Palladium-Catalyzed CS Activation/Aryne Insertion/Coupling Sequence: Synthesis of Functionalized 2-Quinolinones

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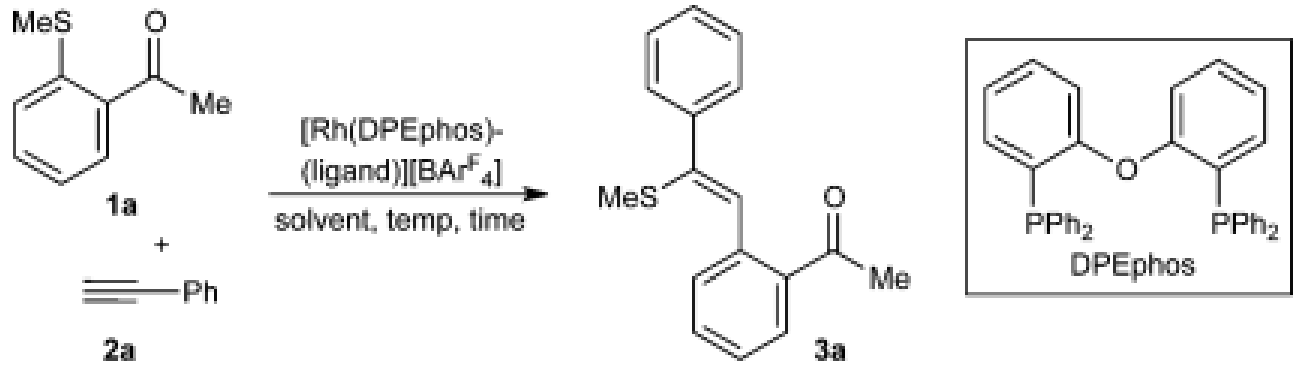
Yohan DUDOGNON, STeRéO group meeting, 24/03/2014

State of art

Synthesis of Xanthones, Thioxanthones, and Acridones by the Coupling of Arynes and Substituted Benzoates

J. Zhao, R. C.Larock, *J. Org. Chem.* **2007**, *72*, 583
doi: 10.1021/jo0620718

Aryl Methyl Sulfides as Substrates for Rhodium-Catalyzed Alkyne Carbothiolation: Arene Functionalization with Activating Group Recycling



J. F. Hooper, A. B. Chaplin, C. Gonzlez-Rodriguez, A. L. Thompson, A. S. Weller, M. C. Willis, *J. Am. Chem. Soc*. **2012**, *134*, 2906
doi: 10.1021/ja2108992

State of art

- **Transition-metal-catalyzed CS bond activation for CC and C–heteroatom bond formation**

S. G. Modha, V. P. Mehta, E. V. V. der Eycken, *Chem.Soc. Rev.* **2013**, *42*, 5042.

L. Wang, W. He, Z. Yu, *Chem. Soc. Rev.* **2013**, *42*, 599

H. Prokopcov, C. O. Kappe, *Angew. Chem.* **2009**, *121*, 2312

- **Applications of arynes in cyclization reactions**

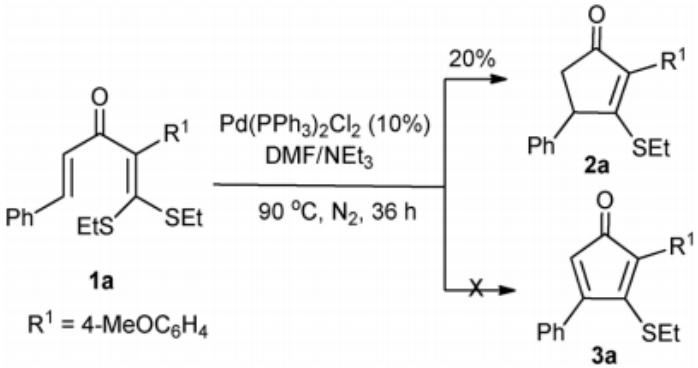
H. Pellissier, M. Santelli, *Tetrahedron* **2003**, *59*, 701

S. A. Worlikar, R. C. Larock, *Curr. Org. Chem.* **2011**, *15*, 3214

A. V. Dubrovskiy, N. A. Markina, R. C. Larock, *Org. Biomol. Chem.* **2013**, *11*, 191

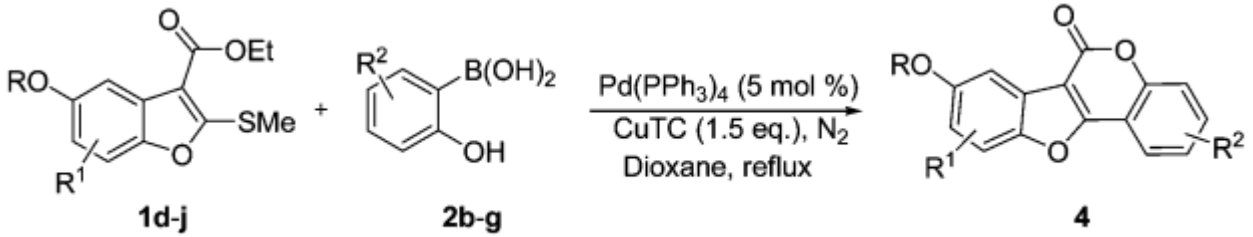
Previous work of the team

Regio- and stereoselective synthesis of 2-cyclopentenones via a hydrogenolysis-terminated Heck cyclization of ß-alkylthio dienones



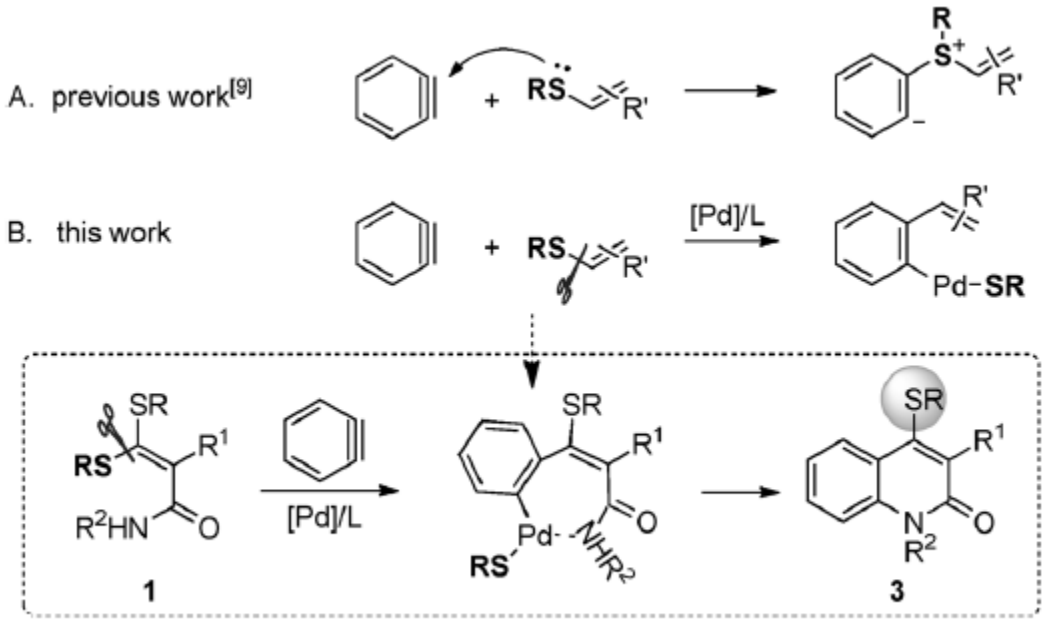
B. Liu, G. Zheng, X.Liu, C. Xu, J. Liu, M. Wang, *Chem. Commun.* **2013**, *49*, 2201

Palladium-catalyzed/copper-mediated desulfitative annulation of 2-methylthiobenzofurans with 2-hydroxyphenylboronic acids



J.-X. Liu, Y.-J. Liu, W.-T. Du, Y. Dong, J. Liu, M. Wang, *J. Org. Chem.*, **2013**, *78*, 7293;

Overview



Scheme 1. Reactions of thioorganics with benzyne.

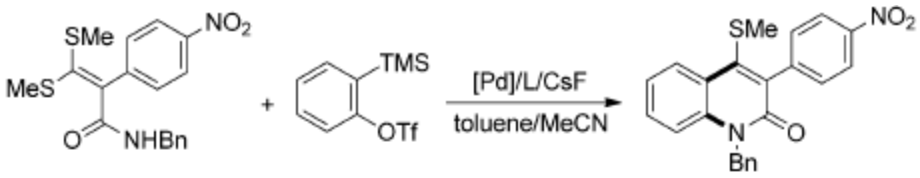
- **Strategy :** Take advantage of : the synthetic power of functionalized ketene dithioacetals
  the tremendous applications of arynes in cyclization reactions

  Use Pd-catalyzed CS activation as the key to developing an annulation between arynes and α-carbamoyl ketene dithioacetals

- **Interests :** Effective synthesis 2-quinolinones which have provoked great interest in chemical and biological field
  Possible versatile transformations of the 4-functionalized 2-quinolinones

- **Challenge :** Avoid the addition of the strongly nucleophilic sulfur atom to the arynes and instead favoring insertion of the arynes into the CS bond.

Screening of the reaction conditions

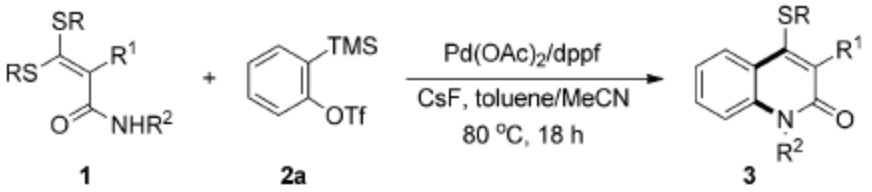


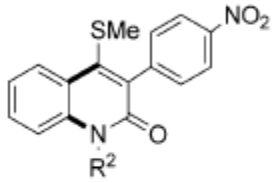
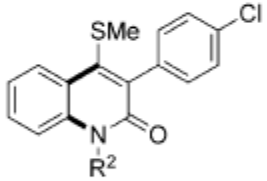
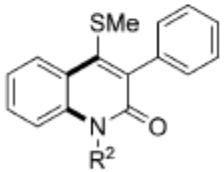
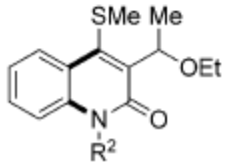
1a **2a** **3a**

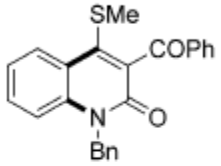
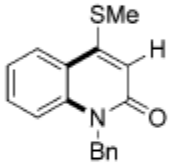
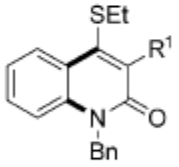
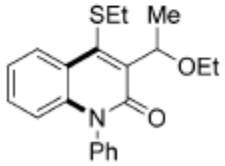
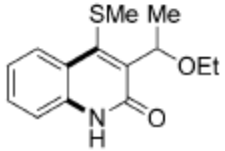
Entry	Pd	Ligand (mol %)	**2a** (equiv)	CsF (equiv)	Toluene/ MeCN	Yield [%][b]
1	$Pd(OAc)_2$	–	1.5	3	0:1	20
2	$Pd(OAc)_2$	–	1.5	3	1:1	33
3	$Pd(OAc)_2$	–	1.5	3	3:1	35
4	$Pd(OAc)_2$	–	2	4	1:1	36
5	Pd(OAc)	–	3	5	1:1	41
6	$[Pd(PPh_3)_4]$	–	3	5	1:1	38
7	$[PdCl_2(PPh_3)_2]$	–	3	5	1:1	63
8	$[PdCl_2dppe]$	–	3	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.

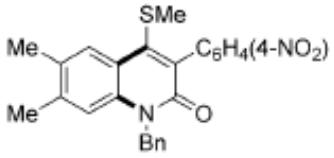
Scope of the ketene dithioacetals



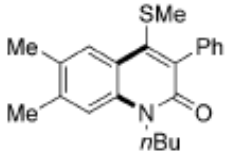
Entry	Products 3		Yield [%][b]
1		1a, 3a, R^2 = Bn	92
2		1b, 3b, R^2 = 4-MePhCH$_2$	86
3		1c, 3c, R^2 = Ph	85
4		1d, 3d, R^2 = *n*Bu	67
5		1e, 3e, R^2 = Cy	73
6		1f, 3f, R^2 = Bn	82
7		1g, 3g, R^2 = *n*Bu	76
8		1h, 3h, R^2 = Bn	85
9		1i, 3i, R^2 = Ph	76
10		1j, 3j, R^2 = *n*Bu	79
11		1k, 3k, R^2 = Bn	82
12		1l, 3l, R^2 = Ph	79

Entry	Products 3		Yield [%][b]
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]

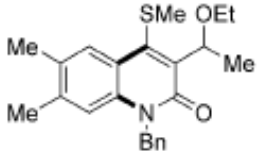
Scope of arynes



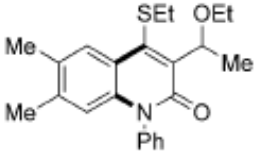
3s, from **1a** and **2b**
87% (51%)[b]



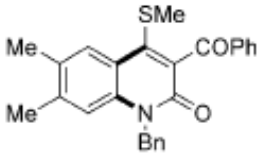
3t, from **1j** and **2b**
77% (41%)[b]



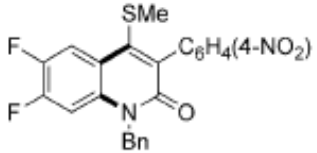
3u, from **1k** and **2b**
80% (45%)[b]



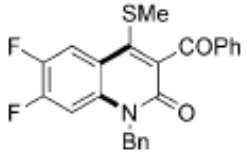
3v, from **1q** and **2b**
82%



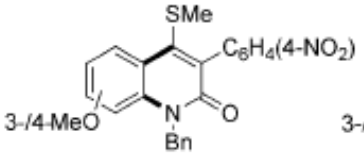
3w, from **1m** and **2b**
84%



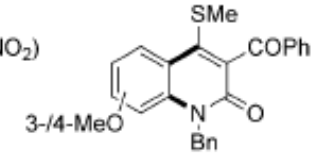
3x, from **1a** and **2c**
51%[c] (47%)[b]



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]

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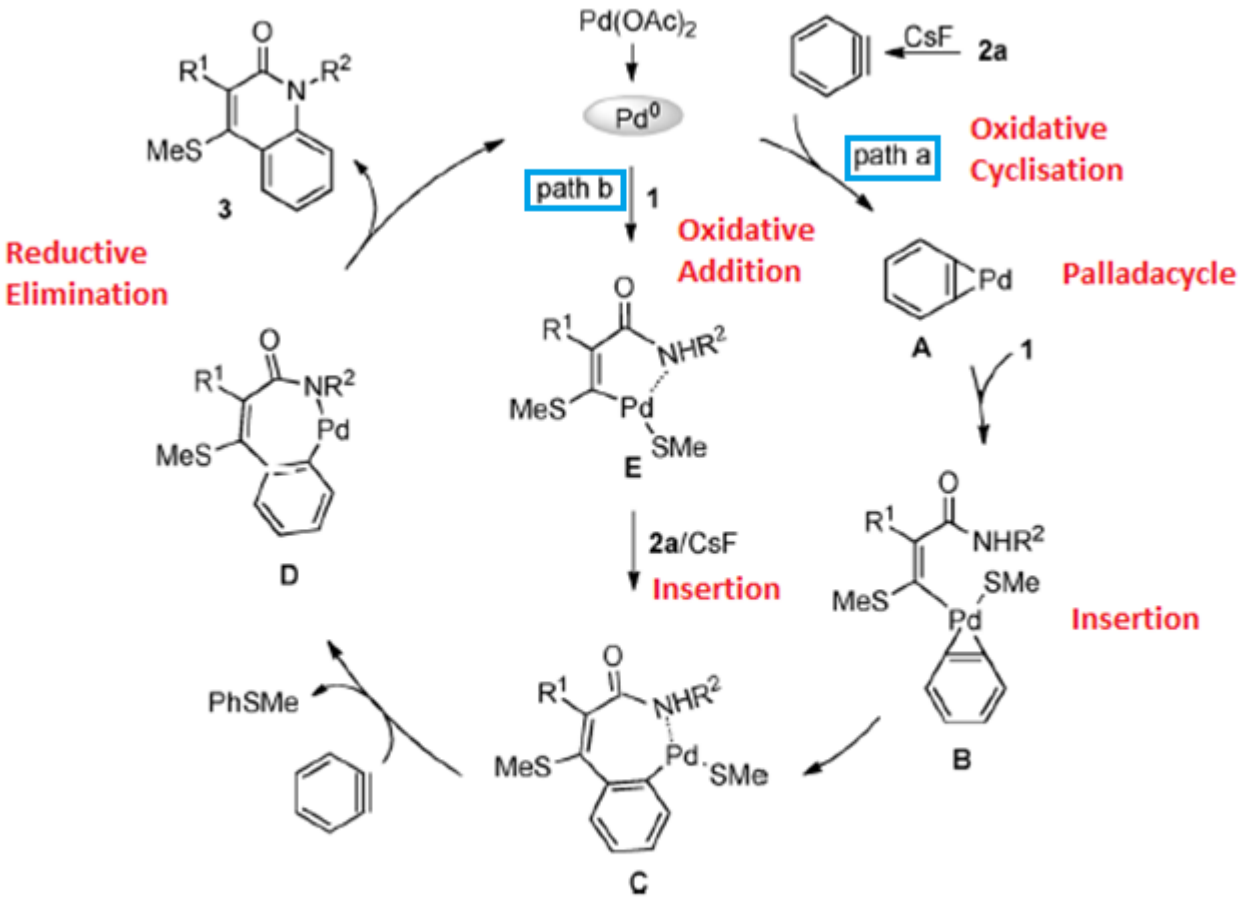
[a] Reaction conditions: **1** (0.3 mmol), **2** (1.5 mmol), CsF (2.1 mmol), $Pd(OAc)_2$ (0.03 mmol), dppf (0.045 mmol), toluene/MeCN (4 mL, 1:1, v/v in a sealed tube, **2** was added in six increments (0.25 mmol/3 h). Yields of isolated products. [b] Yields in parenthesis were obtained by using 0.9 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 ^{1}H NMR spectroscopy, are included within parentheses.

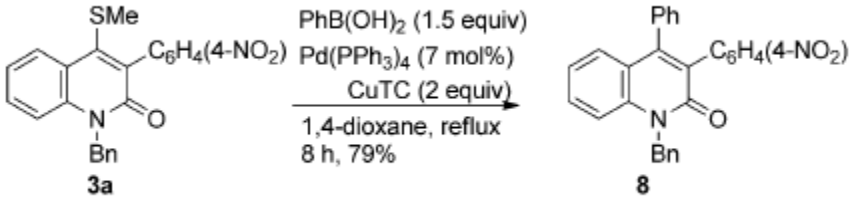
Mechanism



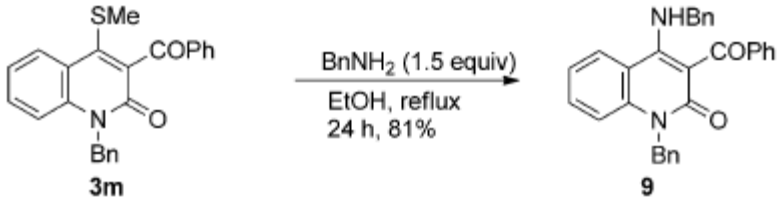
Ligands omitted for clarity

Applications

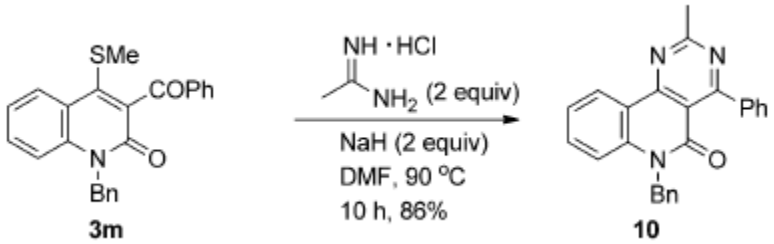
• Palladium-catalyzed crosscoupling with phenylboronic acid in the presence of copper(I)-thiophene-2-carboxylate



• Direct substitution of the 4-methylthio group of with phenylmethanamine give the 4-amino quinolinone



• Synthesis of the pyrimidoquinolin-5-one by the condensation with acetimidamide



Conclusion

- Development of a novel and efficient palladium-catalyzed protocol for the synthesis of 2-quinolinones
- First example for the reaction of arynes with thioorganics based on palladium-catalyzed CS bond activation
- Functionalized 2-quinolinone as useful building blocks
- Discovery of the facile CS bond activation should lead to some new and efficient palladium-catalyzed transformations
- Work on the applications, extension of the scope, mechanistical studies are ongoing