Synthetic Methods

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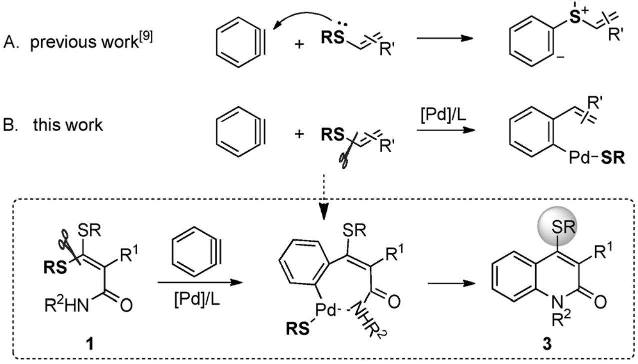
Palladium-Catalyzed C–S Activation/Aryne Insertion/Coupling Sequence: Synthesis of Functionalized 2-Quinolinones**

Ying Dong, Bangyu Liu, Peng Chen, Qun Liu, and Mang Wang**

***Abstract:** The insertion of an aryne into a C–S bond can suppress the addition of an S nucleophile to the aryne in the presence of palladium. Catalyzed by Pd(OAc)$_2$, a wide range of α-carbamoyl ketene dithioacetals readily react with arynes to selectively afford functionalized 2-quinolinones in high yields under neutral reaction conditions by a C–S activation/aryne insertion/intramolecular coupling sequence. The attractive feature of the new strategy also lies in the versatile transformations of the alkythio-substituted quinolinone products.*

Transition-metal-catalyzed C–S bond activation for C–C and C–heteroatom bond formation has fascinated organic chemists for decades.[1] A variety of organosulfur compounds have been utilized and have great potential in these processes[1–3] because of their ready availability, stability, and structural diversity, as compared to the corresponding organic halide coupling partners.[4] Cross-coupling chemistry with thioorganics along with new reaction patterns, exceptional selectivity, or unique reactivity would be highly desirable.

Inspired by palladium-catalyzed desulfitative coupling of thioesters,[1c,2a–d] we recently became interested in transition-metal-catalyzed C–S bond cleavage for C–C bond formation during our research[5] on ketene dithioacetals, which are easily prepared and widely applied as organic intermediates.[6] We have already achieved copper-catalyzed desulfitative C–C cross-coupling of α-oxo ketene dithioacetals with arylboronic acids,[3a] and then palladium-catalyzed/copper-mediated desulfitative annulation of 2-methylthiobenzofurans with 2-hydroxyphenylboronic acids.[3b] More recently, a C–S bond activation protocol for Heck-type cyclization of α-alkenoyl ketene dithioacetals was also developed in our group.[3c] To take advantage of the synthetic power of functionalized ketene dithioacetals[3,5,6] and the tremendous applications of arynes in cyclization reactions,[7] we envisioned the palladium-catalyzed C–S activation as the key to developing an annulation between arynes and α-carbamoyl ketene dithioacetals (**1**; Scheme 1) by the insertion of an aryne into a C–S bond. Furthermore, the expected products are 2-quinolinones (**3**) which have provoked great interest in chemical and biological fields.[8] However, the challenge of this strategy lies in avoiding the addition of the strongly nucleophilic sulfur atom in the substrates to the arynes (Scheme 1 A), and instead favoring insertion of the arynes into the C–S bond.[9,10] To the best of our knowledge, transition-metal-catalyzed C–S bond cleavage for aryne insertion has been seldom reported.[10] Herein, we report that arynes can react with ketene dithioacetals by palladium-catalyzed C–S bond activation followed by cyclization to produce 2-quinolinones, but they remain inactive towards the nucleophilic S-containing group (Scheme 1 B). The new synthetic method is also highlighted by the versatile transformations of the 4-functionalized 2-quinolinones, which are not easily obtained starting from the corresponding organic halides because of the difficulty in the preparation of geminal dihalides.



Scheme 1. Reactions of thioorganics with benzyne.

Initially, the reaction of the α-carbamoyl ketene dithioacetal **1a** with *o*-(trimethylsilyl)phenyl triflate (**2a**), the benzyne precursor, was selected for screening the reaction conditions. Upon treatment of **1a** with **2a** in the presence of CsF in a mixed MeCN or MeCN/toluene solvent at 80 °C under N$_2$ and using 10 mol % of a palladium catalyst (Table 1, entries 1–8), the desired 2-quinolinone **3a**[11] was isolated in 20–63 % yield after 18 hours. However, **3a** was accompanied by an *E*/*Z* isomer mixture of mixed ketene dithioacetals [**4a** and **4a′** (see Ref. [12] for structures) 5–30 % overall yields]. The formation of **4a** and **4a′** may result from the addition of the sulfur atom of **1a** to benzyne, thus leading to a zwitterionic intermediate which is converted into **4** after a water quench (for detailed mechanism, see the Supporting Information).[9,10] When we carried out the reaction of **1a** and **2a** in the absence of a palladium catalyst under otherwise identical reaction conditions, a mixture of **4a** and **4a′** was isolated in

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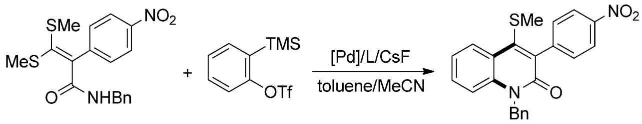
Table 1: Screening the reaction conditions.[a]

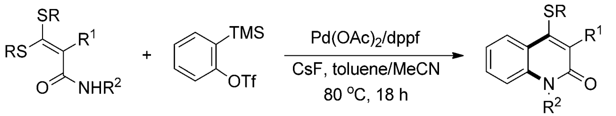


1a **2a** **3a**

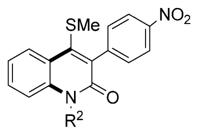
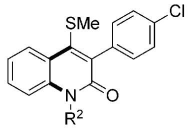
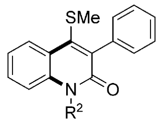
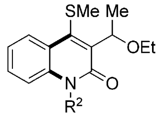
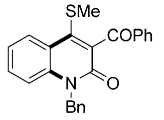
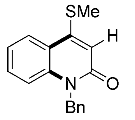
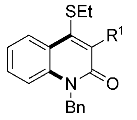
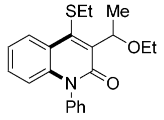
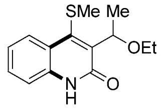
Entry	Pd	Ligand (mol %)	**2a** (equiv)	CsF (equiv)	Toluene/ MeCN	Yield [%][b]
1	Pd(OAc)$_2$	–	1.5	3	0:1	20
2	Pd(OAc)$_2$	–	1.5	3	1:1	33
3	Pd(OAc)$_2$	–	1.5	3	3:1	35
4	Pd(OAc)$_2$	–	2	4	1:1	36
5	Pd(OAc)	–	3	5	1:1	41
6	[Pd(PPh$_3$)$_4$]	–	3	5	1:1	38
7	[PdCl$_2$(PPh$_3$)$_2$]	–	3	5	1:1	63
8	[PdCl$_2$dppe]	–	3	5	1:1	54
9	Pd(OAc)$_2$	dppf (15)	3	5	1:1	92
10	Pd(OAc)$_2$	dppf (15)	3	5	1:1	90[c]
11	Pd(OAc)$_2$	Xantphos (15)	3	5	1:1	87
12	Pd(OAc)$_2$	PCy$_3$ (30)	3	5	1:1	26
13	Pd(OAc)$_2$	PPh$_3$ (30)	3	5	1:1	49
14	Pd(OAc)$_2$	dppf (8)	3	5	1:1	53[d]
15	Pd(OAc)$_2$	dppf (15)	3	5	1:1	28[e]
16	Pd(OAc)$_2$	dppf (15)	3	5	1:1	<5[f]

[a] Reaction conditions: **1a** (0.3 mmol), **2a**, CsF, Pd (10 mol %), toluene/MeCN (4 mL). Reaction was performed in a sealed tube at 80 °C under N$_2$ for 18 h. **2a** was added in six increments (3 h × 6) to avoid homocoupling of benzyne. [b] Yields of isolated products. [c] Reaction was performed in a flask with a condenser under N$_2$. [d] Used 5 mol % of Pd(OAc)$_2$. [e] At 50 °C. [f] At room temperature.

Table 2: Scope of the ketene dithioacetals **1**.[a]



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

Entry	Products **3**		Yield [%][b]
1		**1a**, **3a**, R^2 = Bn	92
2		**1b**, **3b**, R^2 = 4-MePhCH$_2$	86
3		**1c**, **3c**, R^2 = Ph	85
4		**1d**, **3d**, R^2 = *n*Bu	67
5		**1e**, **3e**, R^2 = Cy	73
6		**1f**, **3f**, R^2 = Bn	82
7		**1g**, **3g**, R^2 = *n*Bu	76
8		**1h**, **3h**, R^2 = Bn	85
9		**1i**, **3i**, R^2 = Ph	76
10		**1j**, **3j**, R^2 = *n*Bu	79
11		**1k**, **3k**, R^2 = Bn	82
12		**1l**, **3l**, R^2 = Ph	79
13		**1m**, **3m**	74
14		**1n**, **3n** + **3h**	27 + 20
15		**1o**, **3o**, R^1 = 4-NO$_2$Ph	88
16		**1p**, **3p**, R^1 = PhCO	80
17		**1q**, **3q**	73
18		**1r**, **3r**	<15[c]

[a] Reaction conditions: **1** (0.3 mmol), **2** (0.9 mmol), CsF (1.5 mmol), Pd(OAc)$_2$ (0.03 mmol), dppf (0.045 mmol), toluene/MeCN (4 mL, 1:1, v/v) in a sealed tube. **2** was added in six increments (0.15 mmol/3 h). [b] Yields of isolated products. [c] Yield based on ^{1}H NMR spectroscopy. **3r** could be detected by the NMR and HRMS-ESI studies of the product mixture. However, the isolation of pure **3r** failed.

63 % yield in a ratio of 1:3; no benzyne annulation product **3a** was observed in this case. On the contrary, the use of a ligand for the palladium catalyst dramatically improved the aryne annulation and the yield of **3a** was increased to 92 % by using 15 % of 1,1′-bis(diphenylphosphino) ferrocene (dppf, entries 9 and 10) as the ligand. Under these reaction conditions, **4a** and **4a′** were not detected. Clearly, both palladium and the ligand play a key role in the insertion of benzyne into a C–S bond. Other phosphine-containing ligands, including PCy$_3$, PPh$_3$, and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) were found to be less efficient than dppf for this annulation (entries 11–13). Additionally, either decreasing the amount of the catalyst (entry 14) or lowering the reaction temperature resulted in unsatisfactory yields of **3a** (entries 15 and 16).

With the optimized reaction conditions in hand (Table 1, entry 9), we explored the scope of this palladium-catalyzed selective annulation between the dithioacetals **1** and **2a**. As described in Table 2, a series of α-carbamoyl-α-aryl ketene dimethylthioacetals (**1**) bearing a N-protecting group, including both N-alkyl (R^2 = Bn, Cy and *n*Bu) and N-aryl groups (R^2 = Ph), afforded the desired 2-quinolinones **3a–j** in good yields (entries 1–10). For substrates **1k** and **1l**, bearing an α-alkyl group, the reaction afforded the desired products **3k** (82 %) and **3l** (79 %), respectively (entries 11 and 12). Furthermore, the dithioacetal **1m**, having an electron-withdrawing group (R^1 = PhCO) at the α position, also worked well with **2a** to give **3m** in 74 % yield (entry 13). In comparison, the reaction was more complex for **1n**, which does not have a substituent at the α-position (R^1 = H), and thus afforded the desired product **3n** in only 27 % yield (entry 14) along with **3h** in 20 % yield. In this case, the formation of **3h** may result from the first α-phenylation of **1n** with benzyne by a palladium-catalyzed α-C–H activation[6d]

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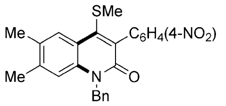
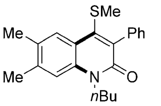
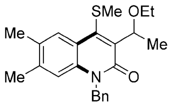
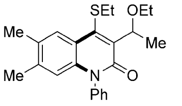
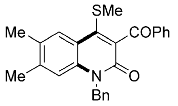
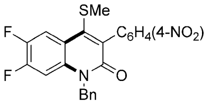
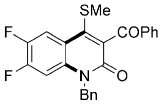
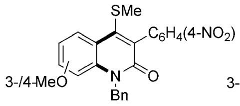
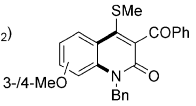
to give **1h**, and subsequent annulation with benzyne (for details, see the Supporting Information). In addition, the ketene dithioacetals **1o–q**, having an ethylthio functional group, also proved to be suitable substrates for this process (entries 15–17). Finally, the reaction was found to be sensitive to the substrate **1r** bearing a free NH_2, and **3r** was only detected by NMR and HRMS-ESI studies of the reaction mixture after running the reaction for 18 hours (entry 18).

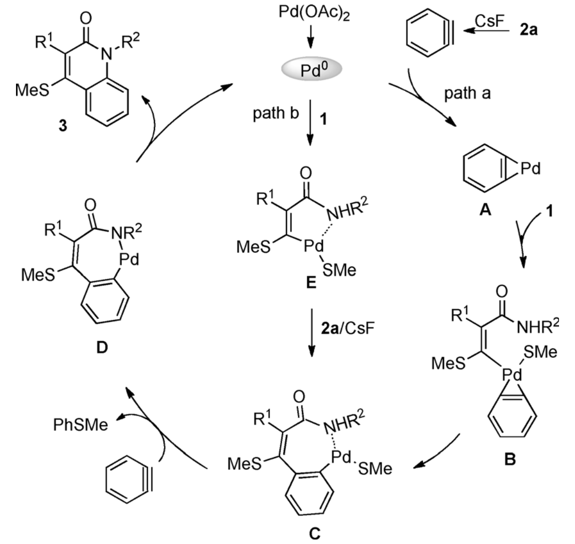
Next, we turned to extending the scope of the annulation with respect to the arynes. Gratefully, all arynes, bearing both electron-withdrawing and electron-donating groups, were compatible with the standard reaction conditions, though moderate yields were often obtained (Table 3; **3s–u**, **3x**, and **3y**, yields within parenthesis). The yields of **3** could be increased (77–87%) when 5 equivalents of an aryne were used (**3s–w**, **3z/3z′**, and **3aa/3aa′**). However, in the case of the aryne **2c**, having an electron-withdrawing group, excess aryne did not benefit the reaction but led to the formation of mixed ketene dithiacetals (**4b/4b′**)[12] in 26% yield. In addition, when the unsymmetrical aryne, 4-methoxy-2-(trimethylsilyl)-phenyl trifluoro methanesulfonate (**2d**) was used in the annulation, the products **3z/3z′** and **3aa/3aa′** were obtained as a mixture of two isomers.

Table 3: Scope of arynes **2**.[a]

 **3s**, from **1a** and **2b** 87% (51%)[b]	 **3t**, from **1j** and **2b** 77% (41%)[b]	 **3u**, from **1k** and **2b** 80% (45%)[b]
 **3v**, from **1q** and **2b** 82%	 **3w**, from **1m** and **2b** 84%	 **3x**, from **1a** and **2c** 51%[c] (47%)[b]
 **3y**, from **1j** and **2c** (42%)[b]	 **3z+3z′**, from **1a** and **2d** 81% (52:48)[d]	 **3aa+3aa′**, from **1m** and **2d** 80% (56:44)[d]

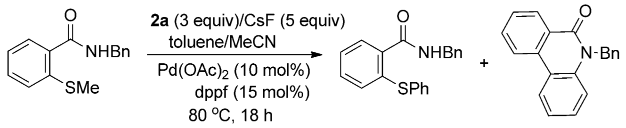
[a] Reaction conditions: **1** (0.3 mmol), **2** (1.5 mmol), CsF (2.1 mmol), $Pd(OAc)_2$ (0.03 mmol), dppf (0.045 mmol), toluene/MeCN (4 mL, 1:1, v/v in a sealed tube, **2** was added in six increments (0.25 mmol/3 h). Yields of isolated products. [b] Yields in parenthesis were obtained by using 0.9 mmol of **2** and 1.5 mmol of CsF. [c] The by-products **4b** and **4b′** were isolated in 26% yield. [d] The ratio of two isomers, based on ^1H NMR spectroscopy, are included within parentheses.

On the basis of the above results and the known work on the paladium-catalyzed reactions involving arynes,[7] two possible mechanisms (path a and path b, Scheme 2) are suggested to account for the present aryne annulation processes. Clearly, the formation of the arylpalladium(II) intermediate **C** is the key for the annulation. In path a, the Pd^0 complex initially undergoes oxidative cyclization with the aryne to generate the palladacycle **A**. Subsequent insertion of **A** into the C–S bond of **1** affords the intermediate **C**, perhaps via the Pd^{IV} **B**. Then, the intramolecular substitution of **C** gives rise to a seven-membered heteropalladacycle **D** along with the loss of methanethiol captured by benzyne. Finally, reductive elimination of **D** affords the observed annulation products **3** and regenerates the Pd^0 catalyst for the next cycle. In comparison, the first palladium oxidative addition step in path b is different from that in path a and involves the direct insertion of Pd^0 into the C–S bond of **1** to generate the intermediate **E**.[3] Then, **E** reacts with the aryne to afford **C**, which goes on to the products **3** by a similar process as in path a. During the reactions, a second, sacrificial equivalent of benzyne was required for scavenging the liberated methanethiol as the reaction proceeds. PhSMe can be detected by HRMS-ESI analysis of the reaction mixture ([M+H^+], calcd, 125.0419; found, 125.0440). However, we do not have any particular evidence for favoring either of these pathways at the presence.



Scheme 2. Proposed mechanism for palladium-catalyzed annulation of **1** with benzyne. Ligands omitted for clarity.

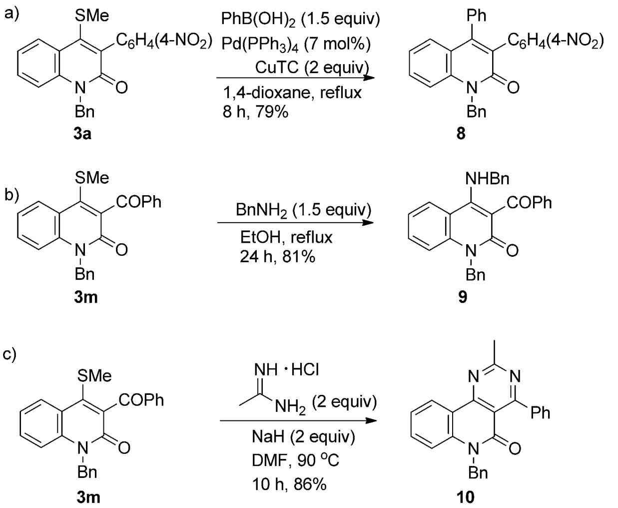
To get more information on the selective insertion of arynes into the C–S bond in the presence of palladium, we performed the reaction of *N*-benzyl-2-(methylthio)benzamide (**5**) with benzyne under the standard reaction conditions. As shown in Scheme 3, the compound **6**, resulting from addition of sulfur to benzyne, was isolated as the main product. The product **7**, which underwent sequential insertion of benzyne into the C–S bond and cyclization, was isolated only in 32% yield.



5 **6** (60%) **7** (32%)

Scheme 3. Reaction of *o*-(methylthio)benzamide (**5**) with benzyne.

It is clear that the dithioacetals **1** have a unique selectivity toward the palladium catalyst in two competing processes, the insertion versus the addition. Thus, a practical palladium-catalyzed annulation to rapidly synthesize a variety of 2-quinolinones (**3**) has been developed. It is noteworthy that the alkylthio functional group retained in **3** should enable further modification of them (Scheme 4). To highlight the synthetic potential of our approach, the palladium-catalyzed cross-coupling of **3a** with phenylboronic acid was first investigated in the presence of copper(I)-thiophene-2-carboxylate (CuTC; Scheme 4a).[1c,2a–d,3a,b] To our delight, 4-phenyl-2-quinolinone[9c–e] (**8**) was separated from the reaction mixture in 79% yield. Additionally, the direct substitution[5e] of the 4-methylthio group of **3m** with phenylmethanamine was also performed to give the 4-amino quinolinone **9** in high yield (Scheme 4b). Another application of **3** was presented in the synthesis of the pyrimidoquinolin-5-one **10** by the condensation of **3m** with acetimidamide (Scheme 4c).



Scheme 4. Applications of the alkylthio-substituted quinolinones **3**.

In summary, we have successfully developed a novel and efficient palladium-catalyzed protocol for the synthesis of 2-quinolinones from the reaction between ketene dithioacetals and arynes, a reaction which proceeds through a unique insertion of arynes into the C–S bond. This process represents the first example for the reaction of arynes with thioorganics based on palladium-catalyzed C–S bond activation. The functionalized 2-quinolinone products are expected to be useful building blocks in library synthesis for the screening of potential bio-/pharmacological compounds. We believe that the discovery of the facile C–S bond activation should pave the way for establishing some new and efficient palladium-catalyzed transformations. Further work on the applications and extension of the scope of the protocol, as well as the detailed reaction mechanism are currently under investigation in our laboratory.

Experimental Section

General procedure for the palladium-catalyzed annulation of **1** with **2** (taking the reaction of **1a** and **2a** as example): The dithioacetal **1a** (112 mg, 0.3 mmol), $Pd(OAc)_2$ (7 mg, 0.03 mmol), and dppf (25 mg, 0.045 mmol) were added, in sequence, to a dried pressure tube. The tube was transferred into a glove box and then CsF (228 mg, 1.5 mmol) and 1 mL of mixed solvent (MeCN/toluene, 1:1) were added. The tube was sealed by a rubber septum. After taking the tube out of the glove box, the mixture was stirred at 80 °C. 2-(Trimethylsilyl)phenyl triflate (**2a**; 0.218 mL, 0.9 mmol) was pre-dissolved in 3 mL of MeCN/toluene (1:1) and was added by syringe to the reaction mixture in six increments over an 18 h period (0.15 mmol/3 h). Then, the reaction mixture was poured into ice water (10 mL) and extracted with CH_2Cl_2 (3 × 6 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to yield the crude reaction mixture, which was purified by silica gel chromatography (20:1, petroleum ether/ethyl acetate) to give **3a** (111 mg, 92%) as a yellow crystal. R_f 0.36 (4:1, petroleum ether/ethyl acetate).

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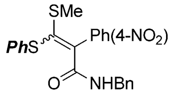
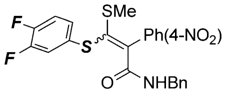


4a and **4a'**



4b and **4b'**