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Synthesis of acridones through palladium-catalyzed carbonylative of 2-Bromo-diarylamines

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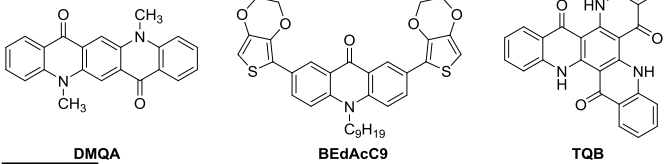
ABSTRACT

A facile protocol for the synthesis of acridone derivatives has been developed through palladium-catalyzed carbonylation/C-H activation sequence from 2-bromo-diarylamines in moderate to excellent yields. The reactions occurred smoothly and allowed both electron-rich and electron-deficient substrates converted to the corresponding acridones.

1. Introduction

Acridone, a type of distinguished Nitrogen-containing heterocycle, is omnipresent structural motif that exists in a wide range of natural products,[1-4] biologically or pharmacologically active compounds[5-9] and organic optoelectronics materials.[10,11] Especially, with the development of organic semi-conductive materials during the last four decades, research on acridone-based organic photoelectric materials has attracted more and more attention.[12-16] For example, **DMQA** was found to be a high performance green-sensitive organic photodiode.[17] **BEdAcC9** was reported as an OLED emitter material by Data and co-workers.[18] **TQB** was proved to be a good thermally activated delayed fluorescence (TADF) material (Scheme 1).[19]

Scheme 1. Representative examples of molecular material containing acridone.



As a consequence, synthetic methods leading to the costruction of this scaffold have been continuously refined in recent decades (Scheme 2). Of these synthetic procedures, closing central six-membered ring is the key step in most employed strategies. As shown in Scheme 2, according to different cyclization approach, the synthetic routes to obtain acridone can be classified into three types: (1) C-N coupling (scheme 2, **a**);[20-22] (2) acid-promoted cyclization (Scheme 2, **b**);[23-25] (3) CO insertion (Scheme 2, **c**).[26, 27] In general, classical routes for acridone synthesis are path **a** (scheme 2) and **b** (scheme 2) . However, CO insertion is an more attractive transformation as it involves the insertion of CO as the cheapest C1 source and meets the requirements of "atom economy", step economy and "green chemistry". Palladium-catalyzed carbonylation reaction is widely recognized as a very important tool in industrial and organic chemistry. In 2015, Jiang firstly described a novel approach to acridones by CO insertion using arynes generated from silylaryl triflate precursors.[27] Greaney,[29] Larock[28, 30,31] also reported their related work in the following years. Recently, Lei's group Reported a palladium/copper co-catalyzed oxidative cardonylation of diphenylamines for the construction of acridones. In this transformation, the oxidant was necessary .[26] Herein, we report our newly developed simple approach for the

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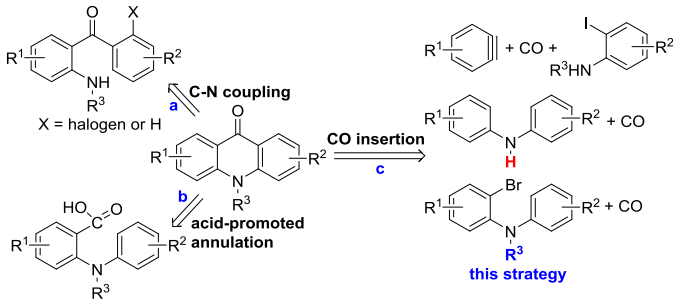
synthesis of acridone by palladium-catalyzed carbonylative C-H arylation under alkaline condition.

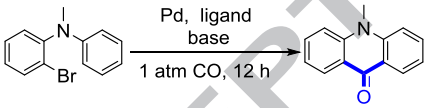
Scheme 2. Approaches towards the synthesis of acridone derivatives



2. Result and discussion

Initially, 2-bromo-N-methyl-N-phenylaniline **1a** was selected as the model substrate for optimization in our initial investigation. As shown in table 1, among the ligands examined, the use of $PCy_3{\cdot}HBF_4$ resulted in the highest yield (49%) of **2a** (Table 1, entry 1), other ligands such as PPh_3 gave the desired product in lower yield (12%) (Table 1, entry 2) and no conversion was observed for $P(t\text{-}Bu)_3{\cdot}HBF_4$ (Table 1, entry 3) or Xantphos (Table 1, entry 4). Then, several solvents were screened. The use of DMF afforded **2a** in comparable yield (48%) (Table1, entry 5). However, if changing the reaction medium to DMA, 1,4-dioxane or NMP, no desired product was obtained (Table 1, entries 6-8). Decreasing the reaction temperature resulted in lower efficiency in terms of chemical yield (Table1, entry 9) and the yield of **2a** was increased to 59% at 120 ℃ (Table1, entry 10), but a further increasing of temperature was adverse to the reaction (Table1, entry 11). No better result was found from changing the Pd source (Table 1, entry 12-13) and base (Tbale1 entry 14-17). Delightfully, in 2 mL DMF, a 72% isolated yield of 2a was obtained (Table 1, entry 12) which was higher than that in 1 mL DMF. Furthermore, if stirring the PdCl2, ligand and CsOPiv in 2 mL DMF at 120 ℃ in advance for 30 minutes before 1a was added to the system, a slight higher yield (78%) could be obtained (Table 1, entry 13). Notably, no desired product was observed for 2-bromo-N-phenylaniline (Table 1, entry 14). The optimum reaction conditions thus far being developed: 1.0 equiv. of 2-bromo-N-methyl-N-phenylaniline (**1a**) (0.2 mmol) was added to the reaction system after 5 mol% of $PdCl_2$, 10 mol% $PCy_3{\cdot}HBF_4$ and 3.0 equiv. of CsOPiv were stirred in 2 mL DMF at 120 °C for 30 minutes. The mixture was then allowed to stir at 120 ℃ for 12 hours before quenched. This procedure provided acridone **2a** in 78% of isolated yield.

Table 1. Condition Optimization of the Palladium-Catalyzed carbonylation of 2-Bromo-diarylamines for the Synthesis of Acridines [a]



1a **2a**

entry	Pd	ligand	base	solvent	temprature (℃)	yield (%)
1	$PdCl_2$	$PCy_3{\cdot}HBF_4$	CsOPiv	toluene	110	49
2	$PdCl_2$	PPh_3	CsOPiv	toluene	110	12
3	$PdCl_2$	$P(t\text{-}Bu)_3{\cdot}HBF_4$	CsOPiv	toluene	110	n.d.
4	$PdCl_2$	Xantphos	CsOPiv	toluene	110	n.d.
5	$PdCl_2$	$PCy_3{\cdot}HBF_4$	CsOPiv	DMF	110	48
6	$PdCl_2$	$PCy_3{\cdot}HBF_4$	CsOPiv	DMA	110	36
7	$PdCl_2$	$PCy_3{\cdot}HBF_4$	CsOPiv	1,4-dioxane	110	29
8	$PdCl_2$	$PCy_3{\cdot}HBF_4$	CsOPiv	NMP	110	26
9	$PdCl_2$	$PCy_3{\cdot}HBF_4$	CsOPiv	DMF	90	n.d.
10	$PdCl_2$	$PCy_3{\cdot}HBF_4$	CsOPiv	DMF	120	59
11	$PdCl_2$	$PCy_3{\cdot}HBF_4$	CsOPiv	DMF	130	34
12	$Pd(OAc)_2$	$PCy_3{\cdot}HBF_4$	CsOPiv	DMF	120	49
13	$Pd_2(dba)_3$	$PCy_3{\cdot}HBF_4$	CsOPiv	DMF	120	30
14	$PdCl_2$	$PCy_3{\cdot}HBF_4$	K_2CO_3	DMF	120	7
15	$PdCl_2$	$PCy_3{\cdot}HBF_4$	Na_2CO_3	DMF	120	5
16	$PdCl_2$	$PCy_3{\cdot}HBF_4$	KOAc	DMF	120	25
17	$PdCl_2$	$PCy_3{\cdot}HBF_4$	K_3PO_4	DMF	120	8
18[b]	$PdCl_2$	$PCy_3{\cdot}HBF_4$	CsOPiv	DMF	120	72
19[b,c]	$PdCl_2$	$PCy_3{\cdot}HBF_4$	CsOPiv	DMF	120	78
20[b,c,d]	$PdCl_2$	$PCy_3{\cdot}HBF_4$	CsOPiv	DMF	120	n.d.

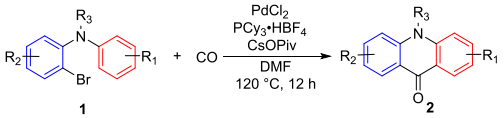
[a] Reaction conditions: **1a** (0.2 mmol), Pd (5 mol %), ligand (10 mol %), base (3.0 equiv.), solvent (1 mL), CO (1 atm), 12h. Isolated yields. [b] DMF (2 mL) was added. [c] The mixture was stirred for 30 minutes at 120 ℃ before **1a** was added. [d] 2-bromo-*N*-methyl-*N*-phenylaniline was replaced by 2-bromo-*N*-phenylaniline.

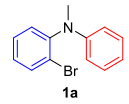
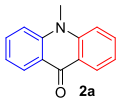
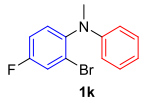
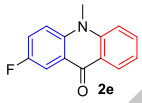
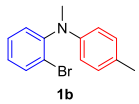
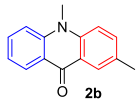
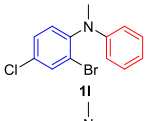
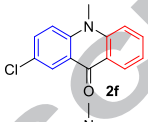
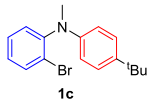
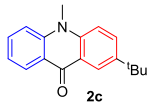
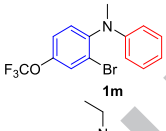
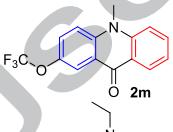
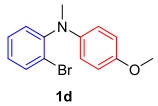
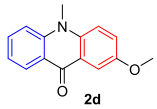
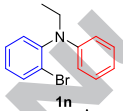
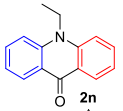
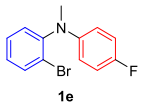
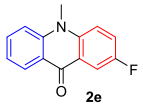
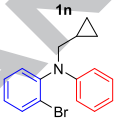
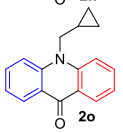
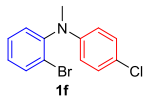
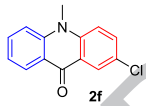
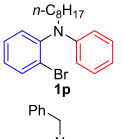
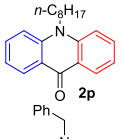
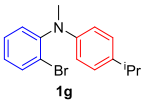
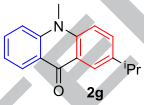
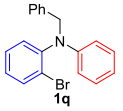
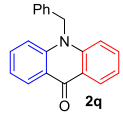
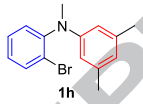
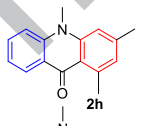
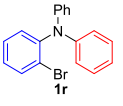
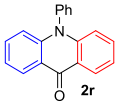
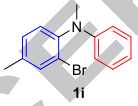
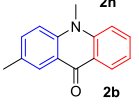
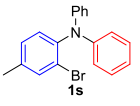
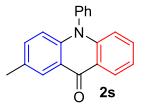
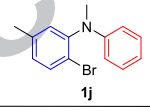
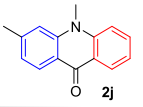
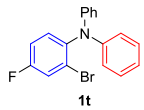
With the optimized conditions established, the substrate scope of this palladium-catalyzed carbonylation/C-H activation tandem reaction was evaluated. The results were summarized in Table 2. Most of employed substrates were well tolerated and proceeded smoothly to afford their corresponding products in moderate to excellent yields. In detail, for 2-bromo-N-(4-substituted-phenyl)-N-methylaniline (Table 2, entries 2-7), substrates bearing electron-donating groups such as $-CH_3$ (Table 2, entry 2), $-CH(CH_3)_2$ (Table 2, entry 7), $-C(CH_3)_3$ (Table 2, entry 3) or electron-withdrawing groups such as –F (Table 2, entry 5) and –Cl (Table 2, entry 6) were proceeded smoothly to afford their corresponding products in good yields. However, the strong electron donating substituent of $-OCH_3$ gave the product **2d** (Table 2, entry 4) in lower yield of 37% and the yield was improved to 75% when the reaction time was extended to 60 hours. Moreover, the sterically hindered N-(2-bromophenyl)-N,3,5-trimethylaniline (**1h**) also underwent a smooth reaction to afford the desired product in good yield of 70% (Table 2, entry 8). Successively, 2-bromo-4-substituted-N-methyl-N-phenylaniline (Table 2, entries 9, 11-13) were examined under the optimized conditions. Differing from 2-bromo-N-(4-substituted-phenyl)-N-methylanilines, the electronic effects of the substituents played a great influence on the yield of corresponding product. The electron-rich substrates (**1i**) obviously worked better than electron-deficient substrates (**1k, 1l, 1m**), and 2-bromo-N,5-dimethyl-N-phenylaniline (**1j**) gave better result than 2-bromo-N,4-dimethyl-N-phenylaniline (**1i**). Moreover, interestingly, 4,N-dimethyl-2-bromoanilin (**1i**) afforded a slightly higher yield than 2-bromo-N-methyl-N-(p-tolyl)aniline (**1b**), while 2-bromo-4-fluoro-N-methyl-N-phenylaniline (**1k**) and 2-bromo-4-chloro-N-methyl-N-phenylaniline (**1l**) produced **2e** and **2f** in the yields of 37% and 29% respectively which were dramatically lower than that of 2-bromo-N-(4-fluorophenyl)-N-methylaniline (**1e**) or 2-bromo-N-(4-chlorophenyl)-N-methylaniline (**1f**). In addition, to further evaluate the scope of the reaction, $N\text{-}CH_3$ was changed to $N\text{-}C_2H_5$, N-Bn, N-Ph and so on (Table 2, entries 14-20). All compounds were reacted smoothly and transformed to the corresponding products (**2n-2t**) in moderate to good yield. Among them, the long-chain-alkyl substrate (**1p**) gave the product **2p** in the lowest yield of 45%. For 2-bromo-4-substituted-N,N-diphenylaniline (**1s**, **1t**), it was also found that the 2-bromo-4-methyl-N,N-diphenylaniline (**1s**) afforded the product **2s** in higher yield than 2-bromo-4-fluoro-N,N-diphenylaniline (**1t**). This was in accordance with the previous studies for 2-bromo-4-substituted-N-methyl-N-phenylaniline which showing that the electron-rich substrates worked better than electron-deficient substrates.

As shown in Scheme 3, the mechanism for this tranformation was postulated based on the earlier reports on palladium catalyzed carbonylation reaction.[32-35] Initially, as the precursors of Pd(0) complex, $PdCl_2$ was readily reduced to Pd(0) by

reducing agents such as CO, phosphines ligand or DMF. Then, oxidative addition of substrate **1** to Pd(0) to afford the arylpalladium species **A**, which followed by insertion of the the coordinated CO into the C−Pd bond to produce the acylpalladium intermediate **B**. In the presence of base, a intramolecular cyclization via C-H activation occurred for intermediate **B** to convert into intermediate **C**. At last, reductive elimination of intermediate **C** afforded the product **2** with simultaneous regeneration of the Pd(0) catalyst.

Table 2. Palladium-catalyzed carbonylation of 2-bromo-diphenylamines: scope and limitation[a]



Entry	Substrate	Product	Yield(%)	Entry	Substrate	Product	Yield(%)
1	 1a	 2a	78%	11	 1k	 2e	37%
2	 1b	 2b	57%	12	 1l	 2f	29%
3	 1c	 2c	81%	13	 1m	 2m	38%
4	 1d	 2d	37% 75%[b]	14	 1n	 2n	55%
5	 1e	 2e	54%	15	 1o	 2o	74%
6	 1f	 2f	73%	16	 1p	 2p	45%
7	 1g	 2g	73%	17	 1q	 2q	53%
8	 1h	 2h	70%	18	 1r	 2r	66%
9	 1i	 2b	64%	19	 1s	 2s	89%
10	 1j	 2j	79%	20	 1t	2t	59%

[a] Reaction conditions: 1.0 equiv. of **1a** (0.2 mmol) was added to the reaction system after 5 mol% of $PdCl_2$, 10 mol% PCy_3·HBF_4 and 3.0 equiv. of CsOPiv were stirred in 2 mL DMF at 120 °C for 30 minutes and then, the mixture was allowed to stir at 120 °C for 12 hours before quenched. Isolated yield. [b] The reaction time was extended to 60 hours.

Scheme 3. The proposed reaction mechanism

3. Conclusion

In summary, a facile protocol for the synthesis of acridone derivatives has been developed through palladium-catalyzed carbonylation/C-H activation sequence using 2-bromo-diphenylamines as substrates. The reactions occurred smoothly and allowed both electron-rich and electron-deficient substrates converted to the corresponding acridones in moderate to excellent yields. This reaction afforded an alternative approach for the synthesis of acridones.

Acknowledgments

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Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

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Graphical Abstract

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Synthesis of Acridones through Palladium-catalyzed Carbonylative of 2-Bromo-diarylamines

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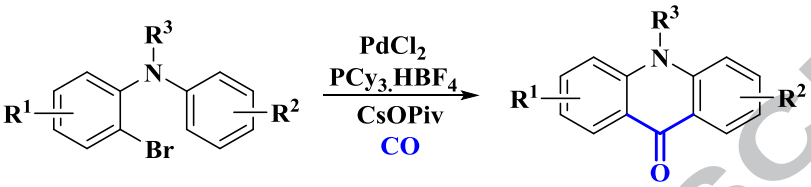
Juan Song[a,*], Keran Ding[a], Wei Sun[b], Songjiang Wang[a], Haisen Sun[a], Kang Xiao[a], Yan Qian[a] and Chao Liu[b,*]



Highlights

- Simple and efficient protocol for the synthesis of acridone derivatives.
- Reaction proceeds via palladium-catalyzed carbonylation of 2-bromo-diarylamines
- Reaction feature broad substrate scope and good functional group tolerance.