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COMMUNICATION

Intramolecular Aryl-Aryl Coupling via C-F Bond Activation Tolerant towards C-I Functionality

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Herein we report a transition-metal free activation of the particulary stable aromatic carbon-fluorine bond allowing to perform intramolecular Aryl-Aryl coupling which is orthogonal to the carbon-iodine functionality.

Aryl-Aryl coupling is undoubtedly the most crucial step in the construction of complex polycyclic aromatic hydrocarbons (PAHs), including nanographenes and carbon nanoribbons[1–4], whereas the C_{aryl}-Hal bond serves as a valuable functional group enabling metal catalysed C-C coupling. In this regard, C-Cl, C-Br, and C-I have found broad application enabling selective Aryl-Aryl coupling under mild conditions. Meanwhile, the C-F bond is one of the strongest bonds available in organic chemistry; therefore, fluorine is commonly perceived as a robust and unreactive substituent but not as a useful functionality. Nevertheless, several general C-C coupling techniques based on C-F bond activation have recently been developed[5–10]. Most methods are based on transition metal C-F bond activation, which leads to the lack of orthogonality between C-Hal bonds (which can be generally used only in the sequence corresponding to the decrease of their reactivity (I>Br>Cl>F)). This problem theoretically can be solved via utilizing main-group catalysts, which have higher affinity to the fluorine atom according to the Pearson acid-base concept (HSAB concept, Hard and Soft Acids and Bases) Among possible solutions, the most prolific approaches of Lewis acid aromatic C-F bond activation are proposed by Siegel[11,12], Ichikawa[13–16] and Amsharov[17–19]. Alumina-mediated C-F bond activation, proposed by our group, seems to surmount this task enabling the rational and regioselective synthesis of fluor-, chlor-, and brominated non-planar PAHs. In our current systematic investigation of the method's capabilities we demonstrate that the strongest C-Hal bond (C-F) can be effectively activated in presence of the weakest (C-I), whereas the latter remains intact (Fig. 1). Additionally, a tolerance towards dibenzothiophene and dibenzofuran cores is also reported.

In this work, we aimed to investigate the influence of different structurally embedded functional groups on the outcome of the alumina-promoted cyclodehydrofluorination (CDHF). The triphenylene's formation was used as a simplest model for CDHF reaction. Nineteen fluorinated terphenylens carrying alkyl groups (Me, t-Bu), heteroatoms (N, O, S), and halogens (Cl, Br, I) were synthesized and investigated as summarized in Scheme S1 (see ESI).

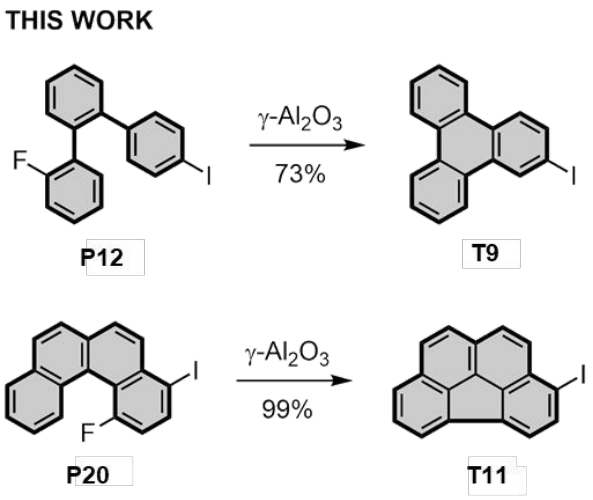

Figure 1: Two representative examples showing effective aryl-aryl coupling leading to the hexagon/pentagon formation via C-F bond activation orthogonal to the C-I functionality.

All CDHF reactions were carried out in the presence of activated γ-aluminum oxide using microwave heating and the reaction outcome was monitored by HPLC/UV analysis and NMR spectroscopy. Firstly, two alkyl-substituted precursors, **P1** (methyl) and **P2** (*tert*-butyl), were investigated. 2-fluoro-4''-

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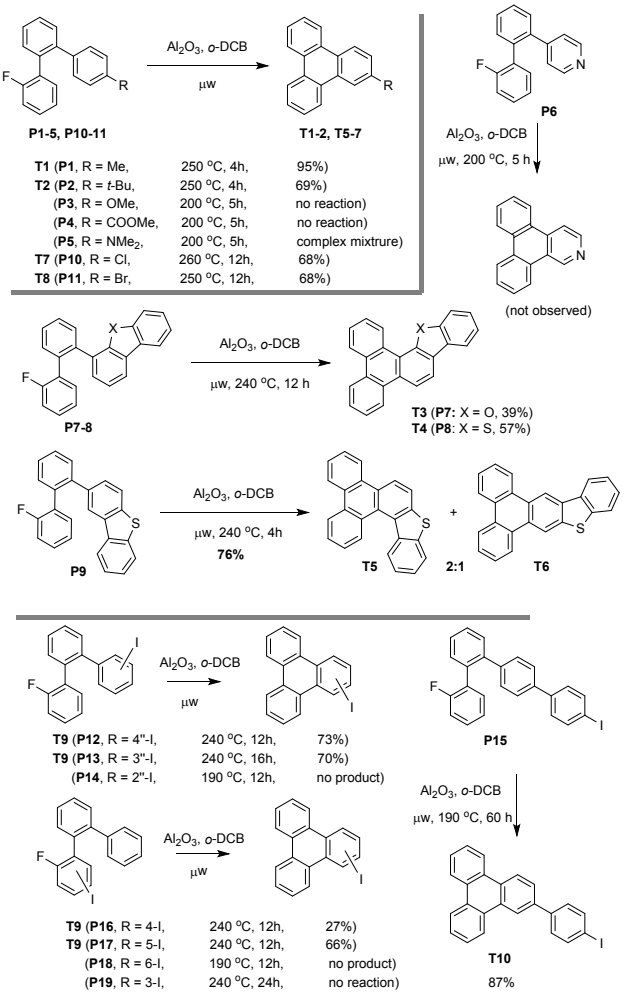
methyl-1,1':2',1''-terphenyl (**P1**) was condensed to the target 2-methyltriphenylene (**T1**) at 250 °C after 4 h. Pure **T1** was isolated in 95 % yield after simple extraction with toluene, followed by solvent evaporation (Scheme 1). Under the same conditions 4''-(*tert*-butyl)-2-fluoro-1,1':2',1''-terphenyl (**P2**) was cyclized to **T2** in 69 % yield (Scheme 1). According to HPLC-UV/vis analysis of the reaction mixture the only impurities found were residues of starting compound and traces of unsubstituted triphenylene (see ESI).

Tolerance or its absence towards functionalities containing heteroatoms is an extremely important aspect of the techniques. Therefore, we aimed to explore the applicability of CDHF for the synthesis of PAHs bearing different hetero-functionalities. Our attempts to implement CDHF of **P3** and **P4** (bearing methoxy- and methoxycarbonyl-substituents, respectively) did not reveal any conversion (see ESI). Additionally, we have exposed **P5** and **P6** (bearing dimethylamine and pyridine moieties) to CDHF conditions. For precursor **P5**, three main products were detected according to HPLC/UV analysis which were separated and characterized by NMR spectroscopy (see ESI). However, based on the number and distribution of signals in the corresponding spectra it was not possible to unambiguously assign chemical structures to the products formed. As a matter of fact, ^{1}H and ^{19}F NMR spectra revealed that the products obtained do contain neither fluoro- nor dimethylamino- substituents. In the case of **P6**, the formation of a complex mixture was observed (see ESI). According to HPLC-UV/vis analysis none of the products was identified as desired dibenzo[*f*,*h*]isoquinoline. We suggest that unsuccessful CDHF of precursors **P3**-**P6** were connected with strong Lewis basicity of the polar substituents, which coordinate on the active Lewis acidic Al(III) sites of the alumina and prevent the C-F activation.

On the other hand, oxygen or sulfur atoms embedded into full aromatic system exhibit way less tendency towards coordination with metals and are often used as rigid platforms for ligands in catalysis[20,21]. We synthesized two precursors **P7** and **P8** containing dibenzofuran or dibenzothiphene moieties and carried out CDHF at 240 °C. The expected products were isolated in 39% and 57% respectively. The condensation of precursor **P9** at 240 °C for 4 h resulted in the clean conversion to the two expected isomers **T5** and **T6** in 2:1 ratio in 76% overall yield. Noteworthy, that after exposure to air a third minor product was observed in the respective HPLC profile (see ESI). This minor product was isolated with 5 % yield and assigned to naphtho[1',2',3',4':4,5]triphenyleno[1,12-*bcd*]thiophene (see ESI).

Finally, three halogenated terphenyls with chlorine (**P10**), bromine (**P11**), and iodine (**P12**) were subjected to CDHF conditions. According to HPLC analysis the cyclization of 4''-chloro-2-fluoro-1,1':2',1''-terphenyl (**P10**) carried out at 250 °C was not completed even after 12 h. This goes in line with the earlier supposed Friedel-Crafts-like mechanism, as phenyl rings substituted with electron withdrawing groups are less prone to undergo cationic attack[22]. Therefore, the reaction temperature was further increased to 260 °C. Under these condition the full conversion was achieved after 12 h yielding target 2-chlorotriphenylene **T7** in 68 % yield. Rather similar efficiency was observed for cyclization of the brominated precursor **P11** to **T8** (250 °C, 12 h, 68 % yield). Iodinated compound **P12** was condensed on alumina at 240 °C for 12 h. The reaction mixture was analyzed by HPLC/UV analysis which displayed full and clean conversion into desired **T9** in 73 % yield. Worth mentioning that only trace amounts of unsubstituted triphenylene were detected (HPLC-UV/vis analysis) indicating selective C-F bond activation in the presence of weaker C-I bond, which became possible presumably due to the big differences between Al-F and Al-I bond energies (650 vs 370 kJ/mol)[23].

Scheme 1: Synthesis of triphenylenes **T1–10** from terphenyl



precursors **P1–19**. Reaction conditions: **P1–10** (~10 mg), γ-Al_2O_3 (2.5–3 g), *o*-DCB (4 mL). Reaction outcome and yields of isolated products.

In order to study the scope and limitations of the C-F bond activation in the presence of the C-I bond we designed precursors containing the iodine in the ring of the attack (**P13** and **P14**), one precursor where iodine is placed far away from the center of the CDHF (**P15**) and four precursors containing iodine in the same ring as fluorine (**P16**-**P19**).

In all causes the formation of 1-iodotriphenylene was found to be prohibited since the formation of unsubstituted triphenylene was found in the reaction mixtures of **P14** and **P18** and no reaction was observed in the case of **P19**. This outcome can be explained by the sterical hindrance of the iodine group in the *bay*-region in the target molecule which prevents the cyclization or leads to the loss of the iodine during the reaction. Important to note that 1-fluorotriphenylene (the product of the cyclodehydroiodination) was not found in any of the reaction mixtures.

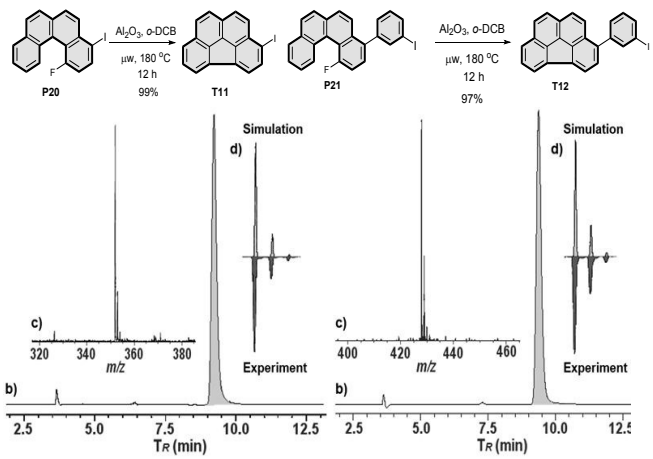


Figure 2: Selective conversion of precursors **P20** and **P21** into target PAHs **T11** and **T12**. Reaction conditons: γ-Al_2O_3, *o*-DCB, µW, 180 °C, 12 h. b) HPLC profile as obtained after reaction showing clean convertion. HPLC conditions: Cosmosil-PBr column, eluent DCM/MeOH 1:1, 35 °C, flow rate 1.0 mL/min. c) LDI-MS spectrum of the reaction mixture as obtained after reaction (without purification), showing high selectivity of the cyclization and d) calculated and experimentally observed isotopic distribution MS patterns of **T11** and **T12**, respectively.

On the other hand, most of CDHF leading to **T9** were successful and only in the case of **P16** bearing iodine in meta-position to fluorine significant loss of iodine was observed. Cyclization of **P15** was possible already at 190 °C, but extended time was needed to achieve the high 87% yield. No loss of iodine was observed in this case.

In order to exclude the possible activation of the C-Hal bond by neighboring π-system, we additionally designed two precursors (2-iodo-1,1':2',1''-terphenyl 1-(2-iodophenyl)naphthalene (**PS1**) and 1-(2-iodophenyl)naphthalene (**PS2**)), which hypothetically can lead to the five- and six-member ring closure via C-I activation. Both precursor were found to be inactive when exposed to activated alumina (see scheme S4 in ESI) confirming the selective activation of C-F bond by alumina.

Worth mentioning that regioselective aryl-aryl couplingin the presence of C-I bond is an important and fundamental aspect, which opens up a synthetic approach towards iodinated PAHs inaccessible otherwise and interesting as building blocks for synthesis of large complex carbon-based architectures through bottom-up approach. Especially, C-I is a very potent functionality for Ullmann-like coupling carried out on metal[24] and metal oxide[25] surfaces.

In this context, pentagons-containing iodinated PAHs represent particularly interesting blocks as incorporation of five-membered rings drastically alters the structure and the properties of the molecule and gives rise to multiple peculiar features. As a matter of fact, alumina-provoked CDHF enables effective pentagon formation[22,26], and in the light of the obtained evidences, we demonstrate the possibility to incorporate pentagons via C-F activation preserving C-I functionality.

1-Fluoro-4-iodobenzo[*c*]phenanthrene (**P20**) and 1-fluoro-4-(3-iodophenyl)benzo[*c*]phenanthrene (**P21**) were chosen as smallest model compounds containing cove region. Both precursors have undergo the CDHF transformation at 180 °C within 12 h yielding desired **T11** and **T12** in nearly quantitative yields. Noteworthy, both target compounds **T11** and **T12** did not require any additional purification steps after extraction from alumina (Fig. 2).

In summary, we have investigated the scope and limitations of the CDHF approach regarding functional group tolerance. Several fluorinated precursors with different functional groups, ranging from alkyl residues and heteroatoms to halogens, were condensed on alumina and the reactions investigated for product formation. Alkyl groups were found to be tolerant in the CDHF process. Precursors with Lewis basic functionalities were found to be not suitable for CDHF. In contrast sulphur or oxygen containing (in the form of dibenzothiophene or dibenzofuran) precursor **P7-P9** were surprisingly clean converted to desired target molecules without any sign of side product formation. Worth mentioning that this transformation provide facile access to the interesting family of sulphur and oxygen containing PAHs. Finally, it was shown that halogens, and especially C-I bonds, remain intact under CDHF.

In general, our results show that the C-F bond, which is widely believed to be the most passive functionality, can be selectively activated in the presence of various functionalities including very labile C-I bond and thus, can be considered as a useful functional group allowing effective orthogonal aryl-aryl coupling. In particular, the unexpectedly discovered tolerance to the carbon-iodine bond adds the reaction to the collection of powerful synthetic tools allowing direct synthesis of iodinated PAHs, which are exceptionally useful building blocks for the construction of complex carbon-based architectures.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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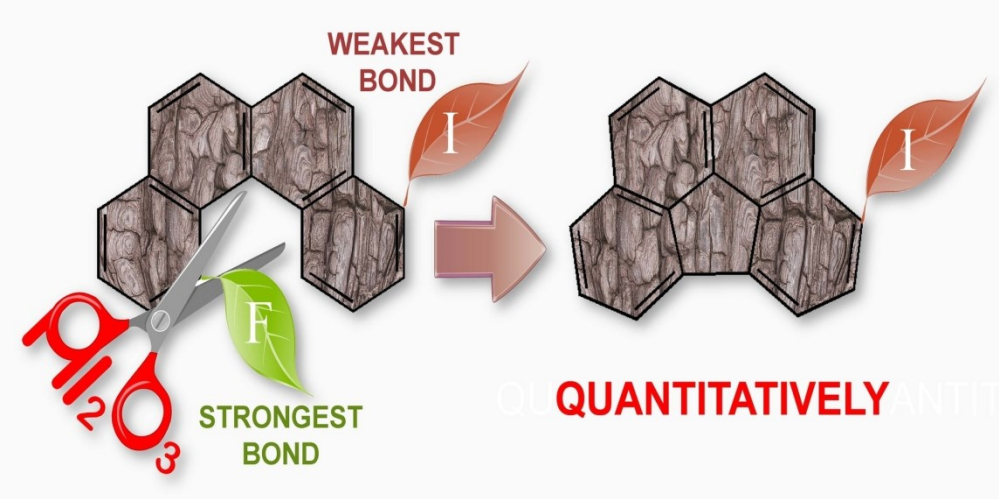

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