Catalyst-Free Synthesis of O-Heteroacenes by Ladderization of Fluorinated Oligophenylenes

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Abstract: A novel catalyst-free approach to benzoannulated oxygen-containing heterocycles from fluorinated oligophenylenes is reported. Unlike existing methods, the presented reaction does not require an oxygen-containing precursor and relies on an external oxygen source, potassium tert-butoxide, which serves as an O2 synthon. The radical nature of the reaction facilitates nucleophilic substitution required for the complete annulation. Also demonstrated is the applicability of the method to introduce five-, six-, and seven-membered rings containing oxygen, whereas multiple annulations also open up a short synthetic path to ladder-type O-heteroacenes and oligodibenzo[cd]furans.

Organic π-conjugated materials have been under constant focus in academia and industry during recent years. Due to their outstanding optical and charge properties, they play a key role in the development of organic light-emitting diodes (OLEDs),[1] organic field-effect transistors (OFETs)[2,3] and organic photovoltaics (OPVs).[4] Herein, we report a new catalyst-free approach to a wide range of O-heteroacenes by “ladderization” of fluorinated oligophenylenes (LooP).

Activated, that is, containing strong electron-withdrawing groups, fluorobenzene derivatives are known to undergo molecular substitution of fluorine in unactivated aromatics is less common.[47] Nevertheless, their outstanding optical and charge properties make them a potential functionality as it, in contrast to other C-Hal bonds, remains intact during conventional Pd-catalyzed C-(aryl)-F bond coupling.[48–50] Therefore, the direct transformation of C–F bond into C–O functionality appears to be a highly attractive approach to O-heteroacenes.

Figure 1. Synthetic approaches to dibenzofuran and scope of this work.

Among the main reasons for such a late splash of interest are synthetic difficulties connected to lability issues of furans. Meanwhile, a fusion of furan ring(s) to an all-carbon aromatic system appears to be a viable strategy for obtaining stable furan derivatives (also called ladder-type O-bridged heteroacenes[20]).[21] Dibenzo[bd]furan (1) serves as a model target compound for the development of new synthetic approaches. Despite a large number of works aimed to develop facile incorporation of the furan ring, the principal synthetic strategies are not so numerous and break down into few categories depicted in Figure 1. The final step includes either transition metal-catalyzed C–C coupling[52–56] or C–O bond creation[17,27–35] which is usually implemented via a two-step deprotection/dehydration procedure.[10,14,18,36–38]

With rare exceptions,[39] the existing synthetic approaches to the dibenzofuran core require an oxygen atom in the precursor’s structure. Meanwhile, a technique enabling the incorporation of oxygen and simultaneous formation of a heterocycle could simplify overall synthesis. In the ideal case, the technique should exploit a functionality that stays unreactive otherwise. In this context, C(aryl)-F bond appears to be a potential functionality as it, in contrast to other C-Hal bonds, remains intact during conventional Pd-catalyzed C-(aryl)-C(aryl) couplings. Therefore, the direct transformation of C–F bond into C–O functionality appears to be a highly attractive approach to O-heteroacenes.

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Activated, that is, containing strong electron-withdrawing groups, fluorobenzene derivatives are known to undergo substitution with O-nucleophiles,[40–46] whereas such intermolecular substitution of fluorine in unactivated aromatics is less common.[47]
We started our investigations with the reactions of 2,2'-difluoro-1,1'-biphenyl (1a) with potassium hydroxide. We have carried the reaction out in HMPA (hexamethylphosphoramide) and under microwave irradiation, which greatly accelerates S_N_Ar reactions. Although the reaction does not proceed in the presence of KOH, the substitution of the latter with tBuOK enables the formation of 1b in 10% yield (Table 1, entry 2). Increasing the amount of tBuOK up to 6 equiv, we have achieved an excellent (93%) yield of 1b (Table 1, entry 6).

Despite the anticipated stability of tert-butyl ether under basic conditions, intermediates containing tert-but oxy substituents were not found in the mixture. The reaction also proceeds in other aprotic solvents such as DMA and DMSO, although in slightly lower yields (Table 1, entry 7–8). Interestingly, 1b was not detected in the experiment with MeOK (Table 1, entry 9). In the case of EtOK the yields do not exceed 20% [Table 1, entry 10; more detailed information is in the Supporting Information (SI)].

Based on the screening, tBuOK can be considered as an optimal oxygen source and the O^- synthon, which enables one-pot substitution of two fluorines yielding benzoannulated furan derivatives. To test the viability of this claim and to investigate the scope and limitation of this reaction, we have studied other fluorinated precursors 2a–11a bearing halogen, methyl, and methoxy substituents (Table 2).

Dibromodibenzo furans 2b and 3b were synthesized in 70% and 92% yields, respectively. Although the method seems to be not compatible with C-I, the tolerance towards C-Br functionality can be achieved by decreasing the reaction temperature to 80°C. As of methylated representatives 6b–8b, the yields vary from 60 to 70%. The yields are slightly decreased due to partial demethylation, the mechanism of which will be discussed later. Notably, the reaction conditions are suitable even for the synthesis of dibenzo furans with strong donor substituents such as OMe group. Thus, 9b bearing methoxy groups in 4- and 8-positions was isolated in 44% yield. It is also interesting, that the reaction reveals a pronounced regioselectivity to fluorine substituents. We have found that the nucleophilic substitution process favors fluorine atoms in 2,2'-positions since 4,8-difluorodibenzofuran (10b) was isolated in 89% yield. However, if biphenyl bears fluorine atoms at 2,2',6,6'-positions, it is not possible to stop the reaction at the formation of 1,9-difluorodibenzofuran, whereas a complex mixture of different oxygen-containing compounds is observed. Meanwhile, the addition of 12 equiv of potassium tert-butoxide allows oxodefluorination and full hydrolysis of the two remaining C–F bonds yielding 11b in 84% yield. We assume that the observed phenomena are connected to mutual activation of C–F functionalities in close proximity, while the second annulation in the case of 11a does not occur due to strain energies needed to be overcome. Surprisingly, we did not observe and isolate any reasonable products in the case of 2,2',4,4'-tetrafluoro-1,1'-biphenyl. We assume that increased acidity of the hydrogen between fluorines facilitate the formation of arene, which leads to the formation of inseparable mixture of compounds. The reaction poorly tolerates CF_3 groups. The furan 12b was isolated only in 4% yield. Moreover, the conditions are also suitable for the synthesis of π-extended

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**Table 1:** Reaction of 2,2'-difluoro-1,1'-biphenyl with different oxygen sources.

| Entry | Oxygen Source | Solvent | Yield [%] |
|-------|---------------|---------|-----------|
| 1     | KOH (2 equiv) | HMPA    | 0        |
| 2     | tBuOK (2 equiv) | HMPA  | 10        |
| 3     | tBuOK (3 equiv) | HMPA  | 25        |
| 4     | tBuOK (4 equiv) | HMPA  | 41        |
| 5     | tBuOK (5 equiv) | HMPA  | 82        |
| 6     | tBuOK (6 equiv) | HMPA  | 93        |
| 7     | tBuOK (6 equiv) | DMSO  | 78        |
| 8     | tBuOK (6 equiv) | DMA   | 72        |
| 9     | MeOK (6 equiv) | HMPA   | 0        |
| 10    | EtOK (6 equiv) | HMPA   | 20        |
| 11    | KOH (6 equiv) | HMPA   | 0        |

[a] Estimated by ^1^H NMR spectroscopy, [b] Yield of isolated product.

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**Table 2:** Synthesis of substituted dibenzofurans from 2,2'-difluoro-1,1'-biphenyl.

| Synthesis | Substituents | Yields [%] |
|-----------|-------------|-----------|
| 1b        |            | 10b, 89    |
|           |            | 11b, 84    |
|           |            | 12b, 4     |
|           |            | 13b, 93    |

Yields are those of the isolated products. [a] 80°C. [b] 12 equiv of tBuOK from 2,2',6,6'-tetrafluorobiphenyl.
homologs of dibenzofuran. Thus, dinaphtofuran 13b was isolated in excellent 93% yield.

Another aspect that we find extremely, if not the most, important is the possibility to implement multiple annulations in one step (Figure 2). Having the established synthetic protocol, we have turned our attention to benzobisbenzofurans 14b–16b containing two oxygen atoms. To our pleasure, excellent efficiency of the double-annulation enables target benzobisbenzofurans in high (up to 91%) yields. Furthermore, the consequential formation of six C–O bonds enables a triple annulation of 17a in 92% yield making the new ladder-type heteroacene 17b readily available through a three-step procedure. Rather unexpectedly, fluorinated meta-oligophenylene 18a transforms solely into trisdibenzo-furan 18b instead of a complicated mixture. Surprisingly high 90% yield indicates that the process has certain preferences over C-F bond substitutions’ sequence and, presumably, is not connected with self-correction (see the SI).[54]

The incorporation of benzoannulated oxygen-containing heterocycles other than five-membered is less-known transformations.[55–60] However, the compounds containing six- and seven-membered rings have some promising applications as OLED materials.[61,62] To test whether our method is capable of tackling such synthesis, we have obtained fluorinated precursors 19a and 20a, which under reactionary conditions transformed into 19b containing pyrane ring and 20b containing oxepine ring (Figure 3). Extrapolation of the approach to other oxepines has been proved successful as 21b and 22b were obtained in excellent 90% and 85% yields.

From the mechanistic perspective, the reaction can be formally broken down into three steps: substitution, deprotection, and second substitution (Figure 4). While the last step represents a well-established S_NAr process exploited for the synthesis of dibenzofurans,[17] the rest of the mechanistic route is less trivial and requires thorough consideration.

To gain additional data, we have exposed the model substrate 23a to the following reaction conditions. Thus, we
have found that in the presence of 3 equiv of iBuOK, the reaction terminates at the formation of the 2-(tert-butoxy)-1,1’-biphenyl 23b, which was isolated in 60% yield. Meanwhile, using 6 equiv of iBuOK, we isolated [1,1’-biphenyl]-2-ol in 93% yield (Scheme 1A). These facts confirm that the transformation occurs via tert-butyli ethers. However, the mechanism of de-tert-butylation remained uncertain. Capturing the volatile products with bromine water, we have observed exclusively brominated acetone/C29 derivatives. For single electron transfer (SET) reactions,[64] we conclude that rapidly interacts with the formed radical 1f undergoes β-scission releasing isobutylene and radical 1g which is reduced by the following SET. Isobutylene was not detected apparently due to the fast radical polymerization, which leads to the increased viscosity of the obtained reaction mixture.

The initiation step including the substitution of fluoride with tert-butoxy anion is the most crucial and at the same time intricate step. Despite low nucleophilicity of iBuOK and its high basicity, aryne mechanism of the substitution is excluded due to the successful transformations of ortho-substituted substrates for example, 3b and 7b. As mentioned earlier, iBuOK can undergo SET and initiate S_{RN1} type of reactions.[63] However, the absence of defluorinated products and dimers evidences against this mechanism. Meanwhile, deiodination and partial demethylation (in the cases of 4b–8b) indicate the radical character of the reaction. The possibility of the alternative radical S_{RN2} mechanism has been discussed elsewhere and is considered as an unlikely event due to charge repulsion and orbital arguments.[66]

Having excluded these mechanisms we end up with the last possible radical pathway (see the SI). SET to 1a generates radical-anion 1c that rapidly interacts with the formed tert-butoxy radical within the solvent cage.[67] Although it is rather problematic to distinct this mechanism from classic S_{Ar} mechanism of substitution of fluorine in electron-rich molecules (9a), low nucleophilicity of iBuOK, and stability of fluoroarene radical-anions[68] prove at least partial participation of the SET-induced S_{Ar} pathway.[69] Moreover, it is impossible to exclude that both mechanisms occur independently since unlike common radical processes the intermediates cannot be quenched with common radical traps such as TEMPO.[70] This outcome was indeed observed in our experiment.

In summary, we have developed a synthetic tool allowing the direct transformation of 2,2′-difluorinated biphenyl moiety into dibenzofuran fragment. The reaction enables multiple annulations providing a facile pathway towards various ladder-type oxygen heteroacenes and dibenzofurans oligomers. Besides oxygen-containing pentagons, the possibility to obtain derivatives of xanthene and oxepine has also been shown.

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Conflict of interest

The authors declare no conflict of interest.

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