Showcasing research from Professor Amsharov laboratory, Marthin-Luther University, Halle (Saale), Germany.

Regioselective terminal bromination of fluorinated oligophenylenes

In the presence of excess iron, terminal bromination of fluorinated biphenylenes and oligophenylenes proceeds at room temperature, delivering up to 98% yield. Iron shields internal rings, "deflecting" Br_2 to the termini, enabling scalable synthesis with exceptional regioselectivity and operational simplicity.

Image reproduced by permission of Konstantin Amsharov from *Chem. Comm.*, 2025, **61**, 16194.

As featured in:

See Nour-Eddine El Alaoui and Konstantin Y. Amsharov, *Chem. Commun.*, 2025, **61**, 16194.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

Registered charity number: 207890

ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2025, **61**, 16194

Received 2nd September 2025,
Accepted 24th September 2025

DOI: 10.1039/d5cc05074j

rsc.li/chemcomm

Regioselective terminal bromination of fluorinated oligophenylenes

Nour-Eddine El Alaoui and Konstantin Y. Amsharov *

Herein, we demonstrate an unprecedentedly selective terminal bromination of fluorinated biphenylenes and oligophenylenes in the presence of excess metallic iron. The reaction can be carried out under ambient conditions at room temperature, yielding the target compounds with up to 98% yield. The high regioselectivity and scalability make this approach superior to existing methods.

Bromoarenes are essential building blocks in the bottom-up synthesis of carbon-based nanostructures. Electrophilic aromatic substitution using molecular bromine remains a powerful synthetic tool, providing facile access to this class of compounds. However, direct bromination often suffers from low selectivity and is rarely applicable to strongly deactivated, fluorine-substituted oligophenylenes. Terminally brominated fluoro-oligophenylenes have been identified as crucial intermediates in the synthesis of intricate carbon-based nanomaterials. The most notable examples are summarized in Fig. 1. Thus, it was shown that HF-zipping of fluorinated oligophenylenes *via* alumina mediated C–F bond activation[1,2] provides facile access to various pristine nanographenes.[1] Kolmer *et al.* reported a challenging synthesis of nanographenes and nanoribbons, by enabling intramolecular fluorine promoted aryl–aryl coupling directly on non-metallic titania surfaces.[3,4] In our group a wide range of heteroacenes were prepared by ladderization of fluorinated oligophenylenes.[5–7] Recently, Gottfried *et al.* reported the synthesis of a unique nonbenzenoid carbon allotrope *via* intermolecular aryl–aryl coupling of fluorinated polyparaphenylene, demonstrating that the cyclodehydrofluorination approach is a powerful tool in the on-surface synthesis.[8] Finally, Itami *et al.* reported unprecedented synthesis of thiophene-fused aromatic belts from fluorinated cycloparaphenylene.[9]

In all of the aforementioned cases, terminally brominated fluorooligophenylenes were employed as key intermediates (Fig. 1). Since fluorinated oligophenylenes are usually constructed by Suzuki coupling, brominated oligophenylenes cannot be obtained directly. In these studies, the introduction of protective groups or masked bromofunctionalization was employed to overcome this issue. Alternatively, a post synthetic *ortho* lithiation-bromination approach can be applied for the introduction of bromine to fluoroarenes.[10–12] However, extended fluoro aromatic scaffolds frequently pose a challenge to lithiation due to low solubility and low stability of intermediates. Direct bromination appears to be a significantly more attractive approach due to the simplicity of the reaction and its scalability. However selective bromination of oligophenylenes has rarely been reported.[13–16] The main reason lies in the large number of centers for electrophilic attack, which leads to a lack of regioselectivity, yielding a complex mixture.

From this perspective, selective bromination of fluorinated oligophenylenes appears even more challenging, as the bromination of the strongly deactivated fluorine-substituted π-system requires harsh conditions, which could further reduce selectivity. In this work, we demonstrate that direct bromination of fluorinated oligophenylenes and model fluorinated biphenylenes using an excess of iron results in unprecedentedly high regioselectivity, yielding terminally brominated oligophenylenes with high yields. The scope and limitations of the reaction are investigated on variously fluorinated biphenylenes and several *ortho*-, *meta*-, and *para*-oligophenylenes.

The terminally dibrominated oligophenylenes serve as ideal starting materials for Pd-catalyzed cross-coupling reactions, enabling the introduction of additional terminal phenyl units. Furthermore, the selective bromination–Suzuki cross-coupling cycle can be repeated multiple times. This offers exceptional flexibility in designing fluorinated oligophenylenes with complex architectures.

In general, this approach provides easy access to differently functionalized oligophenylenes, as the bromine group can be readily converted into various functional groups *via* transition metal-catalyzed reactions.

2,6-Difluorotoluene (**1**) was chosen as the starting material for the synthesis of fluorinated *meta*-phenylenes, which serve as

Institute of Chemistry, Organic Chemistry, Martin-Luther-University, Halle-Wittenberg Kurt-Mothes-Strasse 2, 06120 Halle, Germany. E-mail: konstantin.amsharov@chemie.uni-halle.de

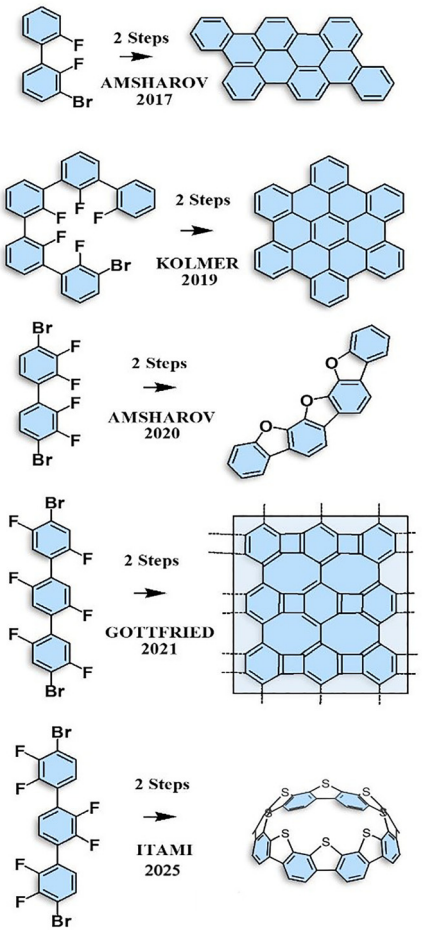

Fig. 1 Representative examples of terminally brominated fluorooligophenylenes employed as key intermediates in the synthesis of carbon-based nanomaterials.

promising building blocks for the construction of fluorinated phenylene-based macrocyclic systems. The presence of a methyl group enables regioselective lithiation and enhances the solubility of the target oligophenylenes. We initiated the synthesis with *ortho*-lithiation of 2,6-difluorotoluene, followed by the addition of 2 equivalents of copper(II) bromide at −78 °C, which promoted homocoupling to afford compounds **2**, **3**, and **4** in yields of 32%, 18%, and 7%, respectively (Fig. 2). Structural assignments were confirmed using ^{1}H, ^{19}F, and ^{13}C NMR spectroscopy, as well as mass spectrometry.

Compound **2** was selected as a model system to explore *ortho*-functionalization relative to fluorine, using butyllithium chemistry to introduce either an iodine or a boronic acid group. Various iodine sources, including elemental iodine and 1,2-diiodoethane, as well as boron sources such as trimethyl borate and isopropoxy pinacolborane, were tested. However, in all cases, no reaction was observed (Fig. 2).

Following unsuccessful attempts to introduce iodine or boronic acid at the *ortho* position, we turned to direct halogenation using the conventional iron catalysed bromination. Initial treatment of the substrate **2** with 2 equivalents of iron and 10 equivalents of bromine resulted in a complex mixture that

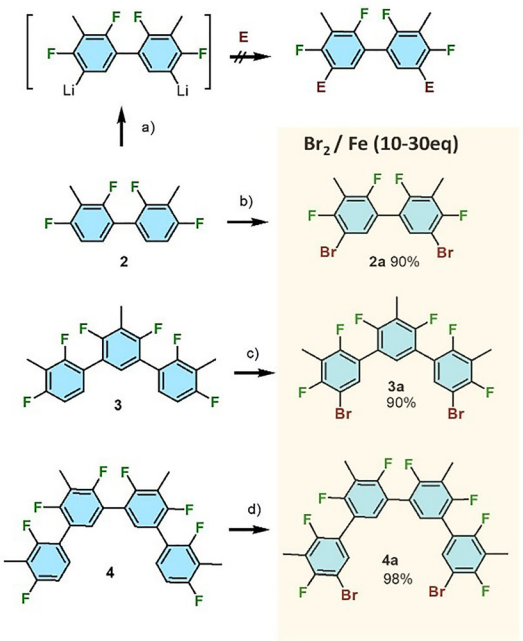

Fig. 2 Bromination of fluorinated biphenyl **2** and oligophenylenes **3** and **4**. Conditions: (a) LDA then **E**: I_2, $C_2H_4I_2$, $B(OEt)_3$, isopropoxy pinacolborane. (b) Fe(30 eq.)/Br_2(3 eq.), rt, 22 h. (c) Fe(20 eq.)/Br_2(3 eq.), rt, 22 h. (d) Fe(10 eq.)/Br_2(eq.), rt, 22 h.

could not be identified or purified by column chromatography or HPLC. Interestingly, reversing the stoichiometry—treating biphenyl **2** with 3 equivalents of bromine and 10 equivalents of iron at room temperature—led to a mixture of the desired dibrominated product **2a** with 65% yield and unreacted starting material **2** (see SI). Increasing the iron loading to 20 equivalents improved the yield to 80%. Further increase to 30 equivalents of iron resulted in virtually complete conversion and afforded the dibrominated product **2a** in a 90% yield. Remarkably, this method exhibited high selectivity for bromination at the *para* position relative to fluorine, even when increasing the amount of bromine to 5 or 7 equivalents. The methyl-activated *para* position remained unreacted under these conditions.

Applying the same optimized protocol to compound **3**, treatment with **20** equivalents of iron produced compound **3a** in 90% yield (Fig. 2). Likewise, compound **4** treated with 10 equivalents of iron and 3 equivalents of bromine yielded compound **4a** virtually quantitatively (98% yield). The products (**2a**, **3a** and **4a**) were fully characterized by NMR spectroscopy (^{1}H, ^{19}F, ^{13}C) and mass spectrometry. In contrast, the use of classical bromination conditions (2 equivalents of iron and 10 equivalents of bromine) with compounds **3** and **4** resulted in complex, uncharacterizable mixtures.

This behaviour suggests that the reaction likely occurs on the surface of metallic iron. To support this hypothesis, we investigated direct bromination using alternative brominating agents. Biphenylene **2** was selected as a model compound, with the aim of preferentially obtaining the dibrominated product **2a**. However, no bromination was observed when using cupric bromide or cuprous bromide as the brominating agents (see SI,

entries 1–8). Similarly, attempts using $FeBr_2$ or $FeBr_3$ (2 eq.) in various stoichiometries (SI entries 9, 10 and 13) did not yield any detectable brominated products. Under more forcing conditions—combinations of Br_2 with $FeBr_2$, complex mixtures were observed (SI entries 11 and 12). Upon increasing the amount of $FeBr_3$, only mixtures of the desired dibrominated product (**2a**) and unreacted starting material (**2**) were obtained (SI entries 14 and 15). Use of bromine with $FeBr_3$ had a disappointing outcome where a complex mixture was detected (SI, entries 16 and 17). Thus, none of the examined conditions matched the selectivity and efficiency achieved with bromination in the presence of excess metallic iron.

Inspired by the high selectivity observed, we extended this approach to other differently fluorinated biphenylenes and compared the bromination selectivity with classical conditions that do not involve a large excess of iron. As a first step we compare bromination of difluorotoluene **1**. These results show that bromination is milder and more selective (Fig. 3). The reaction of 2,6-difluorotoluene was conducted using two approaches. The first method employed 3 equivalents of bromine and 30 equivalents of iron at room temperature, yielding 3,5-dibromo-2,6-difluorotoluene (**1a**) with a high efficiency of 90%. In contrast, the second method utilized conventional conditions with 2 equivalents of iron and 10 equivalents of bromine, producing 3,4,5-tribromo-2,6-difluorotoluene (**1b**) in an 87% yield. The employed method for synthesizing (**1a**) showed a remarkable selectivity for bromination at the *para* position relative to fluorine. Further reactions were conducted with differently fluorinated biphenylenes (Fig. 3) using the optimised conditions obtained above for the synthesis of **2a** from **2**.

Bromination of fluorobiphenyls **5** and **6** using an excess of iron afforded compounds **5a** and **6a** in 76% and 83% yields, respectively, whereas standard bromination conditions led to complex mixtures in both cases. Fluorobiphenyls **7** and **8** were brominated by employing 30 eq. of iron and 3 eq. of bromine affording **7a** and **8a** in yields of 97% and 81%, respectively (Fig. 3). Conventional bromination of **7** gave **7b** in a yield of 68% (tetrabromination). Applying the same bromination condition to **8** resulted in a mixture of **8a** (di-bromination) and **8b** (tribromination) in yields of 7% and 15%, respectively. The reaction of tetrafluorobiphenyl **9** proceeded in both conditions to give dibromo-tetrafluoro-biphenyl **9a** in comparable yields (70% and 67%). Nevertheless, by blocking the *para* position to fluorine with a methyl group (compound **10**), bromination with 30 eq. of iron and 3 eq. of Br_2 leads to selective *ortho* bromination with 73% yield (compound **10a**). However, applying classical conditions gave perbrominated **10b** in 85% yield. In addition, 4,4′-difluoro-1,1′-biphenyl (**11**) and 2,2′,3,3′-tetrafluoro-1,1′-biphenyl (**12**) gave a complex mixture under both conditions. Additionally, in the two different reaction conditions, 2,2′,5,5′-tetrafluoro-1,1′-biphenyl (**13**) was converted to **13a** with yields of 93% and 82%, respectively.

Concluding, we report a selective terminal bromination of fluorinated oligophenylenes using a simple reaction setup, readily available reagents and mild conditions. We demonstrate that this methodology is applicable to a broad range of fluorinated oligophenylenes that are challenging to access through existing synthetic methods. Our results show that the position of the fluorine substituent plays a decisive role in directing bromination to the *para* (*ortho*) positions, enabling the synthesis of the desired dibrominated compounds with high yields and excellent selectivity. This strategy provides a versatile platform for constructing more complex molecular architectures based on these building blocks, and we anticipate that the reaction will find wide application in synthetic chemistry, particularly in materials science.

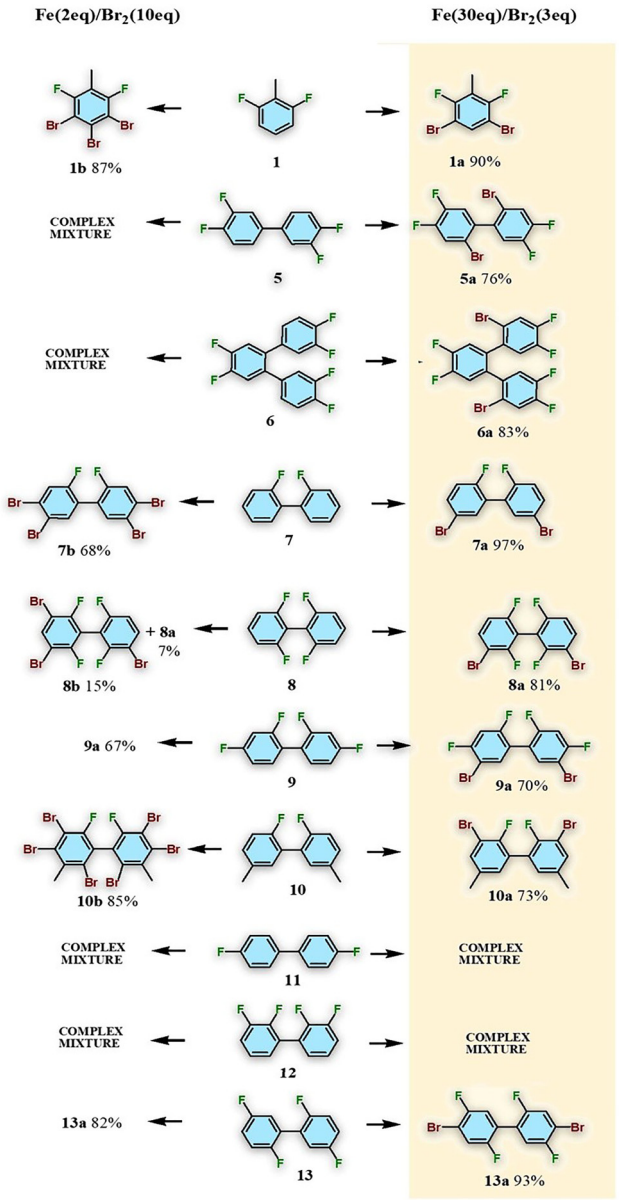

Fig. 3 Bromination of **1** and fluorinated oligophenylenes **5–13**. Conditions (right) Fe(30 eq.)/Br_2(3 eq.), rt, 22 h. (left) Fe(2 eq.)/Br_2(10 eq.), rt, 22 h.

The authors acknowledge support by the German Research Foundation (DFG) through grant no. AM407.

Conflicts of interest

The authors declare no conflict of interest.

Data availability

All data supporting the findings of this study are available within the article and its supplementary information (SI). Supplementary information is available. See DOI: **https://doi.org/10.1039/d5cc05074j**.

Notes and references

1 A. Steiner, D. I. Sharapa, S. I. Troyanov, J. Nuss and K. Amsharov, *Chem. – Eur. J.*, 2021, **27**, 6223–6229.
2 A.-K. Steiner and K. Y. Amsharov, *Angew. Chem., Int. Ed.*, 2017, **56**, 14732–14736.
3 M. Kolmer, R. Zuzak, A. K. Steiner, L. Zajac, M. Engelund, S. Godlewski, M. Szymonski and K. Amsharov, *Science*, 2019, **363**, 57–60.
4 M. Kolmer, A.-K. Steiner, I. Izydorczyk, W. Ko, M. Engelund, M. Szymonski, A.-P. Li and K. Amsharov, *Science*, 2020, **369**, 571–575.
5 M. Feofanov, V. Akhmetov, R. Takayama and K. Amsharov, *Org. Biomol. Chem.*, 2021, **19**, 7172–7175.
6 M. Feofanov, V. Akhmetov, R. Takayama and K. Amsharov, *Angew. Chem.*, 2021, **133**, 5259–5263.
7 M. Feofanov, V. Akhmetov, R. Takayama and K. Y. Amsharov, *J. Org. Chem.*, 2021, **86**, 14759–14766.
8 Q. Fan, L. Yan, M. W. Tripp, O. Krejčí, S. Dimosthenous, S. R. Kachel, M. Chen, A. S. Foster, U. Koert, P. Liljeroth and J. M. Gottfried, *Science*, 2021, **372**, 852–856.
9 H. Shudo, P. Wiesener, E. Kolodzeiski, K. Mizukami, D. Imoto, H. Mönig, S. Amirjalayer, H. Sakamoto, H. Klaasen, B. J. Ravoo, N. Kimizuka, A. Yagi and K. Itami, *Nat. Commun.*, 2025, **16**, 1074.
10 V. Snieckus, *Chem. Rev.*, 1990, **90**, 879–933.
11 K. M. B. Gross and P. Beak, *J. Am. Chem. Soc.*, 2001, **123**, 315–321.
12 P. L. Coe, A. J. Waring and T. D. Yarwood, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2729.
13 Y. Nishii, M. Ikeda, Y. Hayashi, S. Kawauchi and M. Miura, *J. Am. Chem. Soc.*, 2020, **142**, 1621–1629.
14 R. Rathore, Carrie L. Burns, Scott E. Denmark and Shinji Fujimori, *Org. Synth.*, 2005, **82**, 30.
15 L. O. Péres, F. Guillet and G. Froyer, *Org. Biomol. Chem.*, 2004, **2**, 452–454.
16 C. N. Kona, R. Oku, S. Nakamura, M. Miura, K. Hirano and Y. Nishii, *Chem*, 2024, **10**, 402–413.