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Regiocontrolled palladium-catalyzed direct C2-arylations of Methoxalen using benzenesulfonyl chlorides and C2,C3-diarylations using aryl bromides as the aryl sources

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Regiocontrolled palladium-catalyzed direct C2-arylations of Methoxalen using benzenesulfonyl chlorides and C2,C3-diarylations using aryl bromides as the aryl sources

Haoran Li[a], Thierry Roisnel[a], Jean-François Soulé[a,*] and Henri Doucet[a,*]

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Homogeneous catalysis
Palladium
C-H bond functionalization
Methoxalen

ABSTRACT

Conditions for the regioselective palladium-catalyzed direct C2-arylation and C2,C3-diarylation of Methoxalen are described. The use of benzenesulfonyl chlorides as the coupling partner allowed control of the regioselectivity of the arylation in favor of the C2 carbon of Methoxalen. This method tolerates a variety of substituents on the benzenesulfonyl chloride derivative. Notably, 2-, 3-, and 4-bromobenzenesulfonyl chlorides and 4-iodobenzenesulfonyl chloride were coupled with Methoxalen without cleavage of the C-Br or C-I bonds. Conversely, the use of an excess amount of aryl bromides as the aryl source provides access to C2,C3-diarlyated Methoxalenes.

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1. Introduction

Among polycyclic heteroarenes, the linear furanocoumarin 7*H*-furo[3,2-*g*]chromen-7-one (or Psoralen) unit can be found in several drugs and natural products (Fig. 1). For example, Methoxalen (also called Xanthotoxin) and Bergapten are drugs employed in the treatment of psoriasis, eczema, vitiligo, and some cutaneous lymphomas. Trioxsalen is also used for the phototherapy treatment of vitiligo and hand eczema.

Since the seminal work by Ohta and co-workers in 1985 on the Pd-catalyzed arylation of several heteroaromatics, including furans, with aryl halides *via* C-H bond activation,[1] the so-called direct arylation of heteroaryl derivatives has been demonstrated to be an extremely powerful pathway to access arylated heterocycles.[2] When this methodology can be applied to the late-stage functionalization of drugs, it provides an appealing method to build a library of compounds allowing the easy screening of the biological properties of compounds containing a specific bioactive unit.

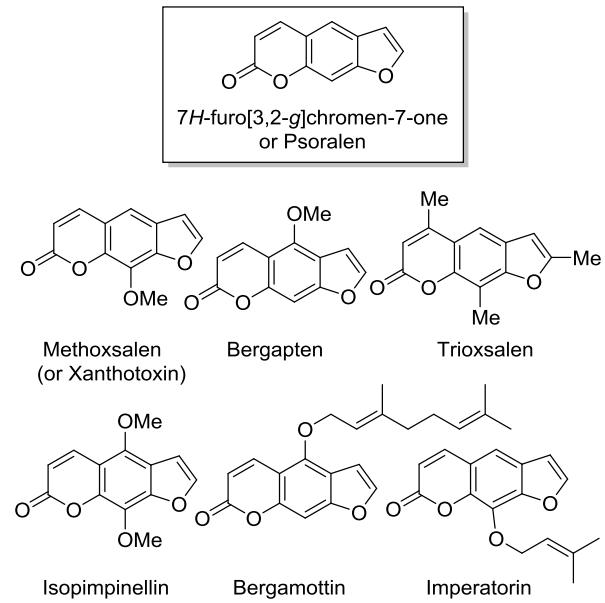


Figure 1. Representative examples of bioactive 7*H*-furo[3,2-*g*]chromen-7-ones.

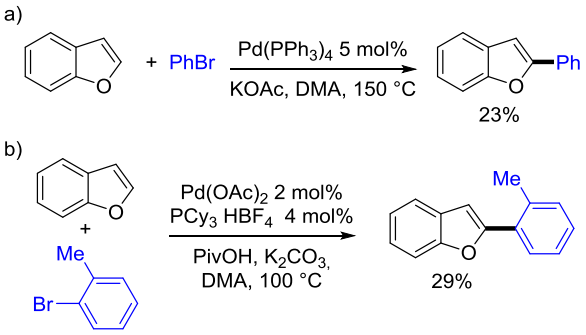
The first example of Pd-catalyzed direct arylation of benzofuran was reported by Ohta and co-workers who obtained 2-phenylbenzofuran from benzofuran and bromobenzene in a low 23% yield using $Pd(PPh_3)_4$ as the catalyst (Scheme 1, a).[1] Fagnou

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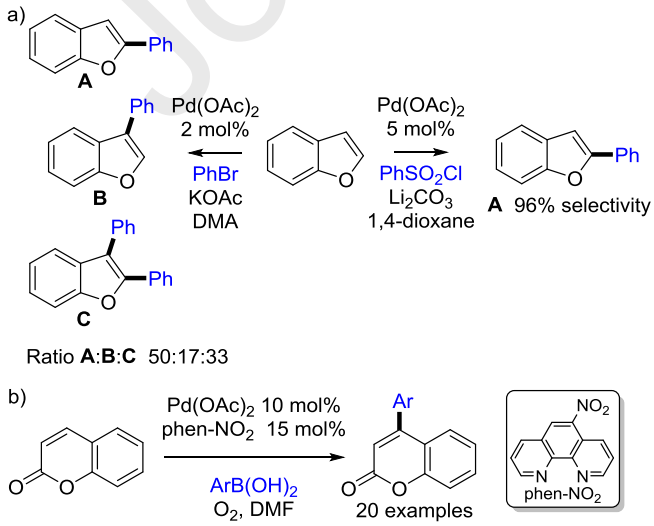
an *via* the coupling of benzofuran with 2-bromotoluene using 2 mol% $Pd(OAc)_2$ and 4 mol% PCy_3 as the catalyst (Scheme 1, b).[3a]



Scheme 1. Pd-catalyzed direct arylations of benzofuran with aryl bromides.

The C2-arylation of benzofurans using aryl halides as the aryl source proceeds *via* a concerted metallation deprotonation (CMD) mechanism.[4] According to Gorelsky calculations, in the CMD process, the C2 carbon of benzofuran should be slightly more reactive than the C3 carbon (energies: 26.3 vs 27.5) (Fig. S1).[4] This minor difference in the energy of activation explains the poor regioselectivity, and therefore the poor yields observed for the Pd-catalyzed arylations of benzofuran with aryl bromides, as mixtures of C2- and C3-arylated and also C2,C3-diarylated benzofurans are obtained (Scheme 1, a left).[3]

In 2009, Dong and co-workers described the Pd-catalyzed desulfitative coupling of a quinoline derivative using benzenesulfonyl chlorides as the aryl source in the presence of Ag_2CO_3 and CuBr. Subsequently, the use of benzenesulfonyl chlorides[5] for the Pd-catalyzed direct arylation has been extended to other heteroarenes by several groups.[6] Our group reported that the use of benzenesulfonyl chlorides as the coupling partner instead of aryl halides allows control of the regioselectivity of the palladium-catalyzed arylation of benzofurans in favor of the C2 carbon (Scheme 2, a right).[7] The first step of the catalytic cycle with benzenesulfonyl chlorides is presumably oxidative addition of the benzenesulfonyl chloride to Pd(II) to afford a Pd(IV) intermediate instead of the Pd(0)/Pd(II) catalytic cycle for the reactions using aryl halides.[8] It should also be noted that the Pd-catalyzed direct C2-arylation of benzofuran using other aryl sources such as aryldiazonium salts or arylboronic acids,[9] or under oxidative coupling conditions,[10] has also been described. In addition, the Pd-catalyzed C4-arylation of coumarins has been reported (Scheme 2, b).[11]

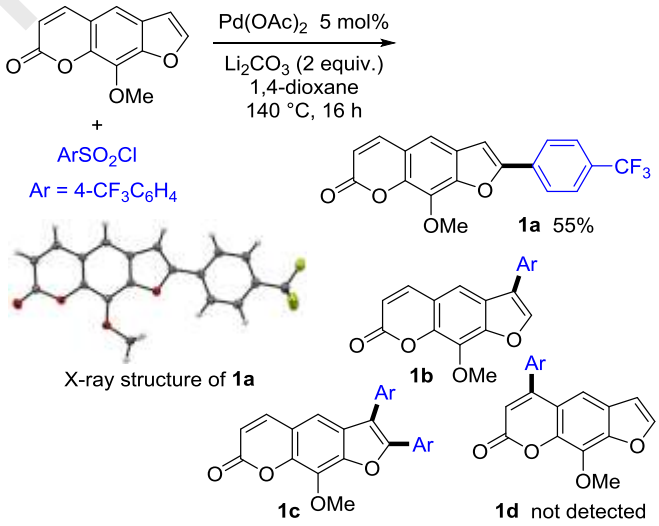


Scheme 2. Influence of the aryl source on the regioselectivity of the Pd-catalyzed direct arylation of benzofuran and arylation of coumarin.[7a,11]

To the best of our knowledge, the Pd-catalyzed direct arylation methodology has not been applied to the synthesis of 2-arylated Psoralenes.[12] Herein, we describe reaction conditions allowing the regioselective direct C2-arylation or C2,C3-diarylation of Methoxalen using readily available catalysts, bases and substrates. The influence of the substituents on the aryl source is also reported.

2. Results and Discussion

Based on our previous results on palladium-catalyzed desulfitative coupling with benzofuran,[7a] we first examined the regioselectivity of the arylation of Methoxalen with 1.5 equiv. of 4-(trifluoromethyl)benzenesulfonyl chloride (Scheme 3). In the presence of 5 mol% $Pd(OAc)_2$ and Li_2CO_3 at 140 °C in 1,4-dioxane, the desired C2-arylated Methoxalen **1a** was regioselectively obtained in 55% yield.[13,14] The structure of **1a** was confirmed by single crystal X-ray analysis.[15] Under these conditions, no formation of C3-arylated Methoxalen **1b** or C2,C3-diarylation product **1c** was detected by GC/MS analysis of the crude mixture; a significant amount of degradation products was also observed. Moreover, no arylation on the pyran-2-one ring to produce compound **1d** was observed. Conversely, as expected, the use of 1.5 equiv. of 4-(trifluoromethyl)bromobenzene as the aryl source, using 2 mol% $Pd(OAc)_2$ and KOAc in DMA, afforded a mixture of the C2- and C3-arylated Methoxalens **1a** and **1b** and also a significant amount of C2,C3-diarylated Methoxalen **1c** which could not be separated by column chromatography on silica gel.



With 4-$CF_3C_6H_4Br$ instead of 4-$CF_3C_6H_4SO_2Cl$ as the aryl source, using 2 mol% $Pd(OAc)_2$, KOAc (2 equiv.), DMA, 150 °C, 16 h, a mixture of **1a**, **1b** and **1c** was obtained.

Scheme 3. Regioselectivity of the Pd-catalyzed direct arylations of Methoxalen with a benzenesulfonyl chloride.

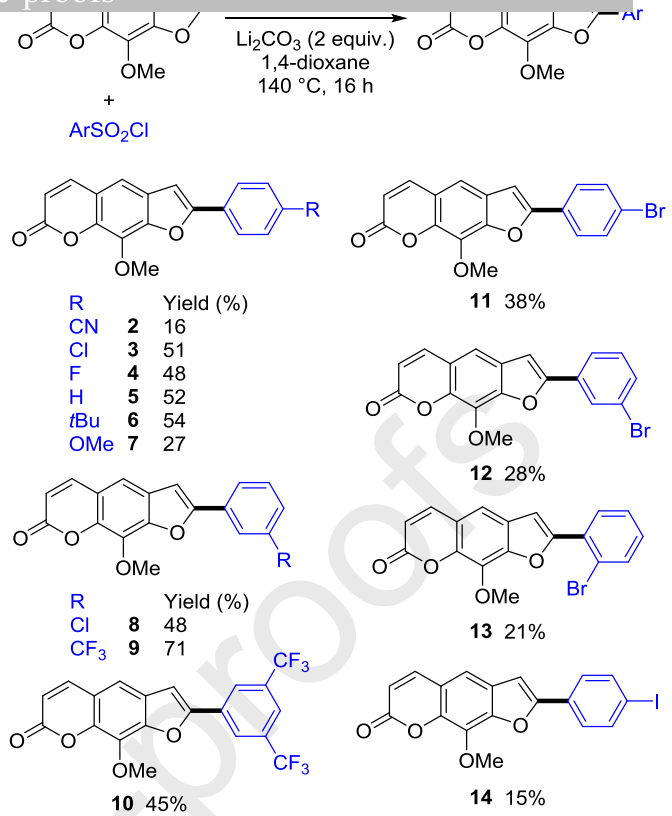
Then, the influence of the substituents on the benzenesulfonyl chlorides for the C2-arylation of Methoxalen was studied using 5 mol% $Pd(OAc)_2$ and Li_2CO_3 in 1,4-dioxane at 140 °C (Scheme 4). We initially employed electron-deficient benzenesulfonyl chlorides. A cyano substituent at the C4-position of the benzenesulfonyl chloride gave product **2** in a low yield; whereas, 4-chlorobenzenesulfonyl chloride afforded the C2-arylated Methoxalen **3** in 51% yield. From the slightly electron-deficient

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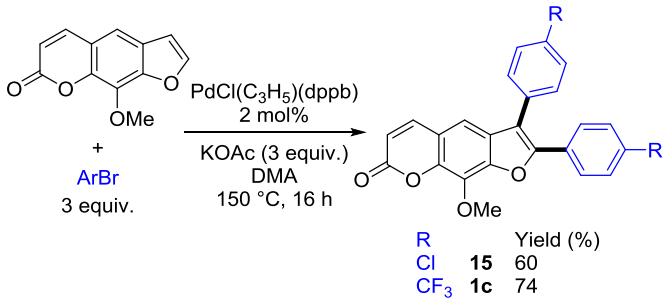
obtained for **4**. The electron-neutral benzenesulfonyl chloride and slightly electron-rich 4-*tert*-butylbenzenesulfonyl chloride gave the desired coupling products **5** and **6** in 52% and 54% yield, respectively. With these substrates, the formation of unidentified degradation products was also observed. On the other hand, the use of more electron-rich 4-methoxybenzenesulfonyl chloride led to the C2-arylated Methoxalen **7** in only 27% yield, due to poor conversion. We also studied the influence of *meta*-substituents on the benzenesulfonyl derivative. With a chloro-substituted benzene derivative, a moderate yield (48%) was obtained for **8**; whereas 3-(trifluoromethyl)benzenesulfonyl chloride gave **9** in 71% yield. From 3,5-bis(trifluoromethyl)benzenesulfonyl chloride, the expected product **10** was formed in 45% yield.

As the use of benzenesulfonyl chlorides as the coupling partners in Pd-catalyzed direct arylations tolerates both bromo- and iodo-substituents,[16] the behavior of a set of halobenzenesulfonyl chlorides for the C2-arylation of Methoxalen was investigated (Scheme 4). The reaction of 1.5 equiv. of 4-bromobenzenesulfonyl chloride and 1 equiv. of Methoxalen in the presence of 5 mol% $Pd(OAc)_2$ regioselectively gave the C2 arylated Methoxalen **11** in 38% yield without cleavage of the C-Br bond of 4-bromobenzenesulfonyl chloride. In the course of this reaction, no formation of the 1,4-diarylated benzene derivative from both C-SO_2Cl and C-Br bonds activation was detected by GC/MS analysis of the crude mixture. The reactivity of 2- and 3-bromobenzenesulfonyl chlorides was also investigated. The target compounds **12** and **13** were isolated in 28% and 21% yields, respectively, again without cleavage of the C-Br bonds. We also examined the reaction of 4-iodobenzenesulfonyl chloride with Methoxalen. The reaction afforded the desired product **14** in only 15% yield due to the formation of unidentified side-products, but without cleavage of the C-I bond, thus allowing further transformations.



Scheme 4. Pd-catalyzed direct C2-arylations of Methoxalen using benzenesulfonyl chlorides.

Finally, as both the C2- and C3-positions of Methoxalen had been found to be reactive for direct arylations with 4-(trifluoromethyl)bromobenzene using $Pd(OAc)_2$ and KOAc in DMA (see Scheme 3), the reactivity of Methoxalen was studied in the one pot C2,C3-diarylation by aryl bromides (Scheme 5). Methoxalen was reacted with 3 equiv. of 4-bromochlorobenzene or 4-(trifluoromethyl)bromobenzene in the presence of 2 mol% $PdCl(C_3H_5)(dppb)$[17] and KOAc in DMA; these conditions were previously found to be effective for the diarylation of benzofuran.[18] The desired C2,C3-diarylated products **15** and **1c** were obtained in 60% and 74% yield, respectively.[19,20]



Scheme 5. Pd-catalyzed direct C2,C3-diarylations of Methoxalen using aryl bromides.

In summary, we report herein the first examples of metal-catalyzed C-H bond functionalizations of Methoxalen and the first methods allowing the preparation of C2-arylated or C2,C3-diarylated Methoxalen derivatives. Low to moderate yields for C2-arylated Methoxalen were obtained using benzenesulfonyl chlorides as the aryl source; whereas, using an excess of aryl bromides the C2,C3-diarylated Methoxalen were produced in good yields. These couplings tolerated a variety of substituents on the benzenesulfonyl chlorides and aryl bromides. Therefore,

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employs commercially available reactants, catalysts and bases, provides a straightforward access to Methoxalen derivatives allowing to tune or modify their biological properties.

Acknowledgments

We thank the China Scholarship Council for a fellowship to HL.

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13. Synthesis of C2-arylated Methoxalens (Scheme 1): To a 25 mL oven dried Schlenk tube, benzenesulfonyl chloride (1.5 mmol), Methoxalen (0.216 g, 1 mmol), Li_2CO_3 (0.148 g, 2 mmol), 1,4–were successively added. The reaction mixture was evacuated by vacuum-argon cycles (5 times) and stirred at 140 °C (oil bath temperature) for 16 hours. After cooling the reaction to room temperature and concentration, the crude mixture was purified by silica column chromatography to afford the C2-arylated Methoxalen.
14. 9-Methoxy-2-(4-(trifluoromethyl)phenyl)-7*H*-furo[3,2-*g*]chromen-7-one **1a**: Following the procedure of ref 13, 4-(trifluoromethyl)benzenesulfonyl chloride (0.367 g, 1.5 mmol) and Methoxalen (0.216 g, 1 mmol), affords **1a** in 55% (0.198 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.1 Hz, 2H), 7.77 (d, *J* = 9.6 Hz, 1H), 7.73 (d, *J* = 8.1 Hz, 2H), 7.37 (s, 1H), 7.16 (s, 1H), 6.40 (d, *J* = 9.6 Hz, 1H), 4.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.4, 156.3, 147.9, 144.3, 143.8, 132.8, 131.0 (q, *J* = 32.7 Hz), , 127.5, 126.1 (q, *J* = 3.8 Hz), 125.3, 124.0 (q, *J* = 273.0 Hz), 117.1, 115.2, 113.1, 103.1, 63.6. elemental analysis: calcd (%) for $C_{19}H_{11}F_3O_4$ (360.29): C 63.34, H 3.08; found: C 63.54, H 3.01.
15. X-ray structure of **1**: CCDC-1921094.
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19. Synthesis of C2,C3-diarylated Methoxalens (Scheme 2): To a 25 mL oven dried Schlenk tube, aryl bromide (3 mmol), Methoxalen (1 mmol), KOAc (0.294 g, 3 mmol), DMA (2 mL) and $PdCl(C_3H_5)$(dppb) (13.6 mg, 0.02 mmol) were successively added. The reaction mixture was evacuated by vacuum-argon cycles (5 times) and stirred at 150 °C (oil bath temperature) for 16 hours. After cooling the reaction to room temperature and concentration, the crude mixture was purified by silica column chromatography to afford the C2,C3-diarylated Methoxalen.
20. 2,3-Bis(4-chlorophenyl)-9-methoxy-7*H*-furo[3,2-*g*]chromen-7-one **15**: Following the procedure of ref 19, 4-bromochlorobenzene (0.573 g, 3 mmol) and Methoxalen (0.216 g, 1 mmol), affords **15** in 60% (0.262 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 9.6 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.16 (s, 1H), 6.37 (d, *J* = 9.6 Hz, 1H), 4.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.4, 151.5, 146.8, 144.2, 143.8, 135.4, 134.6, 132.7, 131.0, 130.0, 129.9, 129.2, 128.8, 128.3, 128.0, 117.0, 116.6, 115.2, 111.7, 61.6. elemental analysis: calcd (%) for $C_{24}H_{14}Cl_2O_4$ (437.27): C 65.92, H 3.23; found: C 65.99, H 3.08.

Supplementary Material

Experimental procedures, product characterization and copies of the ^{1}H and ^{13}C NMR for all compounds.

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Highlights

- First examples of metal-catalyzed C-H bond functionalizations of Methoxalen.
- One pot access to C2-arylated or C2,C3-diarylated Methoxalen derivatives.
- A variety of substituents on the benzenesulfonyl chlorides and aryl bromides tolerated.
- Commercially available reactants, catalysts and bases.

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