Palladium-catalysed C-H bond functionalisation of 6,6-diphenylfulvenes: an easier access to C1-arylated and C1,C4-diarylated fulvenes

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ABSTRACT: Conditions allowing the palladium-catalysed regioselective direct arylation of fulvene derivatives are reported. The nature of the aryl source exhibits an important influence on the yield. The reaction of fulvenes with aryl bromides gave poor yields; whereas, the use of benzenesulfonyl chlorides gave rise to fulvenes arylated at C1- and C4-positions on the 5-membered ring in good yields. The reaction tolerates various substituents such as nitrile, nitro, fluoro, trifluoromethyl, chloro or even bromo on the benzenesulfonyl chloride.

Fulvenes (Fig. 1) are on the borderline between true aromatic compounds and conjugated dienes, and exhibit high polar character and charge transfer properties. Some fulvene derivatives also display important biological properties such as lorfulfene, which is currently evaluated against castration-resistant prostate cancer. They also exhibit important photophysical properties with possible photovoltaic applications. Fulvenes are also commonly employed as ligands in organometallic chemistry. As a result, there is a continuing interest in the development of versatile methods to access substituted fulvenes.

Figure 1. Structure of fulvene and an example of bioactive fulvene derivative

As most commercially available fulvenes such as 6,6-diphenylfulvene do not present any reactive functional groups, their modification requires the activation of C-H bonds. The Pd-catalysed direct arylation or vinylation of (hetero)aromatics has recently emerged as a very powerful method for the preparation of substituted (hetero)aromatics. However, there are still important limitations for these C-H bond functionalization reactions in terms of regioselectivity and substrate scope. To our knowledge, the Pd-catalysed C-H bond functionalization of fulvenes has not been described so far. Moreover, very few methods allowing the synthesis of C1-arylated fulvenes have been reported. In 1999, Hong et al. described the reaction of 6-(dimethylamino)fulvene with benzoquinones to prepare hetero[6+3] cycloaddition adducts in good yields (Scheme 1, a). The reaction of 1,3-diphenyl-1,3-cyclopentadiene with aldehydes affords 1,3-diphenylfulvene derivatives (Scheme 1, b). With this method, no functionalized aryl substituents were employed. A few methods for the preparation of C2-arylated fulvenes have also been reported. In 2002, Casez et al. described the dehydration of a cyclopentenol to afford (3-cyclohexyldene)cyclopenta-1,4-dien-1-yl)benzene in 48% yield (Scheme 1, c). Recently, the preparation of a few other 2,3-diarylfulvene derivatives has been reported by Nair el al. from 1,6-diarylcyclohexa-1,5-diene-3,4-diones using a N-heterocyclic carbene as organocatalyst (Scheme 1, d).
The Pd-catalysed direct arylation of fulvenes would allow the preparation of arylated fulvenes in only one step, without prefunctionalisation of the fulvene moiety, which represents a considerable advantage (Scheme 1, bottom). In addition, such couplings are expected to tolerate a variety of useful functional groups on arenes, which would allow a straightforward modification of the aryl substituents and hence of the properties of the resulting fulvene derivatives. Therefore, reactivity of fulvenes in Pd-catalysed direct arylation needed to be investigated.

We now (i) report on the influence of the reaction conditions and aryl source in the Pd-catalysed direct arylation of 6,6-diphenylfulvene, and (ii) show the scope of the sp² functionalisation of 6,6-diphenylfulvene.

Using conditions employed for the direct arylation of various heteroaromatics in our previous works,⁷ we initially examined the influence of the nature of base and catalyst for the coupling of 1.5 equiv of 6,6-diphenylfulvene with 1 equiv of 4-bromonitrobenzene using DMA as the solvent (Table 1). The use of KOAc as base and 5 mol % Pd(OAc)₂ as catalyst resulted in the regioselective formation of product 1a (arylation at C1-position on the 5-membered ring, see Fig. 1) but in low yield; whereas, the use of PdCl(C₅H₅)(dppb) catalyst gave no product (Table 1, entries 1 and 2). The use of CsOAc, NaOAc or Li₂CO₃ as bases did not allow to improve the yield in 1a (Table 1, entries 3-5). Benzenesulfonyl chlorides represent useful alternative coupling partners to aryl halides in palladium-catalysed direct arylation.⁹,¹¹ Their use, instead of aryl halides, drastically modify the reaction outcome of some direct arylation due to a change in the catalytic cycle.¹² Moreover, the use of benzenesulfonyl chloride as aryl source is very attractive as the reactions performed with such substrates tolerates a variety of substituents.¹²

Table 1. Influence of the reaction conditions for palladium-catalysed direct coupling of 6,6-diphenylfulvene with nitrobenzene derivatives.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst (mol %)</th>
<th>base</th>
<th>nitrobenzene substituent</th>
<th>solvent</th>
<th>yield in 1a (%)</th>
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<tr>
<td>1</td>
<td>Pd(OAc)₂ (5)</td>
<td>KOAc</td>
<td>Br</td>
<td>DMA</td>
<td>28</td>
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<tr>
<td>2</td>
<td>PdCl(C₅H₅)(dppb)</td>
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<td>Br</td>
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<td>27</td>
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<tr>
<td>4</td>
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<td>Br</td>
<td>DMA</td>
<td>13</td>
</tr>
<tr>
<td>5</td>
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<td>Br</td>
<td>DMA</td>
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</tr>
<tr>
<td>6</td>
<td>Pd(OAc)₂ (5)</td>
<td>Li₂CO₃</td>
<td>Br</td>
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<tr>
<td>7</td>
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<tr>
<td>8</td>
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<td>KOAc</td>
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<td>1,4-dioxane</td>
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<td>9</td>
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<td>&lt;5⁷</td>
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<tr>
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<td>15</td>
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<td>Li₂CO₃</td>
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<td>43⁹</td>
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Conditions: 6,6-diphenylfulvene (1.5 mmol), 4-bromonitrobenzene or 4-nitrobenzenesulfonyl chloride (1 mmol), base (2 mmol), under argon, 4 h, 150 °C, GC and NMR conversions, isolated yields. * 140 °C. b In CPME (cyclopentyl methyl ether) at 110 °C. c In DEC (diethyl carbonate) at 130 °C.

Based on our previous results on Pd-catalysed desulfitative coupling with heteroarene derivatives,¹² we first examined the reaction outcome using 1.5 equiv of 6,6-diphenylfulvene with 1 equiv of 4-nitrobenzenesulfonyl chloride in the presence of 5...
mol % Pd(OAc)$_2$ catalyst and Li$_2$CO$_3$ as the base at 140 °C. Under these conditions, the regioselective formation of 1a in 82% yield was obtained; whereas, no formation of 1b or diarylation product 1c was detected by GC/MS analysis of the crude mixture (Table 1, entry 7). The use of KOAc, NaOAc, CsOAc or K$_2$CO$_3$ as bases led to very low yields in 1a showing the crucial role of the base in such desulfitative couplings (Table 1, entries 8-11). Reactions performed in DMF or DMA gave no product; whereas cyclopentyl methyl ether and diethyl carbonate afforded 1a in low yields (Table 1, entries 12-15).

Finally, we also studied the reactivity of benzenesulfinic acid sodium salt as the coupling partner instead of 4-nitrobenzenesulfonyl chloride under the same reaction conditions. However, no formation of coupling product was detected by GC–MS analysis of the crude mixture.

Using 5 mol % Pd(OAc)$_2$ catalyst, Li$_2$CO$_3$ base in 1,4-dioxane, the scope of the Cl-arylation of 6,6-diphenylfulvene with various benzenesulfonyl chlorides was investigated (Scheme 2). Moderate yields of 54% and 52% in 2 and 3 were obtained by coupling of 6,6-diphenylfulvene with benzenesulfonyl chlorides bearing fluoro or methyl para-substituents. Products 2 and 3 were only observed in trace amount when aryl bromides were employed as aryl source; whereas, from the more electron deficient 4-bromobenzonitrile and 6,6-diphenylfulvene, the desired product 4 was obtained in 38% yield. The higher yields in 1a and 4 obtained with electron deficient aryl bromides might come from their easier oxidative addition to palladium. Then, we examined the reactivity of a few ortho-substituted benzenesulfonyl chlorides. Good yields of 62% and 61% in 5 and 6 were obtained from 2-chloro- and 2-cyano-substituted benzenesulfonyl chlorides. From 2-nitrobenzenesulfonyl chloride and 6,6-diphenylfulvene, product 7 was only obtained in 47% yield due to the formation of some degradation products. The use of 2-bromonitrobenzene as aryl source did not allowed to improve the yield in 7. Benzenesulfonyl chlorides containing two Cl, CF$_3$- or NO$_2$ substituents also gave the expected 1-arylfulvenes 8-10 in good yields. As the use of ArSO$_2$Cl as coupling partners in Pd-catalysed direct arylation tolerates bromo substituents, the behaviour of two bromobenzenesulfonyl chlorides for coupling with 6,6-diphenylfulvene was investigated. Reaction performed in the presence of ArSO$_2$Cl containing a 2-bromo- or 3,4-dibromo-substituents gave 11 and 12 in satisfactory yields without cleavage of the C-Br bonds, allowing further transformations. Polyfluorinated molecules are ubiquitous in medicinal chemistry, owing to fluorine atom properties which induces a dramatic change in the molecules behaviour. The use of ArSO$_2$Cl containing fluoride atoms should offer a straightforward route to polyfluorinated fulvenes. From 2,3,4-trifluorobenzenesulfonyl chloride and 6,6-diphenylfulvene, the desired product 13 was obtained in 70% yield. The regioselectivity of these arylation was unambiguously assigned by X-ray analysis of 10 (Scheme 2). It should be mentioned that for the reactions with 4-fluoro, 4-methyl- and 2-chloro-substituted benzenesulfonyl chlorides, low amounts of diarylated fulvenes were detected by GC/MS analysis of the crude mixtures.

Under the same reaction conditions, but using 3 equiv of benzenesulfonyl chloride derivative, the access to symmetrical 1,4-diarylfulvenes was found to proceed in moderate to good yields (Scheme 3). From 4-chloro- or 3,4-difluoro-substituted benzenesulfonyl chlorides, the 1,4-diarylated fulvenes 14 and 15 were obtained in 62% and 67% yields, respectively. The 1,4-diarylated fulvene derivative 16 was obtained in a slightly lower yield of 60% from 4-bromobenzenesulfonyl chloride. Again no cleavage of the C-Br bonds was observed.

The one pot direct C1,C4-diarylation of 6,6-diphenylfulvene is possible (see scheme 3); however, the major advantage of such direct arylation is to allow the formation of 1,4-diarylated fulvenes containing two different aryl groups via successive arylation. Using a set of benzenesulfonyl chlorides and (2-(4-nitrophenyl)cyclopenta-2,4-dien-1-ylidene)methylene)dibenzene 1a, under the same reaction conditions than for the first arylation, the synthesis of such non-symmetrically substituted 1,4-diarylfulvenes was studied (Scheme 4). In all cases, good to high yields in the desired products 17-25 were obtained. The reaction tolerates both electron-withdrawing and electron-donating substituents on the benzenesulfonyl chloride. Moreover, the reaction with 2-
bromobenzensulfonyl chloride gave 23 in 78% yield, again without cleavage of the C-Br bond.

Scheme 4. Palladium-catalysed direct C4-arylation of C1-arylated 6,6-diphenylfulvene 1a.

In summary, we have demonstrated that the Pd-catalysed C-H bond functionalisation of fulvenes is possible when appropriate reaction conditions are employed. The reaction of 6,6-diphenylfulvene with a set of benzenesulfonyl chlorides in the presence of Pd(OAc)₂ catalyst affords regioselectively the C1-arylated fulvenes. Moreover using an excess of benzenesulfonyl chlorides or from C1-arylated fulvenes, the formation of C1,C4-diarylated fulvenes also proceed in good yields. The reported conditions offer routes for fast and direct access to aryalted fulvene derivatives from commercially available compounds, catalyst and inexpensive base. This protocol is applicable to a range of functions on the benzenesulfonyl chloride, including reactive ones. Such functional group tolerance should allow the easy modification of these products, a strategy enabling the tuning of their properties.

ASSOCIATED CONTENT
Supporting Information
Proposed catalytic cycle, experimental procedures, ¹H and ¹³C NMR of all compounds, UV-vis absorption spectra of products 3, 9, 10, 13, 14, 19, 21. X-ray analysis of 10. The Supporting Information is available free of charge on the ACS Publications website.

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Author Contributions
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