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ARTICLE TYPE

# Carbonannulation of *ortho*-Vinylanilines with Dimethyl Sulfoxide to Access 4-Aryl Quinolines

**Jin Yuan, Jin-Tao Yu, Yan Jiang and Jiang Cheng***

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**A palladium-catalyzed annulation of *ortho*-vinylanilines with dimethyl sulfoxide was developed to access 4-aryl quinolines in moderate to good yields. Activated by 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct (DABSO), DMSO served as a "=CH-" fragment in this transformation. It represents a facile pathway leading to 4-aryl quinolines.**

Dimethyl sulfoxide (DMSO) was well known as aprotic polar solvent[1] and oxidant in organic reactions, such as Swern oxidation,[2] Kornblum oxidation,[3] Pfitzner-Moffatt oxidation[2a,4] and Corey-Chaykovsky reaction.[5] The typical employment of DMSO as building block in organic synthesis[6] was Pummerer reaction, where the fragment of "-$CH_2SMe$" was incorporated into the final product.[7] With the development of organometallic chemistry, DMSO was widely employed in many synthetic routes after proper activations, including DMSO-based methylation,[8] methylenation,[9] formylation,[10] cyanation,[11] thiomethylation,[12] and methylsulfonylation.[13] Besides, DMSO could also provide "=CH-" fragment in sequential annulation/aromatization reaction, allowing rapid access to hetero- aromatic compounds. For example, recently, Yuan reported the preparation of pyridine via the four component cyclization of two methyl ketones, DMSO and ammonium (Scheme 1, eq. 1). [14] Zhang described the copper-catalyzed annulation of amidine and DMSO toward quinazolines (Scheme 1, eq. 2).[15] Very recently, Ma developed the annulation of 2-aminobenzophenone, aqueous ammonium and DMSO leading to quinazoline.[16] Undoubtedly, the application of DMSO as a synthon in organic synthesis greatly depends on the development of new way to activate DMSO.

Quinoline skeleton is among the most prevalent heterocycles found in biologically active molecules.[17] In the light of its importance, its preparation has attracted much attention over the past few years. Classic synthetic methods include the base-catalyzed Friedlaender reaction and acid-catalyzed Knorr reaction.[18] Recently, approaches catalyzed by transition metals have been proved to be effective for quinolinone synthesis.[19] Herein, we wish to report a palladium-catalyzed annulation of *ortho*-vinylanilines with DMSO which serves as a "=CH-" fragment leading to 4-aryl quinolones (Scheme 1, eq. 3).

**Scheme 1**. DMSO as "=CH-" fragment in the constuction of heterocycle

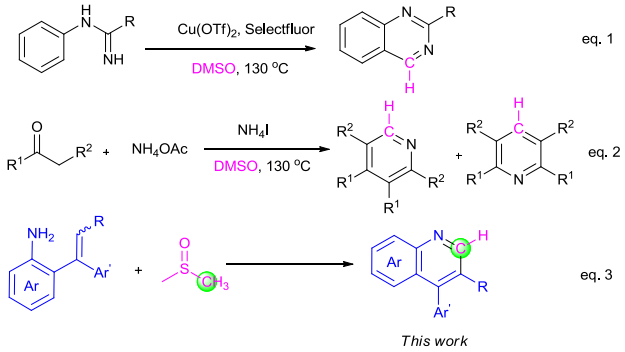


**Table 1.** Screening the optimized reaction conditions[a]


| Entry | Catalyst | Additive (equiv) | Yield(%) |
|---|---|---|---|
| 1 | $Pd(dba)_2$ | DABCO·HCl (0.5) | 8 |
| 2 | $Pd(dba)_2$ | DABCO·HOAc (0.5) | < 5 |
| 3 | $Pd(dba)_2$ | DABCO·$H_2SO_4$ (0.5) | 53 |
| 4 | $Pd(dba)_2$ | DABCO $CH_3I$ (0.5) | < 5 |
| 5 | $Pd(dba)_2$ | DABCO $C_3H_5Br$ (0.5) | < 5 |
| 6 | $Pd(dba)_2$ | DABCO (0.5) | < 5 |
| 7 | $Pd(dba)_2$ | DABSO (0.5) | 80, 14[b], 57[c] |
| 8 | $Pd_2(dba)_3$ | DABSO (0.5) | 61 |
| 9 | $Pd(PPh_3)_4$ | DABSO (0.5) | 67 |
| 10 | $Pd(OAc)_2$ | DABSO (0.5) | 70 |
| 11 | $PdCl_2$ | DABSO (0.5) | 58 |
| 12 | $Pd(CF_3COO)_2$ | DABSO (0.5) | 65 |
| 13 | $Pd(acac)_2$ | DABSO (0.5) | 72 |
| 14 | $Pd(PPh_3)_2Cl_2$ | DABSO (0.5) | 62 |
| 15 | $Pd(dba)_2$ | DABSO (0.2) | 60 |
| 16 | $Pd(dba)_2$ | DABSO (1.0) | 69 |
| 17 | -- | DABSO (0.5) | 24 |

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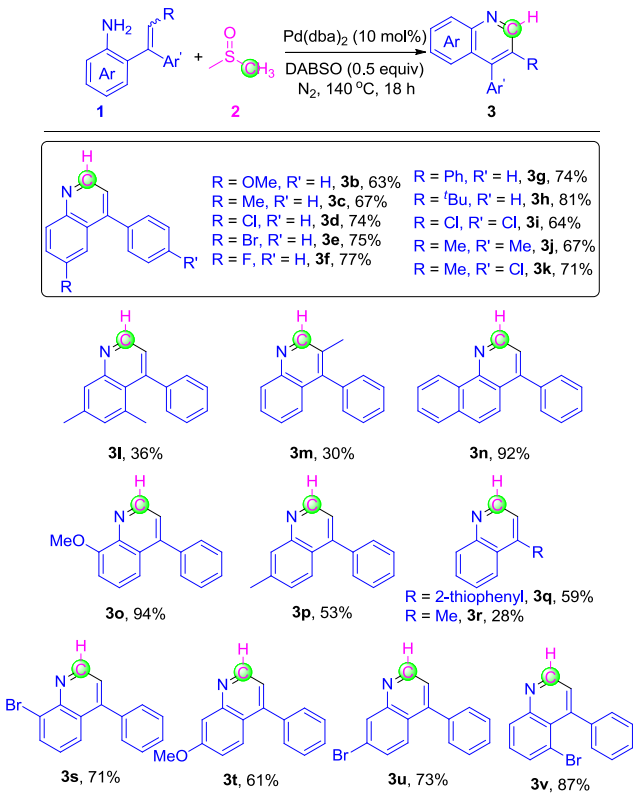
| | | | |
|---|---|---|---|
| 18 | $Pd(dba)_2$ | -- | 0 |
| 19 | $Pd(dba)_2$ | DABSO (0.5) | 21[d], 74[e], 60[f] |

[a] Reaction conditions: 2-(1-phenylvinyl)aniline **1a** (0.1 mmol), Pd (10 mol%), additive (0.5 equiv), in DMSO (2 mL), under $N_2$, 140 °C, 18 h, in sealed tube. [b] Under $O_2$. [c] Under air. [d] 130 °C. [e] 150 °C. [f] 12 h.

Initially, we tested the reaction of 2-(1-phenylvinyl)aniline **1a** in DMSO under $N_2$ at 140 °C in the presence of $Pd(dba)_2$ (10 mol%) and DABCO·HCl (0.5 equiv, DABCO = 1,4-diazabicyclo[2.2.2]octane, Table 1, entry 1). After 18 h, the desired product 4-phenyl quinoline **3a** was isolated in 8% yield (Table 1, entry 1). Replacing DABCO·HCl with DABCO·HOAc resulted in no reaction (Table 1, entry 2). To our delight, the yield dramatically increased to 53% by using DABCO·$H_2SO_4$ (Table 1, entry 3). Encouraged by this inspiring result, DABCO and its adducts, such as DABCO·$CH_3I$, and DABCO·$C_3H_5Br$ were tested, but all failed to work (Table 1, entries 4-6). However, 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct (DABSO) showed high efficiency with 80% yield (Table 1, entry 7). The reaction efficiency decreased under either $O_2$ (14%) or air (57%). Other palladium catalysts, such as $Pd_2(dba)_3$ (61%), $Pd(PPh_3)_4$ (67%) , $Pd(OAc)_2$ (70%) ,$PdCl_2$ (58%) and $Pd(acac)_2$ (72%) were all inferior to $Pd(dba)_2$ (Table 1, entries 8-14). Changing the loading of DABSO slightly decreased the reaction efficiency (Table 1, entries 15 and 16). Without palladium, the yield dropped to 24% (Table 1, entry 17); while it did not work in the absence of DABSO (Table 1, entry 18). An inferior result was obtained when the temperature was changed to 130 °C or 150 °C. The yield dropped to 60% when the time was shortened to 12 h (Table 1, entry 19).

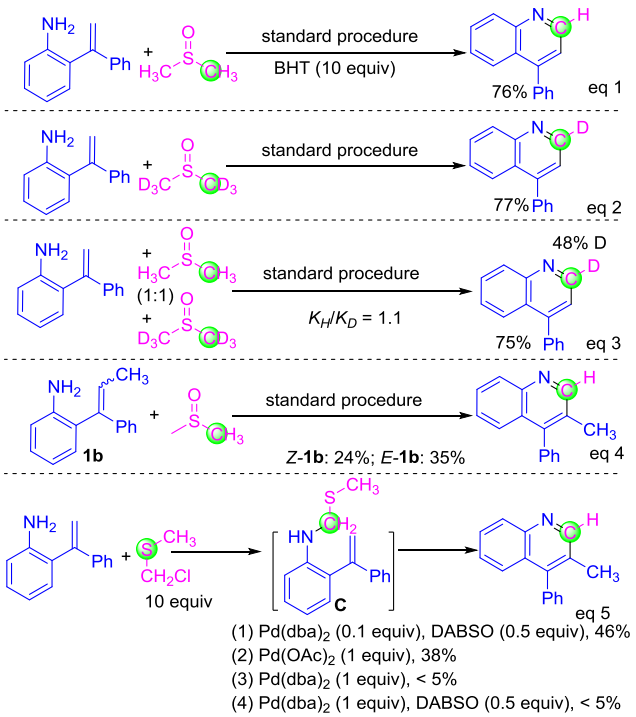
**Scheme 2**. Substrate scope of 2-(1-arylvinyl)anilines.[a]




[a] Reaction conditions: substituted 2-(1-arylvinyl)aniline **1** (0.1 mmol), $Pd(dba)_2$ (10 mol%), DABSO (0.5 equiv), in DMSO (2 mL), under $N_2$, 140 °C, 18 h, sealed tube.

After the establishment of the optimized conditions, this procedure was applied to access a variety of 4-aryl quinoline derivatives. The procedure tolerated methyl, chloro, bromo and fluoro groups, which provided handles for potentially further functionalizations. As expected, 6-substituted-4-aryl quinolines (**3b**-**3k**) were prepared in moderate to good yields (63-81%). Importantly, besides 6-substituted-4-aryl quinolines, this procedure allowed to access n-substituted analogues quickly (n = 3, 5, 7, 8). For example, 5,7-dimethyl-4-phenyl quinoline **3l** (36%), 3-methyl-4-phenyl quinoline **3m** (30%), 8-methoxyl-4-phenyl quinoline **3o** (94%) and 7-methyl-4-phenyl quinoline **3p** (53%) were accessed facilely, respectively. Notably, 4-phenyl-benzo[*h*]quinoline **3n** was isolated in 92% yield. Importantly, this procedure was applicable to access the analogues with 4-hetero-aromatic ring and alkyl, since **3q** and **3r** were isolated in 59% and 28% yields, respectively. Moreover, other 5-, 7-, 8-substituted-4-aryl quinolones (**3s**-**3v**) were obtained in moderate to good yields (61-87%). However, any attempt to access 2-substituted-4-aryl quinoline failed since replacing DMSO with diethyl sulfoxide, and methyl phenyl sulfoxide resulted in no reaction under the standard procedure. The practicability of this transformation was further increased as **3a** was isolated in an acceptable 67% yield in a 2 mmol scale reaction.

**Scheme 3.** Preliminary mechanism studies.




To gain some insights into the reaction mechanism, some control experiments were conducted. First, the reaction could not be shut down even though 10 equivalents of 2,6-di-*tert*-butyl-p-cresol (BHT) was added, indicating no radical pathway was involved (Scheme 3, eq 1). Second, replacing DMSO with DMSO-$D_6$, 2-D-4-phenyl quinoline was isolated in 77% yield,

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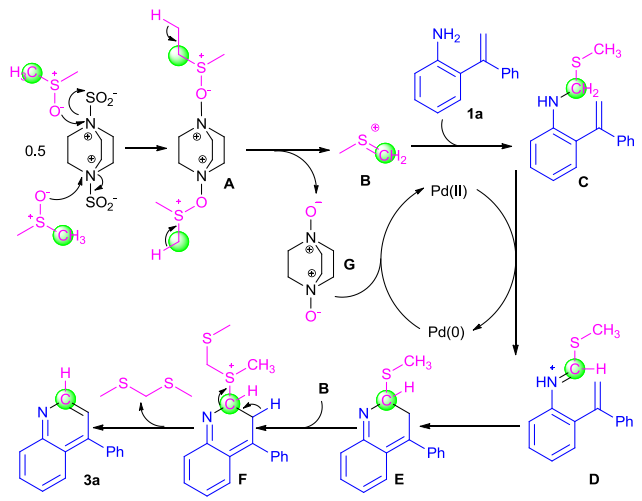
which not only confirmed the participation of DMSO in the annulation reaction, but also provided a facile pathway to access 2-deuterized quinoline derivatives (Scheme 3, eq 2).[20] Third, the intra molecular kinetic isotope effect (KIE, $K_H/K_D$) of the methyl in DMSO was found to be 1.1, indicating the cleavage of C-H bond in DMSO was not the rate determining step (Scheme 3, eq 3). Fourth, both *Z* (24%) and *E* (35%) configuration of **1b** served as reaction partners, which was consistent with the electrocyclic pathway (Scheme 3, eq 4).[21] Finally, the presumed intermediate **C** was not stable enough to be detected by GC-MS and to be isolated for further characterizations. However, after the reaction of 2-(1-phenylvinyl)aniline and chloromethyl methyl sulfide (10 equiv) in DMSO, we found: (1) 4-phenyl quinolone was isolated in 46% yield with the combination of $Pd(dba)_2$ (0.1 equiv) and DABSO (0.5 equiv), indicating the possibility of compound **C** serving as the intermediate; (2) cyclization took place with 38% yield in the presence of stoichiometric of $Pd(OAc)_2$; (3) it did not work in the presence of either $Pd(dba)_2$ (1 equiv) or the combination of $Pd(dba)_2$ (1 equiv) and DABSO (0.5 equiv) (Scheme 3, eq 5). This results revealed Pd(II) may serve as oxidant in the transformation of tertiary amine to other intermediate, which was probably iminium. And it was other species rather than DABSO oxidized Pd(0) to Pd(II).

Based on these experimental results, a proposed mechanism was outlined in Scheme 4. Firstly, the activation of DMSO by DABSO produces intermediate **A**.[22] Then, the deprotonation of intermediate **A** provides a thionium ion intermediate **B**, which encounters the nucleophillic attack by substrate **1a** leading to intermediate **C**. Meanwhile, Pd(0) is oxidized to Pd(II) by DABCO oxide **G**. Then, intermediate **C** is transformed into iminium ion **D** by the oxidation of Pd(II).[23] After that, Pd(II) is regenerated by the oxidation of DABCO oxide **G**. Subsequently, the 6π-electrocyclic takes place to produce intermediate **E**, which reacts with **B** to access intermediate **F**.[24] Finally, as confirmed by GC-MS, the elimination of $CH_3SCH_2SCH_3$ delivers the final product **3a**.[25]

**Scheme 4**. A tentative mechanism




In conclusion, we have developed a palladium-catalyzed DMSO-based annulation/aromatization leading to 4-aryl quinolines. DMSO served as a "=CH-" fragment in this transformation. DABSO played dual roles in this procedure: one is to activate DMSO; the other is to regenerate the palladium catalyst by the oxidation of DABCO oxide. It represents a facile pathway leading to n-substituted-4-aryl quinolines (n = 3, 5-8).

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## Notes and references

*School of Petrochemical Engineering, Jiangsu Key Laboratory of Advanced Catalytic Materials and Technology, Jiangsu Province Key Laboratory of Fine Petrochemical Engineering, Changzhou University, Changzhou 213164, P. R. China; E-mail: jiangcheng@cczu.edu.cn*

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