E-mail: lihuijing@iccas.ac.cn or ycwu@iccas.ac.cn
[b] School of Materials Science and Engineering, Harbin Institute of Technology, Weihai 264209, P. R. China
[c] Beijing National Laboratory for Molecular Sciences (BNLMS), Institute of Chemistry Chinese Academy of Sciences, Beijing 100190, P. R. China

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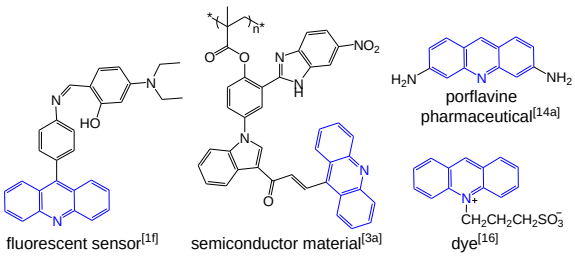
Abstract. A facile oxidative annulation of cyclohexanones and 2-aminophenyl ketones that uses molecular oxygen as the sole oxidant is described. The reaction provides a direct approach to acridines, a structural motif for a large number of fluorescent sensors, functional materials, ligands, and pharmaceuticals. In the presence of a palladium catalyst, high regioselectivity is observed when using non-symmetric 3-substituted cyclohexanones. With the use of oxygen as the terminal redox moderator, the electron gap of the global redox condensation process is filled and the reaction efficiency is significantly promoted. This protocol possesses many advantages such as using non-hazardous oxidant and readily available starting materials, high regioselectivity, and water as the only by-product.

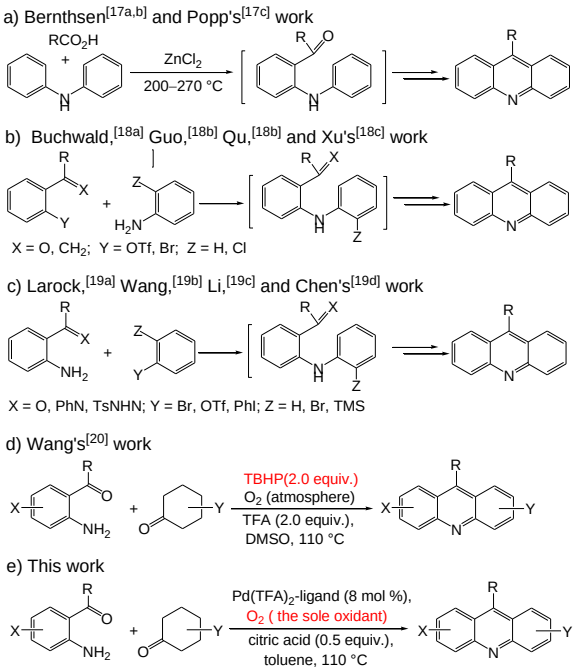
Keywords: Palladium-catalyzed; Aerobic oxidation; Synthesis; Acridines; Regioselective

Acridines have been a subject of consistent interest due to the presence of their structural motifs in a large number of fluorescent sensors,[1] ligands,[2] semiconductor materials,[3] pharmaceuticals, [4–15] and dyes[16] (Scheme 1). Acridines display a broad range of important biological activities, such as antioxidant,[4] antifungal,[5] antibacterial,[6] antiparasitic,[7] antimalarial,[8] antiviral,[9] antiprion,[10] antileukemia,[11] antileukemia,[11] anticancer,[12] and anti-HIV[13] properties. As representative members of bioactive acridines, porflavine, aminacrine, and ethacridine have been already approved by the FDA as antibacterial drugs.[14] Acrisorcin, a new agent for the control of tinea versicolor, has also been approved by the FDA as a drug.[15]

The significance and prevalence of this class of compounds has served to stimulate continual interest in synthetic community.[17–21] Brenthsen acridine synthesis (Scheme 2a),[17] one of the earliest acridine synthetic methods, was achieved in 1878 by heating a diphenylamine and a carboxylic acid together with zinc chloride ($ZnCl_2$) under harsh reaction conditions



Scheme 1. Selected useful acridines.



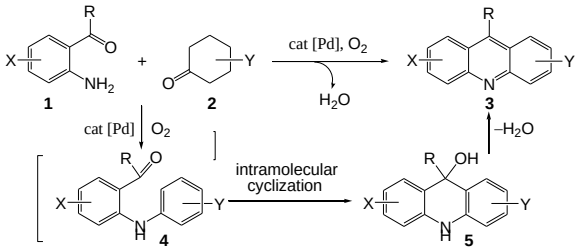
Scheme 2. Acridine synthesis.

(200–270 °C). Since the seminal work reported by Brenthsen, a series of useful methods have been developed for the construction of acridines using various *in situ*-generated diphenylamine derivatives as the substrates (Scheme 2b and Scheme 2c).[18,19] However, these methods often suffer from certain drawbacks such as using two different aromatic substrates as multi-step synthesized starting materials, hazardous by-products and limited substrate scopes.

Recently, Wang and co-workers have developed an elegant synthesis of acridines by treatment of readily available 2-aminophenyl ketones, cyclohexanones, and *tert*-butyl hydroperoxide (TBHP, 2 equiv.) with trifluoroacetic acid (TFA, 2 equiv.) in an oxygen atmosphere (Scheme 2d).[20] It is inspiring except that TBHP is a quite hazardous oxidation agent because of its capability of self-decomposition when being heated or exposed to sunlight.[22a] The hydroperoxy group of TBHP is intrinsically incompatible or unstable with heat, acids, bases, metal ions, and other impurities via the decomposition pathway of free radial or ionic species.[22b] Hazards associated with TBHP include explosion, fire, and toxicity.[22c] The initial exothermic decomposition temperature of TBHP is 69.50 °C under the adiabatic condition.[22a] The TBHP-protic acid, such as *p*-TsOH and aqueous HCl, mixtures undergo exothermic decomposition with an onset temperature as low as 50 °C.[22c] Unsurprisingly, the thermal explosion incidents caused by stored TBHP had ever happened.[22d,e] To circumvent this problem, the *in situ* generation of TBHP or the use of a non-hazardous oxidation agent becomes a high priority.

Compared with other oxidation agents, O_2 is undoubtedly the most appealing oxidant because it is abundant, inexpensive, and non-hazardous. O_2 as an oxidant produces water as the only by-product, which offers attractive industrial prospects in the view point of green and sustainable chemistry. As a consequence, a huge amount of efforts has been dedicated to the oxidation of cyclohexanones with O_2 as an oxidation agent.[23] It is not an exaggeration to declare that using molecular oxygen as the sole oxidant would be a significant breakthrough in acridine synthesis in terms of atom efficiency and product separation. In connection with our consistent interest in the synthesis of functional compounds in agreement with the principles of green chemistry,[24] herein we would like to report a facile synthesis of acridines **3** via a Pd-catalyzed regioselective oxidative annulation of cyclohexanones **2** and 2-aminophenyl ketones **1** by using molecular oxygen as the sole oxidant (Scheme 2e).[25]

The initial synthesis analysis on acridines **3** is shown in Scheme 3. As it is known that the aerobic aromatization of cyclohexanones with anilines to afford diphenylamines,[26] the aerobic aromatization of cyclohexanones **2** with 2-aminophenyl ketones **1** might be possible to generate 2-arylaminophenyl ketones **4**, which, in turn, would undergo dehydrating intramolecular cyclization to afford acridines **3** (Scheme 3). [17–19]



Scheme 3. Initial synthesis analysis on acridines **3**.

The reaction of 2-aminobenzophenone (**1a**) with cyclohexanone (**2a**) was used as a probe for evaluating the reaction conditions, and the representative results are summarized in Table 1. Pd (II) catalysts are highly attractive for applications in catalytic oxidation partly due to their ability to effectively use molecular oxygen as a terminal oxidant and the relatively predictable organometallic reaction manifolds that can be accessed.[27] The treatment of **1a** (1 equiv.), **2a** (1.2 equiv.) in the presence of a catalytic amount of $Pd(OAc)_2$ (5 mol %) in toluene at 110 °C under an atmosphere of air (1 atm) gave 9-phenylacridine (**3a**) in 20% yield within 2 days (Table 1, Entry 1). A series of catalysts were further tested for this reaction, in which $Pd(TFA)_2$ was found to be a relatively effective catalyst (Entries 1–5). Reaction atmosphere played an important role in this transformation. With the use of argon (1 atm) in comparison to air (1 atm), a lower yield was observed (*i.e.*, 18% *versus* 31%, Entries 5 and 6). However, this confirmed the perspectives of further investigations on dehydrogenation conditions. To our delight, the yield of acridine **3a** was increased from 31% to 42% when this reaction was performed under an atmosphere of oxygen (1 atm, Entries 5 and 7). With the use of O_2 as the terminal redox moderator, the electron gap of this reaction is filled and the reaction efficiency is promoted. Further parameter optimization identified the most effective catalyst loading as 8 mol % (Entries 7–9). The choice of ligand was important for this reaction using $Pd(TFA)_2$ as the catalyst (Entries 8 and 10–14). With the addition of 1,10-phenanthroline (5 mol %), 2-dimethylaminopyridine (5 mol %), 2-methylamino-pyridine (5 mol %), and 5-diazafluoren-9-one (5 mol %) to the reaction system, obviously shorter reaction times and relatively lower product yields were observed (Entries 8 and 10–13). In contrast, acridine **3a** was obtained in a higher yield with 2-aminopyridine (5 mol %) was used as the ligand (*i.e.*, 52% *versus* 57%, Entries 8 and 14). The yield of acridine **3a** was further increased to 63% when the loading of 2-aminopyridine was increased from 5 mol % to 8 mol % (Entry 15). No further increase was observed when the loading of 2-aminopyridine exceeded 8 mol %. The choice of additive was also important for this reaction. With the addition of $PhCO_2H$ (0.5 equiv.) to the reaction system under otherwise identical conditions, acridine **3a** was obtained in a relatively lower yield (Entries 15 and

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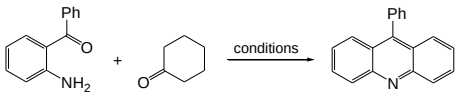
Table 1. Optimization of the reaction conditions [a)]



1a **2a** **3a**

Entry	Catalyst	Ligand	Additive	Yield [b)]
1 [c,d)]	$Pd(OAc)_2$			20%
2 [c,d)]	$Cu(OAc)_2$			12%
3 [c,d)]	$Co(OAc)_2$			trace
4 [c,d)]	Ru/C			15%
5 [c,d)]	$Pd(TFA)_2$			31%
6 [c,e)]	$Pd(TFA)_2$			18%
7 [c)]	$Pd(TFA)_2$			42%
8	$Pd(TFA)_2$			52%
9 [f)]	$Pd(TFA)_2$			49%
10 [g)]	$Pd(TFA)_2$	Ligand I		47 %
11 [g)]	$Pd(TFA)_2$	Ligand II		36%
12 [g)]	$Pd(TFA)_2$	Ligand III		29%
13 [g)]	$Pd(TFA)_2$	Ligand IV		21%
14 [g)]	$Pd(TFA)_2$	Ligand V		57%
15	$Pd(TFA)_2$	Ligand V		63%
16	$Pd(TFA)_2$	Ligand V	$PhCO_2H$	47%
17	$Pd(TFA)_2$	Ligand V	*p*-TsOH	68%
18	$Pd(TFA)_2$	Ligand V	citric acid	83%
19 [h)]	$Pd(TFA)_2$	Ligand V	citric acid	74%
20 [i)]	$Pd(TFA)_2$	Ligand V	citric acid	68%
21 [j)]	$Pd(TFA)_2$	Ligand V	citric acid	76%
22 [k)]	$Pd(TFA)_2$	Ligand V	citric acid	80%
23 [l)]	$Pd(TFA)_2$	Ligand V	citric acid	39%
24 [m)]	$Pd(TFA)_2$	Ligand V	citric acid	43%
25 [n)]	$Pd(TFA)_2$	Ligand V	citric acid	56%
26 [o)]	$Pd(TFA)_2$	Ligand V	citric acid	69%
27 [p)]	$Pd(TFA)_2$	Ligand V	citric acid	82%

[a)] General conditions: **1a** (0.10 mmol), **2a** (0.12 mmol), catalyst (8 mol %), ligand (8 mol %), and additive (0.5 equiv.) in toluene (2.0 mL) at 110 °C under an atmosphere of oxygen (1 atm) for 18 hours. [b)] Isolated yields. [c)] 5 mol % of catalyst. [d)] 1 atm of air. [e)] 1 atm of argon. [f)] 10 mol % of catalyst. [g)] 5 mol % of ligand. [h)] 0.4 equivalent of citric acid. [i)] 0.6 equivalent of citric acid. [j)] 100 °C. [k)] 120 °C. [l)] N,N-dimethylformamide (DMF). [m)] dimethyl sulfoxide (DMSO). [n)] xylene. [o)] N-methyl pyrrolidone (NMP). [p)] Reaction was carried out at 1.98 g scale of **1a** (10.0 mmol). Ligand I = 1,10-phenanthroline. Ligand II = 2-dimethylaminopyridine. Ligand III = 2-methylamino-pyridine. Ligand IV = 4,5-diazafluoren-9-one. Ligand V = 2-aminopyridine. Ac = acetyl. Ph = phenyl. TFA = trifluoroacetic acid. *p*-TsOH = *p*-toluenesulfonic acid.

16). In contrast, a higher yield of acridine **3a** was achieved when *p*-TsOH (0.5 equiv.) was used as the additive (Entries 15 and 17). However, citric acid (0.5 equiv.) was chosen in our next investigations because it led to the best yield (Entries 15–18). Further parameters optimization identified the most effective ligand loading and the most effective reaction temperature as 0.8 equivalent and 110 °C, respectively (Entries 18–22). The solvent did also play an important role in this reaction. With the use of DMF, DMSO, xylene and NMP in comparison to toluene, lower yields were observed (Entries 18 and 23–26). Furthermore, scaling up **1a** to 1.98 g (10.0 mmol) the reaction provided the yield at an excellent level (Table 1, Entries 27).

With the optimized reaction conditions in hand, the scope of the reaction was subsequently investigated, and the representative results are summarized in Table 2. With the 4-position bearing a hydrogen atom (Table 2, Entry 1), an alkyl group (Entries 2–6) and an aryl group (Entry 7), cyclohexanones **2a**–**g** reacted smoothly with 2-aminobenzophenone (**1a**) in the presence of $Pd(TFA)_2$ (8 mol %), 2-aminopyridine (8 mol %) and citric acid (0.5 equiv.) in toluene at 110 °C in an oxygen atmosphere (1 atm) to afford acridines **3a**–**g** in 43–83% yields within 18 hours. With the 4-position bearing a sterically hindered group such as a *tert*-butyl group (Entry 4) and a phenyl group (Entry 5), cyclohexanones **2d** and **2e** reacted with **1a** under the standard conditions to give acridines **3d** and **3e** with decreased yields, indicating that the steric factor of the 4-substituents of cyclohexanones **2** affects the reaction (Entries 1–5). Only one acridine regioisomer was obtained when a non-symmetric 3-substituted cyclohexanone was used (Entries 6 and 7), demonstrating an excellent regioselectivity. 3-Benzylcyclohexanone (**2h**) has also been investigated, which reacted with **1a** under the standard conditions to generate acridine **3h** as the sole regioisomer, in which the concurrent acridine-formation and diarylmethane-oxidation was achieved in a one-pot fashion (Entry 8). With the aromatic rings bearing weak electron-withdrawing groups (Entries 9–19) and an electron-donating group (Entry 20), 2-aminobenzophenones **1b**–**g** reacted smoothly with cyclohexanones **2a**–**b** and **2e**–**f** under the standard conditions to give acridines **3i**–**t** in good yields, irrespective of whether the 4-position of cyclohexanone substrate bearing a sterically hindered group (Entries 9–20). 2-Aminoacetophenone (**1h**) has also been investigated, which reacted uneventfully with cyclohexanones **2a**–**b** and **2e**–**f** under the standard conditions to generate acridines **3u**–**x** in moderate to good yields (Entries 21–24). 2-Aminophenyl ketones **1i**–**j** reacted with **1a** uneventfully under the standard conditions to afford acridines **3y**–**z** in 60% and 46% yields, respectively (Entries 25–26). However, 2-aminophenyl ketone **1k**, with one of its aromatic ring bearing a nitro group, was not a suitable substrate and its reaction with **1a** was complex under the standard conditions (Entry 27). These reactions are extremely easy to perform without the need of using hazardous oxidation agents and water as the only by-product. High regioselectivity was observed when using a non-symmetric 3-substituted cyclohexanone (Entries 6–8, 13, 17 and 24).

The feasibility of the reaction was also checked by using other membered cyclic ketones (**2i**–**k**) and an acyclic ketone (**2l**) to get diversified core structures (Scheme 4). The treatment of cyclopentanone (**2i**)

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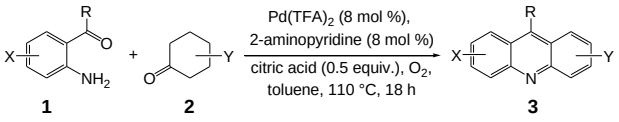
Table 2. Synthesis of acridines **3** via oxidative annulation of cyclohexanones **2** and 2-aminophenyl ketones **1** using molecular oxygen as the sole oxidant [a]



1 **2** **3**

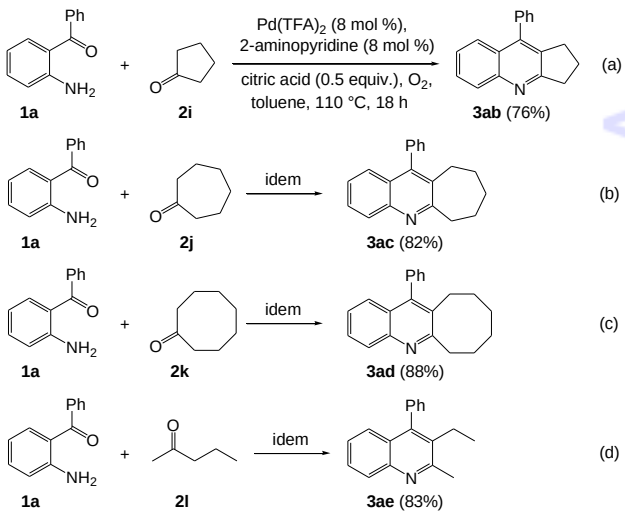
Entry	1	2 (Y)	3 (Y)	Yield [b]
1	**1a**	**2a** (H)	**3a** (H)	83%
2	**1a**	**2b** (4-Me)	**3b** (2-Me)	71%
3	**1a**	**2c** (4-Et)	**3c** (2-Et)	61%
4	**1a**	**2d** (4-*t*-Bu)	**3d** (2-*t*-Bu)	47%
5	**1a**	**2e** (4-Ph)	**3e** (2-Ph)	43%
6	**1a**	**2f** (3-Me)	**3f** (3-Me)	63%
7	**1a**	**2g** (3-Ph)	**3g** (3-Ph)	55%
8	**1a**	**2h** (3-PhCH$_2$)	**3h** (3-PhCO)	38%
9	**1b**	**2a**	**3i**	62%
10	**1c**	**2a** (H)	**3j** (H)	81%
11	**1c**	**2b** (4-Me)	**3k** (2-Me)	71%
12	**1c**	**2e** (4-Ph)	**3l** (2-Ph)	68%
13	**1c**	**2f** (3-Me)	**3m** (3-Me)	74%
14	**1d**	**2a** (H)	**3n** (H)	79%
15	**1d**	**2b** (4-Me)	**3o** (7-Me)	73%
16	**1d**	**2e** (4-Ph)	**3p** (7-Ph)	61%
17	**1d**	**2f** (3-Me)	**3q** (6-Me)	63%
18	**1e**	**2a**	**3r**	69%
19	**1f**	**2a**	**3s**	54%
20	**1g**	**2a**	**3t**	48%

Table 2. (Continued)

Entry	1	2 (Y)	3 (Y)	Yield [b]
21	**1h**	**2a** (H)	**3u** (H)	65%
22	**1h**	**2b** (4-Me)	**3v** (2-Me)	62%
23	**1h**	**2e** (4-Ph)	**3w** (2-Ph)	45%
24	**1h**	**2f** (3-Me)	**3x** (3-Me)	60%
25	**1i**	**2a**	**3y**	60%
26	**1j**	**2a**	**3z**	46%
27	**1k**	**2a**	**3aa**	0

[a] General conditions: **1** (0.10 mmol), **2** (0.12 mmol), Pd(TFA)$_2$ (8 mol %), 2-aminopyridine (8 mol %), and citric acid (0.5 equiv.) in toluene (2.0 mL) at 110 °C in an oxygen atmosphere (1 atm) for 18 hours. [b] Isolated yields. Me = methyl. Et = ethyl. *t*-Bu = *tert*-butyl.

with 2-aminobenzophenone (**1a**) in the presence of Pd(TFA)$_2$ (8 mol %), 2-aminopyridine (8 mol %) and citric acid (0.5 equiv.) in toluene at 110 °C in an oxygen atmosphere afforded quinoline **3ab** in 76% yield within 18 hours (Scheme 4a). As in the case of cyclopentanone (**2i**), the condensation of cycloheptanone (**2j**) and cyclooctanone (**2k**) with 2-aminobenzophenone (**1a**) under the stand conditions gave quinolines **3ac** and **3ad** in 82% and 88% yields, respectively (Scheme 4b and 4c). When non-symmetric acyclic ketone **2l** was subjected to this procedure, quinoline **3ae** was obtained in 83% yield



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Scheme 4. Investigation of the reaction with other ketones.

Scheme 5. Verification experiments.

as a sole regioisomer, demonstrating an excellent regioselectivity (Scheme 4d).

The reaction mechanism of this acridine synthetic method was next studied, and the representative results were illustrated in Scheme 5. By treating 2-aminobenzophenone (**1a**) with cyclohexanone (**2a**) in the presence of 2-aminopyridine (8 mol %) in toluene at 110 °C under an atmosphere of oxygen (1 atm) for 18 hours, no reaction took place and the starting materials were recovered (Scheme 5a). With the use of citric acid (0.5 equiv.) instead of 2-aminopyridine (8 mol %) under otherwise identical conditions, the reaction of **1a** and **2a** afforded 1,2,3,4-tetrahydroacridine **6a**, in 93% yield, as the sole product, and no acridine **3a** (Scheme 5b). As mentioned in Table 1, acridine **3a** could be obtained in 52% yield by treating **1a** and **2a** in the presence of $Pd(TFA)_2$ (8 mol %) in toluene at 110 °C in an atmosphere of oxygen (1 atm) for 2 days (Table 1, Entry 8). Higher yields of acridine **3a** within a shorter reaction time were observed with the addition of 2-aminopyridine (8 mol %) and citric acid (0.5 equiv.) to the reaction system (Table 1, Entries 8, 15 and 18). These results indicated that $Pd(TFA)_2$ is of significance to the formation of acridine **3a**, and 2-aminopyridine and citric acid justly make the reaction more efficient. Subsequently, treatment of 1,2,3,4-tetrahydroacridine **6a** under the standard conditions gave acridine **3a** in 80% yield (Scheme 5c). Without the use of citric acid (0.5 equiv.) under otherwise the standard conditions, dehydrogenation of 1,2,3,4-tetrahydroacridine **6a** went smoothly to generate acridine **3a** in a slightly higher yield (Scheme 5c and Scheme 5d), reflecting the little contribution of citric acid to this Pd-catalyzed dehydrogenation of tetrahydroacridines. Moreover, a higher yield of acridine **3a** was observed with the use of the starting materials of 2-aminophenyl ketone **1a** and cyclohexanone **2a** in comparison to 1,2,3,4-tetrahydroacridine **6a** under the standard conditions (Entry 18 of Table 1 & Scheme 5c). Therefore, except 1,2,3,4-tetrahydroacridine **6a**, there should be some other intermediates in this Pd-catalyzed acridine synthesis from 2-aminophenyl ketone **1a** and cyclohexanone **2a**. Then, we envisaged checking the possibility of diphenylamine formation via aerobic aromatization of cyclohexanones with anilines mentioned in Scheme 3. Indeed, the treatment of aniline **7** and cyclohexanone **2a** in the presence of $Pd(TFA)_2$ (8 mol %), 2-aminopyridine (8 mol %) and citric acid (0.5 equiv.) in toluene at 110 °C in an atmosphere of oxygen (1 atm) afforded diphenylamine **8** in 47% yield within 18 hours (Scheme 5d). This might provide an alternative possible process for the formation of acridine **3a**.

Based on the above results and related reports in the literature,[26] a possible reaction mechanism is illustrated in Scheme 6. The Friedländer annulation of 2-aminophenyl ketones **1** and cyclohexanones **2** in the presence of citric acid affords 1,2,3,4-tetrahydroacridines **6**, which, in turn, undergo an imine-enamine tautomerization under thermal/acidic conditions to form enamine species **7** (Scheme 6).[20] The palladation of the enamine species **7** followed by a β-hydride-elimination will give intermediates **9** and a metal-hydride species (Pd^{II}-H).[26a] The metal-hydride species Pd^{II}-H could be regenerated into the initial catalyst Pd^{II} in the presence of oxygen, [26a] and the intermediates **9** will be converted to acridines **3** in a second catalytic cycle. On the other hand, the

Scheme 6. Proposed mechanism.

dehydrating condensation of 2-aminophenyl ketones **1** and cyclohexanones **2** in the presence of citric acid forms imines **10**, which undergo an imine-enamine tautomerization to generate enamine species **11**.[26a] The palladation of the enamine species **11** followed by β-hydride-elimination forms intermediates **13** and the metal-hydride species Pd^{II}-H.[26a] 2-Arylamino-phenyl ketones **4** will be formed from intermediates **13** in a second catalytic cycle followed by a tautomerization of intermediates **14**.[26a] Finally, the intramolecular Friedel–Crafts acylation of 2-arylaminophenyl ketones **4** followed by an intramolecular dehydration affords acridines **3**.[17–19]

In summary, we have developed a new aerobic oxidative annulation of cyclohexanones and 2-aminophenyl ketones, which provides a facile and direct synthesis of acridines from readily available starting materials. With the use of non-symmetric 3-substituted cyclohexanones as substrates, a high regioselectivity is observed for this Pd-catalyzed acridine synthesis. The use of molecular oxygen as the sole oxidant produces water as the only by-product, which offers attractive industrial prospects in the view point of green and sustainable chemistry. Further mechanistic investigations as well as applications of this method are in progress.

Experimental Section

General procedure for the synthesis of acridines

The mixture of 2-aminobenzophenone (**1a**, 19.72 mg, 0.1 mmol), cyclohexanone (**2a**, 12.4 uL, 0.12 mmol), citric acid (10.5 mg, 0.05 mmol), $Pd(TFA)_2$ (2.65 mg, 8 mol %), and 2-aminopyridine (0.76 mg, 8 mol %) in toluene (2.0 mL) was stirred at 110 °C under the atmosphere of oxygen for 18 hours, then water (5 mL) and ethyl acetate (10 mL) were added. The two layers were separated, and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed by brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (100–200 mesh) to afford 9-phenylacridine (**3a**) in 83% yield. A pale yellow solid; 21.2 mg, m.p. = 186–187 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 8.30 (d, *J* = 8.8 Hz, 2H), 7.80–7.76 (m, 2H), 7.71 (d, *J* = 8.8 Hz, 2H), 7.62–7.59 (m, 3H), 7.46–7.41 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 148.7, 147.4, 135.9, 130.4, 130.0, 129.5, 128.5, 128.4, 126.9, 125.6, 125.2. FTIR (film): ν_{max} = 2923, 2853, 1719, 1703, 1690, 1461, 1388, 1260, 1084, 1041, 997, 759, 558 cm^{-1}. HRMS (ESI) *m/z*: Calcd for $C_{19}H_{13}NNa$ $[M+Na]^+$: 278.0940. Found: 278.0946.

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References

[1] a) Ò. Rubio-Pons, L. Serrano-Andrés, M. Merchán, *J. Phys. Chem. A* **2001**, *105*, 9664; b) P. Yan, A. Xie, M. Wei, L. M. Loew, *J. Org. Chem.* **2008**, *73*, 657; c) R. D. Dsouza, U. Pischel, W. M. Nau, *Chem. Rev.* **2011**, *111*, 7941; d) Y. Wang, X.-Y. Hu, L. Wang, Z.-B. Shang, J.-B. Chao, W.-J. Jin, *Sens. Actuators B* **2011**, *156*, 126; e) D. Zhang, X. Jiang, H. Yang, A. Martinez, M. Feng, Z. Dong, G. Gao, *Org. Biomol. Chem*. **2013**, *11*, 3375; f) X.-J. Jiang, Y. Fu, L.-H. Xu, H.-L. Lu, S.-Q. Zang, M.-S. Tang, T. C. W. Mak, *Sens. Actuators B* **2014**, *202*, 388.

[2] a) E. C. Constable, C. E. Housecroft, M. Neuburger, C. X. Schmitt, *Polyhedron* **2006**, *25*, 1844; b) S. Sparapani, S. M. Haider, F. Doria, M. Gunaratnam, S. Neidle, *J. Am. Chem. Soc.* **2010**, *132*, 12263; c) A. K. Cook, M. H. Emmert, M. S. Sanford, *Org. Lett.* **2013**, *15*, 5428.

[3] a) R. Selvam, K. Subramanian, *J. Polym. Sci. Pol. Chem*. **2017**, *55*, 997; b) Y. Liu, N. Aghdassi, Q. Wang, S. Duhm, Y. Zhou, B. Song, *Org. Electron*. **2016**, *35*, 6.

[4] R. Kalirajan, V. Kulshrestha, S. Sankar, S. Jubie, *Eur. J. Med. Chem*. **2012**, *56*, 217.

[5] N. A. Patel, S. C. Sruthi, R. D. Patel, M. P. Patel, *Phosphorus, Sulfur, Silicon Relat. Elem*. **2008**, *183*, 2191.

[6] a) M. Wainwright, *J. Antimicrob. Chemother*. **2001**, *47*, 1; b) H. P. Kavitha, *Asian J. Chem*. **2004**, *16*, 1191; c) A. R. Benoit, C. Schiaffo, C. E. Salomon, J. R. Goodell, H. Hiasa, D. M. Ferguson, *Bioorg. Med. Chem. Lett*. **2014**, *24*, 3014.

[7] a) P. A. Stocks, P. G. Bray, V. E. Barton, M. A. Helal, M. Jones, N. C. Araujo, P. Gibbons, S. A. Ward, R. H. Hughes, G. A. Biagini, J. Davies, R. Amewu, A. E. Mercer, G. Ellis, P. M. O'Neill, *Angew. Chem. Int. Ed*. **2007**, *46*, 6278; b) C. D. Giorgio, K. Shimi, G. Boyer, F. Delmas, J. P. Galy, *Eur. J. Med. Chem*. **2007**, *42*, 1277; c) C. Fattorusso, G. Campiani, G. Kukreja, M. Persico, S. Butini, M. P. Romano, M. Altarelli, S. Ros, M. Brindisi, L. Savini, E. Novellino, V. Nacci, E. Fattorusso, S. Parapini, N. Basilico, D. Taramelli, V. Yardley, S. Croft, M. Borriello, S. Gemma, *J. Med. Chem*. **2008**, *51*, 1333.

[8] C. Teixeira, N. Vale, B. Perez, A. Gomes, J. R. B. Gomes, P. Gomes, *Chem. Rev*. **2014**, *114*, 11164.

[9] a) I. B. Taraporewala, *Tetrahedron Lett*. **1991**, *32*, 39; b) M. Tonelli, G. Vettoretti, B. Tasso, F. Novelli, V. Boido, F. Sparatore, B. Busonera, A. Ouhtit, P. Farci, S. Blois, G. Giliberti, P. La Colla, *Antiviral Res*. **2011**, *91*, 133.

[10] T. Nguyen, Y. Sakasegawa, K. Dohura, M.-L. Go, *Eur. J. Med. Chem*. **2011**, *46*, 2917.

[11] B. F. Cain, R. N. Seelye, G. J. Atwell, *J. Med. Chem*. **1974**, *17*, 922.

[12] a) N. S. Burres, S. Sazesh, G. P. Gunawardana, J. J. Clement, *Cancer Res*. **1989**, *49*, 5267; b) A. Kumar, N. Kumar, P. Roy, S. M. Sondhi, A. Sharma, *Med. Chem. Res*. **2015**, *24*, 3272.

[13] Y. Lee, S. Hyun, H. J. Kim, J. Yu, *Angew. Chem. Int. Ed*. **2007**, *47*, 134.

[14] a) E. S. DeJong, C. Chang, M. K. Gilson, J. P. Marino, *Biochemistry* **2003**, *42*, 8035; b) E. D. Horowitz, N. V. Hud, *J. Am. Chem. Soc*. **2006**, *128*, 15380; (c) M. Bellinzoni, S. Buroni, F. Schaeffer, G. Riccardi, E. D. Rossi, P. M. Alzari, *J. Bacteriol*. **2009**, *191*, 7531; d) A. Varvaresou, K. Iakovou, *J. Mol. Model*. **2011**, *17*, 2041; e) J. R. Bolla, S. V. Do, F. Long, L. Dai, C.-C. Su, H.-T. Lei, X. Chen, J. E. Gerkey, D. C. Murphy, K. R. Rajashankar, Q. Zhang, E. W. Yu, *Nucleic Acids Res*. **2012**, *40*, 9340; f) Y. Musdal, U. M. Hegazy, Y. Aksoy, B. Mannervik, *Chem. Biol. Interact.* **2013**, *205*, 53; g) M. Wainwright, *J. Antimicrob. Chemother*. **2001**, *47*, 1; h) Q. Mei, X. L. Li, H. J. Liu, H. B. Zhou, *Eur. J. Obstet. Gynecol. Reprod. Biol.* **2014**, *178*, 12; i) R. Kumar, M. Kaur, M. Kumari, *Acta Pol. Pharm.* **2012**, *69*, 3.

[15] a) J. O. Jones, W. F. An, M. I. Diamond, *ACS Chem. Biol*. **2009**, *4*, 199; b) D. Shahinas, M. Liang, A. Datti, D. R. Pillai, *J. Med. Chem*. **2010**, *53*, 3552.

[16] C. D. Geddes, *Dyes Pigm*. **2000**, *45*, 243.

[17] a) A. Bernthsen, *Justus Liebigs Ann. Chem*. **1878**, *192*, 1; b) A. Bernthsen, *Justus Liebigs Ann. Chem*. **1884**, *224*, 1; c) F. D. Popp, *J. Org. Chem*. **1962**, *27*, 2658; d) J. S. Baum, M. E. Condon, D. A. Shook, *J. Org. Chem*. **1987**, *52*, 2983.

[18] a) D. Tsvelikhovsky, S. L. Buchwald, *J. Am. Chem. Soc*. **2010**, *132*, 14048; b) H.-M. Guo, R.-Z. Mao, Q.-T. Wang, H.-Y. Niu, M.-S. Xie, G.-R. Qu, *Org. Lett*. **2013**, *15*, 5460; c) T.-J. Wang, W.-W. Chen, Y. Li, M.-H. Xu, *Org. Biomol. Chem*. **2015**, *13*, 6580.

[19] a) D. C. Rogness, R. C. Larock, *J. Org. Chem*. **2010**, *75*, 2289; b) Z. Huang, Y. Yang, Q. Xiao, Y. Zhang, J. Wang, *Eur. J. Org. Chem.* **2012**, 6586; c) X. Pang, C. Chen, X. Su, M. Li, L. Wen, *Org. Lett*. **2014**, *16*, 6228; d) X. Pang, Z. Lou, M. Li, L. Wen, C. Chen, *Eur. J. Org. Chem*. **2015**, 3361.

[20] G. C. Senadi, G. K. Dhandabani, W.-P. Hu, J.-J. Wang, *Green Chem*. **2016**, *18*, 6241.

[21] a) J. S. Baum, M. E. Condon, D. Shook, *J. Org. Chem*. **1987**, *52*, 2983; b) D. G. Pintori, M. F. Greaney, *Org. Lett*. **2010**, *12*, 168; c) I. Hyodo, M. Tobisu, N. Chatani, *Chem. Commun*. **2012**, *48*, 308; d) X.-D. Han, Y.-L. Zhao, J. Meng, C.-Q. Ren, Q. Liu, *J. Org. Chem*. **2012**, *77*, 5173; e) Y. Lian, J. R. Hummel, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2013**, *135*, 12548; f) Q. Su, P. Li, M. He, Q. Wu, L. Ye, Y. Mu, *Org. Lett*. **2014**, *16*, 18; g) R. Morioka, K. Hirano, T. Satoh, M. Miura, *Chem. Eur. J.* **2014**, *20*, 12720.

[22] a) H. Liu, L. Gu, P. Zhu, Z. Liu, B. Zhou, *Proced. Eng*. **2012**, *45*, 574; b) Y.-S. Duh, H.-Y. Kuo, C.-S. Kao, *J. Therm. Anal. Calorim*. **2017**, *127*, 1047; c) Y.-S. Duh, X. H. Wu, C.-S. Kao, *Process Saf. Prog*. **2008**, *27*, 89; d) T.-C. Ho, Y.-S. Duh, *Process Saf. Prog*. **1998**, *17*, 259; e) J.-M. Hsu, M.-S. Su, C.-Y. Huang, Y.-S. Duh, *J. Hazard Mater*. **2012**, *217–218*, 19.

[23] a) Y. Izawa, D. Pun, S. S. Stahl, *Science* **2011**, *333*, 209; b) T. Diao, S. S. Stahl, *J. Am. Chem. Soc.* **2011**, *133*, 14566; c) M.-O. Simon, S. A. Girard, C.-J. Li, *Angew. Chem. Int. Ed*. **2011**, *51*, 7537; d) D. Pun, T. Diao, S. S. Stahl, *J. Am. Chem. Soc.* **2013**, *135*, 8213; e) T. Diao, D. Pun, S. S. Stahl, *J. Am. Chem. Soc.* **2013**, *135*, 8205; f) M. Sutter, N. Sotto, Y. Raoul, E. Métay, M. Lemaire, *Green Chem*. **2013**, *15*, 347; g) M. Sutter, M.-C. Duclos, B. Guicheret, Y. Raoul, E. Métay, *ACS Sustainable Chem. Eng*. **2013**, *1*, 1463; h) X. Cao, Y. Bai, Y. Xie, G.-J. Deng, *J. Mol. Catal. A–Chem.* **2014**, *383–384*, 94; i) K. Taniguchi, X. Jin, K. Yamaguchi, N. Mizuno, *Catal. Sci. Technol*. **2016**, *6*, 3929; j) T. Xue, Z. Lin, C.-Y. Chiu, Y. Li, L. Ruan, G. Wang, Z. Zhao, C. Lee, X. Duan, Y. Huang, *Sci. Adv*. **2017**, *3*, e1600615.

[24] a) H.-J. Li, C.-C. Wang, S. Zhu, C.-Y. Dai, Y.-C. Wu, *Adv. Synth. Catal.* **2015**, *357*, 583; b) Q. Wang, M. Wang, H.-J. Li, S. Zhu, Y. Liu, Y.-C. Wu, *Synthesis* **2016**, *48*, 3985.

[25] For a recent acridine synthesis from cyclohexanones and 2-aminophenyl ketones through a palladium-catalyzed condensation/cyclization/tautomerization sequence at 160 °C, see: X. Chen, Y. Xie, C. Li, F. Xiao, G.-J. Deng, *Eur. J. Org. Chem*. **2017**, 577.

[26] a) S. A. Girard, X. Hu, T. Knauber, F. Zhou, M.-O. Simon, G.-J. Deng, C.-J. Li, *Org. Lett.* **2012**, *14*, 5606; b) A. Hajra, Y. Wei, N. Yoshikai, *Org. Lett.* **2012**, *14*, 5488; c) K. Taniguchi, X. Jin, K. Yamaguchi, K. Nozaki, N. Mizuno, *Chem. Sci.* **2017**, *8*, 2131.

[27] a) K. M. Gligorich, M. S. Sigman, *Chem. Commun*. **2009**, 3854; b) A. C. Bueno, A. O. de Souza, E. V. Gusevskaya, *Adv. Synth. Catal*. **2009**, *351*, 2491; c) J.-L. Wang, L.-N. He, C.-X. Miao, Y.-N. Li, *Green Chem*. **2009**, *11*, 1317; d) G. Zhang, H. Yu, G. Qin, H. Huang, *Chem. Commun*. **2014**, *50*, 4331; e) Y.-F. Wang, Y.-R. Gao, S. Mao, Y.-L. Zhang, D.-D. Guo, Z.-L. Yan, S.-H. Guo, Y.-Q. Wang, *Org. Lett.* **2014**, *16*, 1610; f) S. Nakai, M. Matsui, Y. Shimizu, Y. Adachi, Y. Obora, *J. Org. Chem.* **2015**, *80*, 7317; g) Y.-C. Chen, M.-K. Zhu, T.-P. Loh, *Org. Lett.* **2015**, *17*, 2712; h) Q. Huang, X. Zhang, L. Qiu, J. Wu, H. Xiao, X. Zhang, S. Lin, *Adv. Synth. Catal*. **2015**, *357*, 3753.

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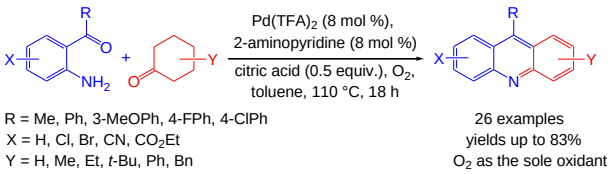
UPDATE

Palladium-Catalyzed Regioselective Oxidative Annulation of Cyclohexanones and 2-Aminophenyl Ketones Using Molecular Oxygen as the Sole Oxidant

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

Wan-Lu Mu, Meirong Wang, Hui-Jing Li,* Deng-Ming Huang, Yi-Yun Zhang, Chao-Yi Li, Ying Liu and Yan-Chao Wu*



R = Me, Ph, 3-MeOPh, 4-FPh, 4-ClPh
X = H, Cl, Br, CN, CO_2Et
Y = H, Me, Et, *t*-Bu, Ph, Bn

26 examples
yields up to 83%
O_2 as the sole oxidant