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Synthesis of chiral sequence-defined oligomers via sulfur–fluoride and sulfur–phenolate exchange reactions

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Sequence-defined oligomers have been synthesized with increasing complexity, but the participation of chiral centres in the oligomerization process remains challenging. Here we report the synthesis of sequence-defined oligosulfonimidates (up to thirteen-mers) obtained via a series of sulfur–fluoride exchange and sulfur–phenolate exchange reactions. Next, we demonstrate that the use of chiral sulfonimidoyl fluorides allows the construction of chiral oligomers, in which the chirality of each linking S-centred site can be tuned independently of the rest of the molecule, thereby opening a way to a potentially vast increase in the information density of such oligomers. Finally, by activating a dormant fluorous tag used for the separation of oligomers, a tail-to-head-type sulfur–phenolate exchange polymerization strategy was developed using these oligomers, resulting in sequence-controlled polymers. The high variability of sulfonimidates and the chiral control provided to macromolecules through this technique results in another step towards full control over nature-mimicking polymers.

Precise control over molar mass, sequence and chirality is crucial for the functioning of biological polymers, such as proteins and nucleic acids. Mimicking the characteristics of such natural sequence-defined polymers[1] is considered as the holy grail in polymer science[2]. In addition, such endeavours are of substantial interest because of their potential applications in information storage[3,4], catalysis[5], self-assembly[6–8] and molecular recognition[9]. In some respects such artificial polymers could even surpass natural biomolecules, as shown by DNA analogues like peptide nucleic acids (PNA) that overcome some of the vulnerability of DNA to hydrolysis[10,11]. Moreover, the introduction of specific functional groups in synthetic sequence-defined polymers could facilitate the interpretation of sequences and provide the capacity to store more information by incorporating large diversity of monomers[12].

Due to the prominent advantages of synthetic sequence-defined polymers, the construction of various types of sequence-defined polymer has become a hot topic in polymer science in recent years. Iterative stepwise growth (ISG)[13] and iterative exponential growth (IEG)[14,15] are the two commonly used strategies to synthesize sequence-defined oligomers, and many reactions have been applied for this. Given the characteristics of click reactions[16–18], evidently these are of interest in this field, and for example both the copper-catalysed azide–alkyne cycloaddition (CuAAC)[14,19] and sulfur–fluoride exchange (SuFEx)[20,21] reactions have been used. However, site-specific control over chirality has, to the best of our knowledge, not yet been reported. So far, the use of chiral monomers that incorporate non-reactive chiral moieties near the reactive site has been a common method to make chiral oligomers. In 2018, Boyer and co-workers developed stereospecific oligomers using alternating radical chain growth and sequential photoinduced reversible addition–fragmentation chain-transfer single unit monomer insertion (photo-RAFT SUMI). They found the stereochemistry of cyclic

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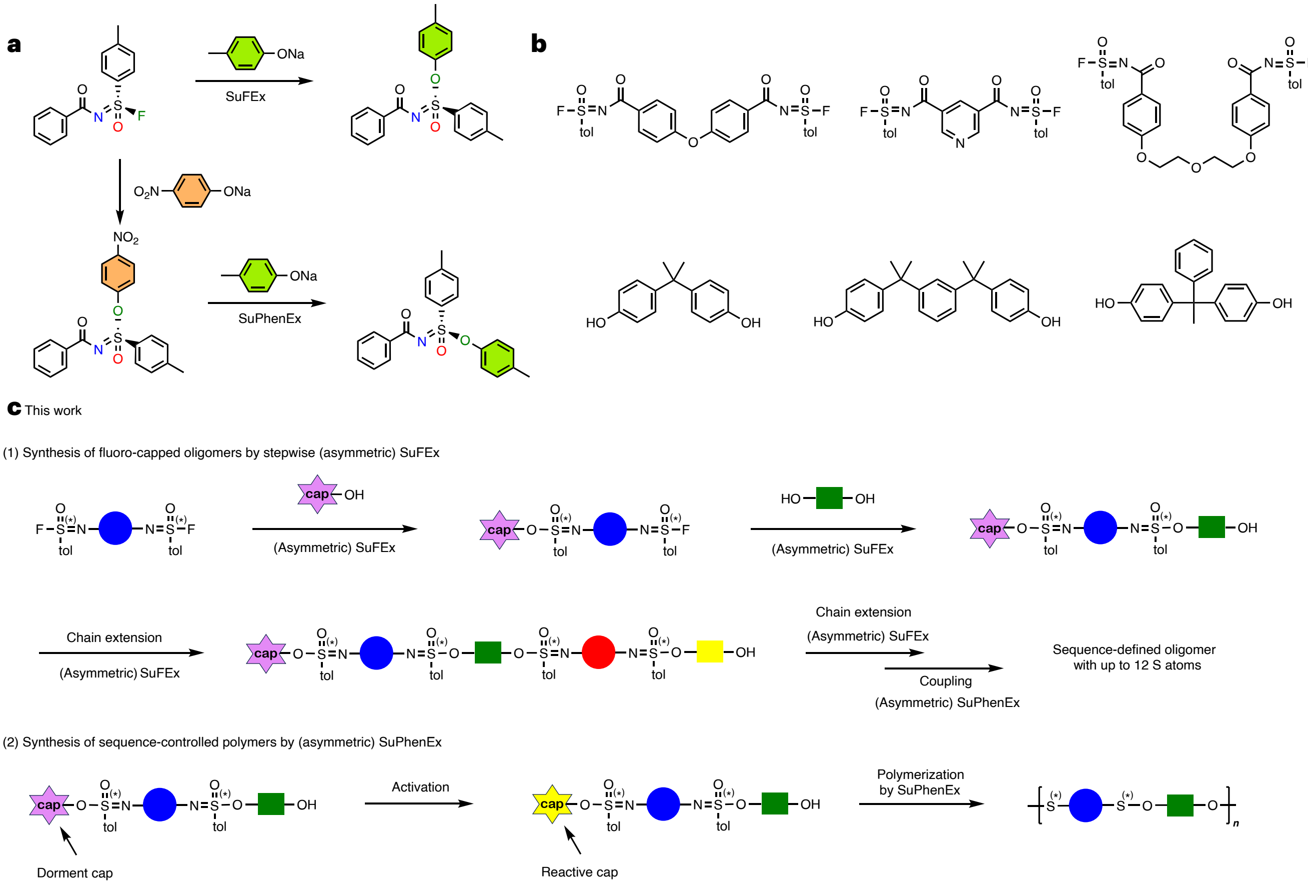

Fig. 1 | Overview of sulfonimidate syntheses. a, General scheme for chiral SuFEx and SuPhenEx reactions towards the synthesis of two enantiomeric sulfonimidates from one chiral sulfonimidoyl fluoride[24,26]. **b**, Representative monomers of di-sulfonimidoyl fluorides (di-SFs) and diphenols as used in this study. **c**, Overview of this work. SuFEx, sulfur–fluoride exchange reaction; SuPhenEx, sulfur–phenolate exchange reaction. Tol, *p*-tolyl.

monomer insertion into the RAFT agents is *trans*-selective due to steric hindrance from the repeating monomer units[22]. More recently, Du Prez and co-workers developed stereocontrolled sequence-defined oligomers through the ring opening of chiral thiolactone isocyanate, in which the chiral carbon centre adjacent to the carbon reactive site of the ring-opening reaction can be functionalized[23]. However, full and enantiospecific control of chirality at the reactive site has not been reported, and this biomimetic goal of being able to define for each monomer in an oligomer both the composition and spatial orientation at will is still high on the wish list of this field.

We hypothesized that two developments from our group, however, could make this possible. In 2020, we developed an intrinsically enantiospecific click reaction, namely the SuFEx reaction, starting from chiral sulfonimidoyl fluorides (SFs, Fig. 1a)[24]. While highly effective it still relied on the availability of both enantiomers of the SFs—synthesized in five steps from commercial sources—either via two parallel syntheses or via preparative chiral high-performance liquid chromatography (HPLC). This limitation was overcome by the realization that with a good leaving group, the sulfonimidate formed from the SuFEx reaction may undergo another chirality-inverting S(VI) exchange reaction with another, more electron-rich phenol, leading to sulfur–phenolate exchange (SuPhenEx, Fig. 1a). This reaction was also shown to be both quantitative and enantiospecific[25,26], and as such requires only one of the chiral SFs to be synthesized to still easily access both S-centred stereoisomers.

In this Article, we report a synthetic strategy for the synthesis of SuFEx-based sequence-defined oligomers by a stepwise iterative approach, in which series of symmetric bisphenols and di-SFs (Fig. 1b) were used as two types of building blocks. Next, using chiral SFs and stereoinversion via the SuPhenEx reaction, we obtained sequence-defined oligomers in which the stereochemistry at the reactive site can be independently controlled during the synthetic procedure. Finally, a tail-to-head-type polymerization strategy was developed to synthesize SuPhenEx-based sequence-controlled polysulfonimidate polymers. This allows the transfer of sequence and chirality control from oligomers to polymers.

Results and discussion

Synthesis of sequence-defined oligomers

In our initial investigations, the symmetric building blocks *N*′,*N*′′-[4,4′-oxybis(benzoyl)]bis(4-methylbenzenesulfonimidoyl fluoride) **1a** and bisphenol A **2a** were employed for a proof-of-concept synthesis of sequence-defined oligomers (Fig. 2a). The first critical choice in this synthesis was the introduction of a perfluoro-tagged phenol **A1**, in which the tag links to the phenol via an S atom. This tag allows for the easy purification of reaction products during the oligomerization[27–31] but also (see below) provides access to further functionalization. The perfluoro-tagged phenol **A1** (116 mg, 0.201 mmol, 1.0 equiv.) underwent a SuFEx reaction with excess **1a** (568 mg, 1.000 mmol, 5 equiv.), to ensure monosubstitution, in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (45 µl, 0.301 mmol, 1.5 equiv.) as the base at room temperature for 30 min. After the reaction was completed, the reaction mixture was loaded onto fluorous silica gel. There the sequence of fluorophobic eluents (85% methanol/H_2O) and fluorophilic eluents (tetrahydrofuran or acetonitrile) first washed out the excess of monomer **1a**, which was followed by the purified product, dimer **A2**, which was obtained in an isolated yield of 85% (190 mg, 0.170 mmol) and di-substitution by-product **M1** that was isolated in 3% yield (10 mg,

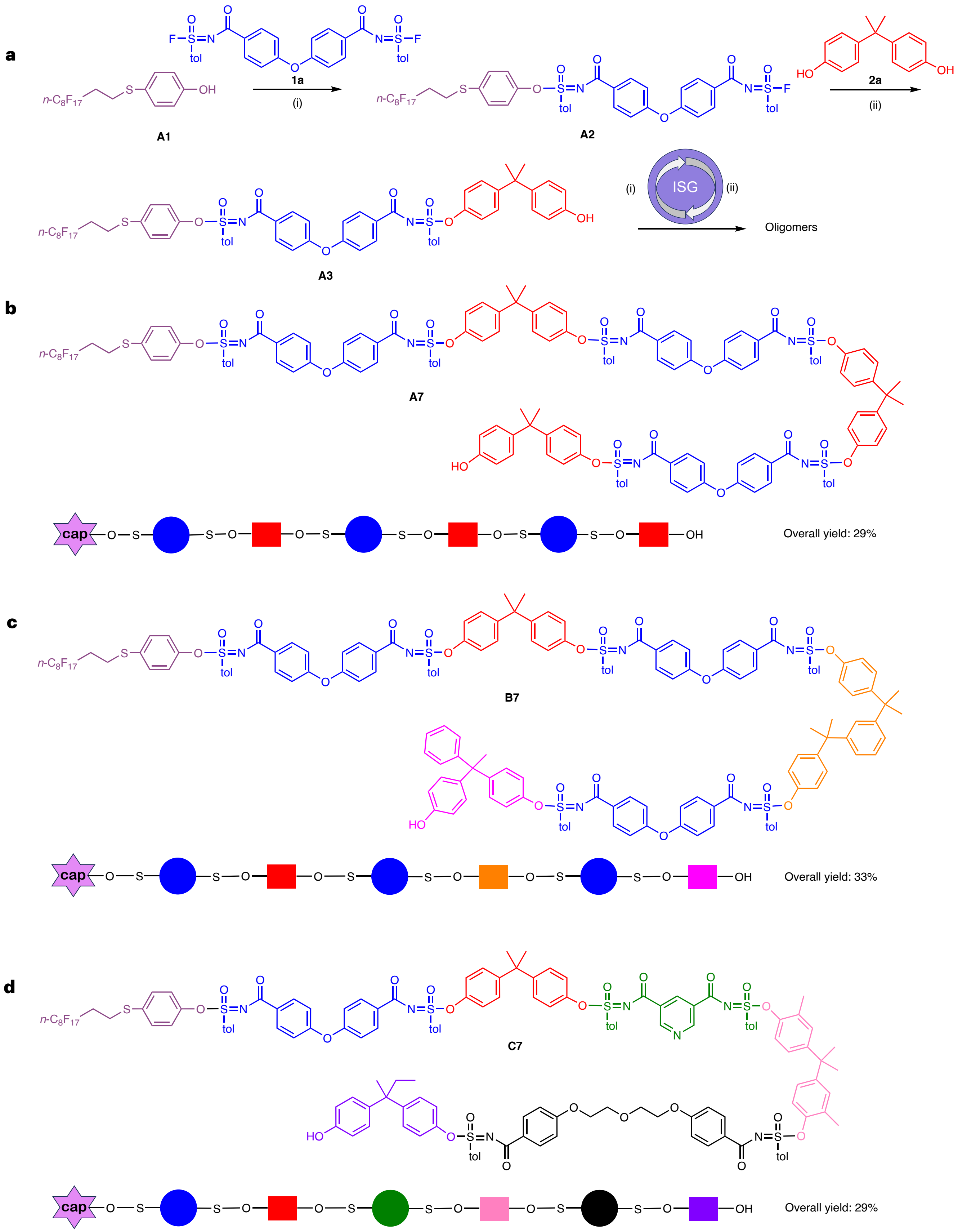

Fig. 2 | Synthesis of oligosulfonimidates. **a**, General synthesis of oligosulfonimidates: (i) Coupling of oligomers with di-sulfonimidoyl fluorides using DBU as a base (in molar ratio 1:5:1.5) at room temperature (r.t.); (ii) Coupling of oligomers with bisphenols using DBU as a base (in molar ratio 1:5:5) in THF at r.t. **b**, Synthesized oligosulfonimidate **A7** consisting of **1a** and **2a** units. **c**, Synthesized oligosulfonimidate **B7** with constant di-SF and three different di-phenols. **d**, Synthesized oligosulfonimidate **C7** with three different di-phenols and di-SFs. DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; THF, tetrahydrofuran; tol, *p*-tolyl.

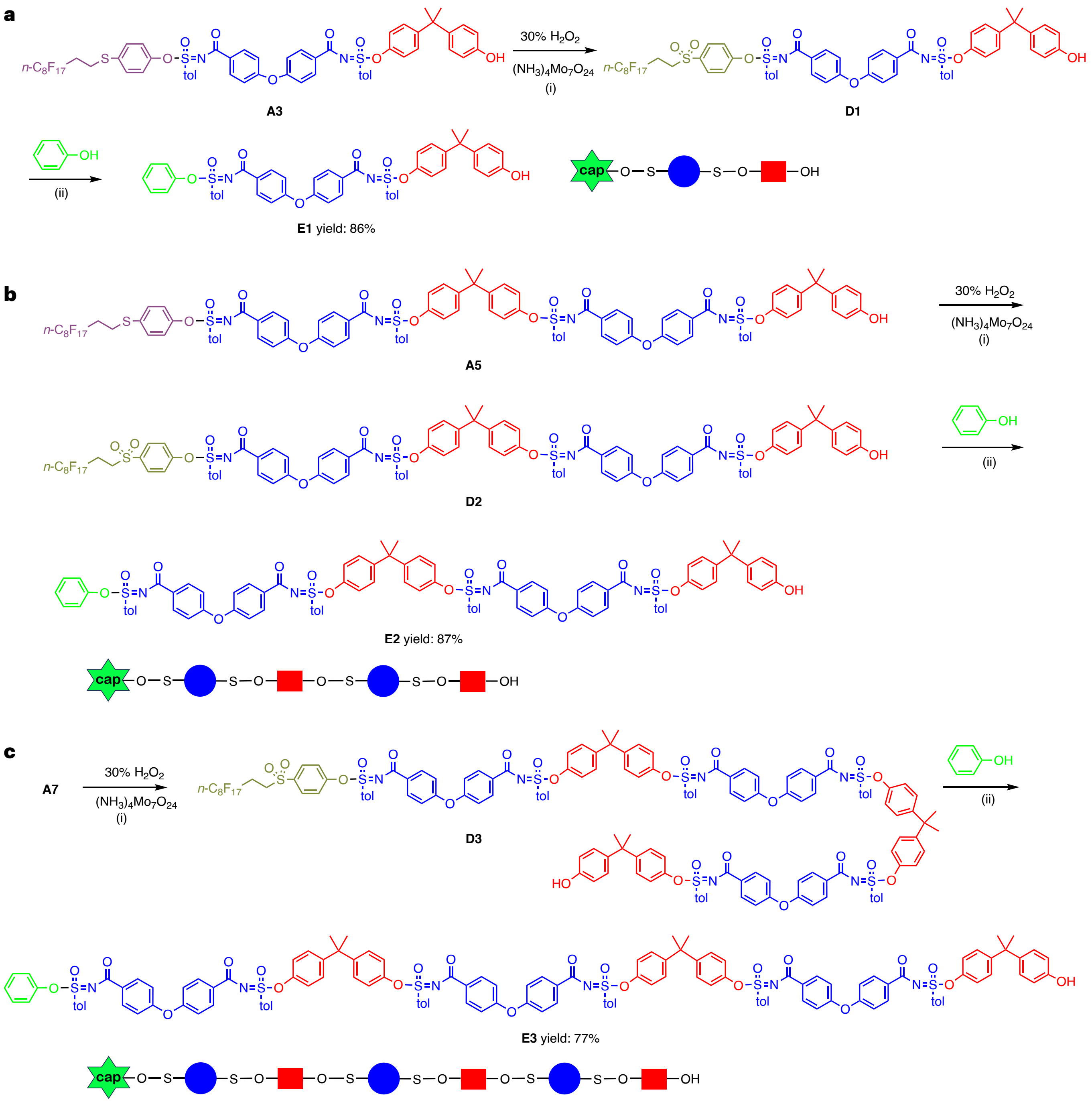

Fig. 3 | Oxidative activation and SuPhenEx-based substitution. a, Synthesis of **E1** from **A3**. **b**, Synthesis of **E2** from **A5**. **c**, Synthesis of **E3** from **A7**. Reaction conditions: (i) Oligomer with fluoro-tag (**A3, A5** or **A7**, 1 equiv.), ammonium molybdate tetrahydrate (0.1 equiv.), 30% H_2O_2 (18 equiv.), THF, r.t., 2 h; (ii) Oxidized intermediate (**D1**–**D3**, 1 equiv.), phenol (10 equiv.), DBU (3 equiv.), THF, r.t., 2 h. DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; THF, tetrahydrofuran; tol, *p*-tolyl.

6 μmol, see Supplementary Section 3 for details). Subsequently, the remaining sulfonimidoyl fluoride of **A2** (190 mg, 0.170 mmol, 1 equiv.) reacted with diphenol **2a** (193 mg, 0.846 mmol, 5 equiv.), retaining a phenol reactive site, which allowed the oligomer to be further extended. Following four more steps of stepwise iterative growth, heptamer **A7** (42 mg, 0.015 mmol) (Fig. 2b) was obtained with an overall yield of 29% over six steps. Purifying compounds **A2** and **A3** by normal-phase chromatography is extremely challenging due to the similar polarity between **A2** and di-SF, as well as between **A3** and bisphenol A. Therefore, using fluorous solid-phase extraction (FSPE) can significantly simplify the purification process. However, as the oligomer chain extends, the resulting longer oligomers (for example after the pentamer stage) have a very different polarity than the monomers, allowing excess monomers to be easily separated by normal-phase chromatography[32]. To demonstrate the versatility of this method, a variety of di-phenols was employed to elongate the oligomer chains. Analogous to the synthesis of **A7**, we aimed to synthesize sequence-defined oligosulfonimidates **B7** and **C7** to check on the scope of our approach. Whereas oligomer **A7** has a repetitive structure with only one type of di-SF and one type of diphenol, in heptamer **B7** the di-SF was still kept constant, but the diphenol was varied (Fig. 2c), while finally in heptamer **C7** both the di-SF and the diphenol were varied (Fig. 2d). We were pleased to

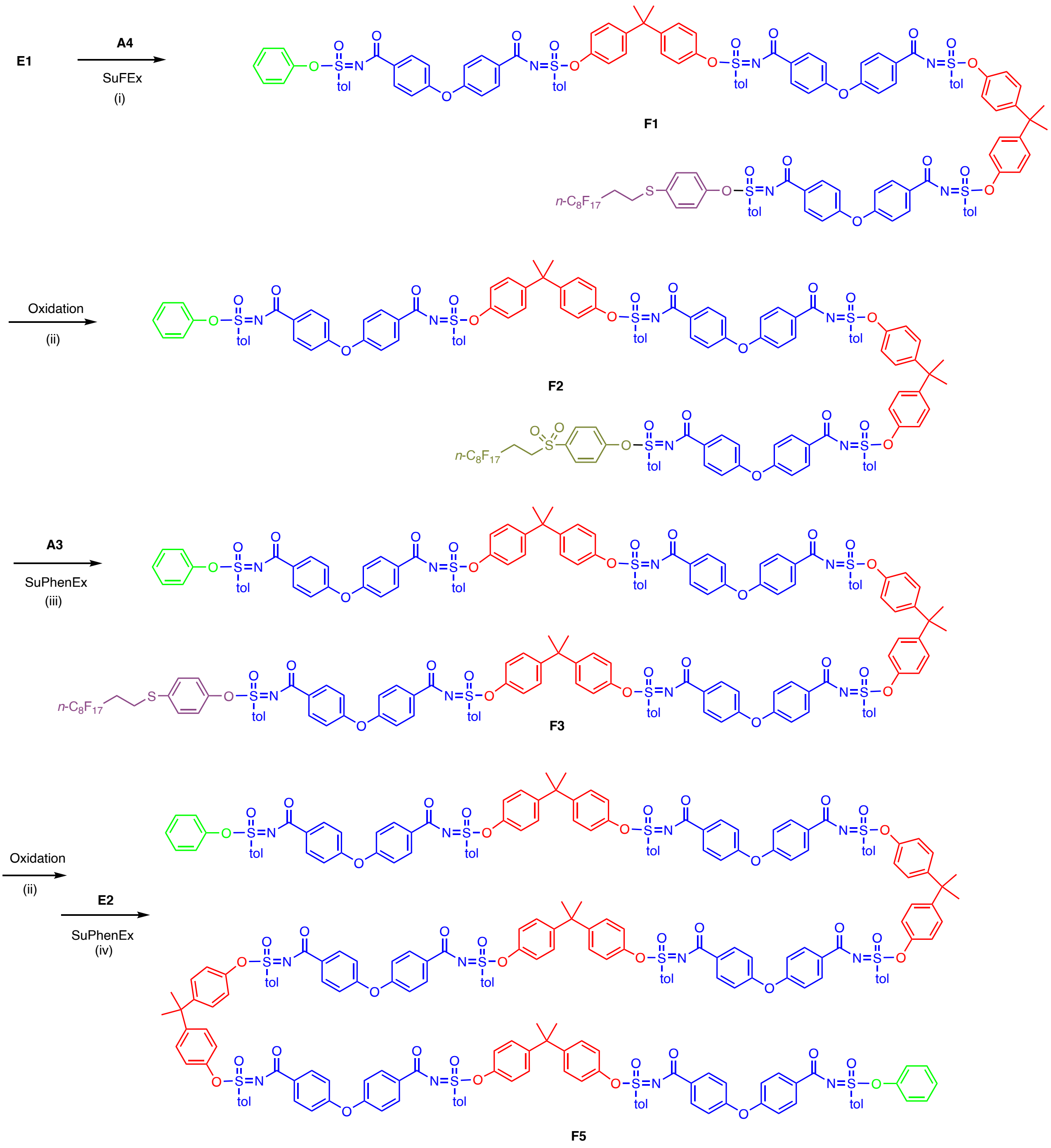

Fig. 4 | Divergent synthetic routes towards chain elongation via a combination of SuFEx and SuPhenEx reactions. Reaction conditions: (i) **A4** (1 equiv.), **E1** (1.1 equiv.), DBU (1.2 equiv.), THF, r.t., 2 h; (ii) Oligomer with fluoro-tag (**F1** or **F3**, 1 equiv.), ammonium molybdate tetrahydrate (0.1 equiv.), 30% H_2O_2 (18 equiv.), THF, r.t., 2 h; (iii) **F2** (1 equiv.), **A3** (5 equiv.), DBU (5 equiv.), THF, 60 °C, 16 h; (iv) Oxidized intermediate (1 equiv.), **E2** (1.5 equiv.), TBD (1.6 equiv.), THF, r.t., 2 h. SuFEx, sulfur–fluoride exchange reaction; SuPhenEx, sulfur–phenolate exchange reaction; THF, tetrahydrofuran; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; TBD, 1,5,7-triazabicyclo[4.4.0]dec-5-ene; tol, *p*-tolyl.

observe that this synthetic route displayed the versatility hoped for, with an average isolated yield of >80% in each step, ranging from 70 to 91%. This yield did not decrease with increasing oligomer length, so that the final products could be obtained in overall yields of 33% (83 mg, 0.027 mmol) and 29% (82 mg, 0.028 mmol), respectively. Such consistently high yields are specifically of interest, since in several routes towards sequence-defined oligomers the yields rapidly drop with increasing oligomer length, sometimes from already the trimer stage onwards[27]; that we do not observe that here demonstrates the potential of our approach. Structures of the obtained products were confirmed by a combination of NMR spectroscopy and high-resolution mass spectrometry. Gel permeation chromatography showed the expected mono-dispersity of the formed oligomers and the decrease in retention time with an increase of the oligomer chain length (Supplementary Section 8).

After demonstrating that both di-phenols and di-SFs could be varied, we aimed to investigate modulation of the phenol-linked fluorous cap with the idea that, after having been extremely useful

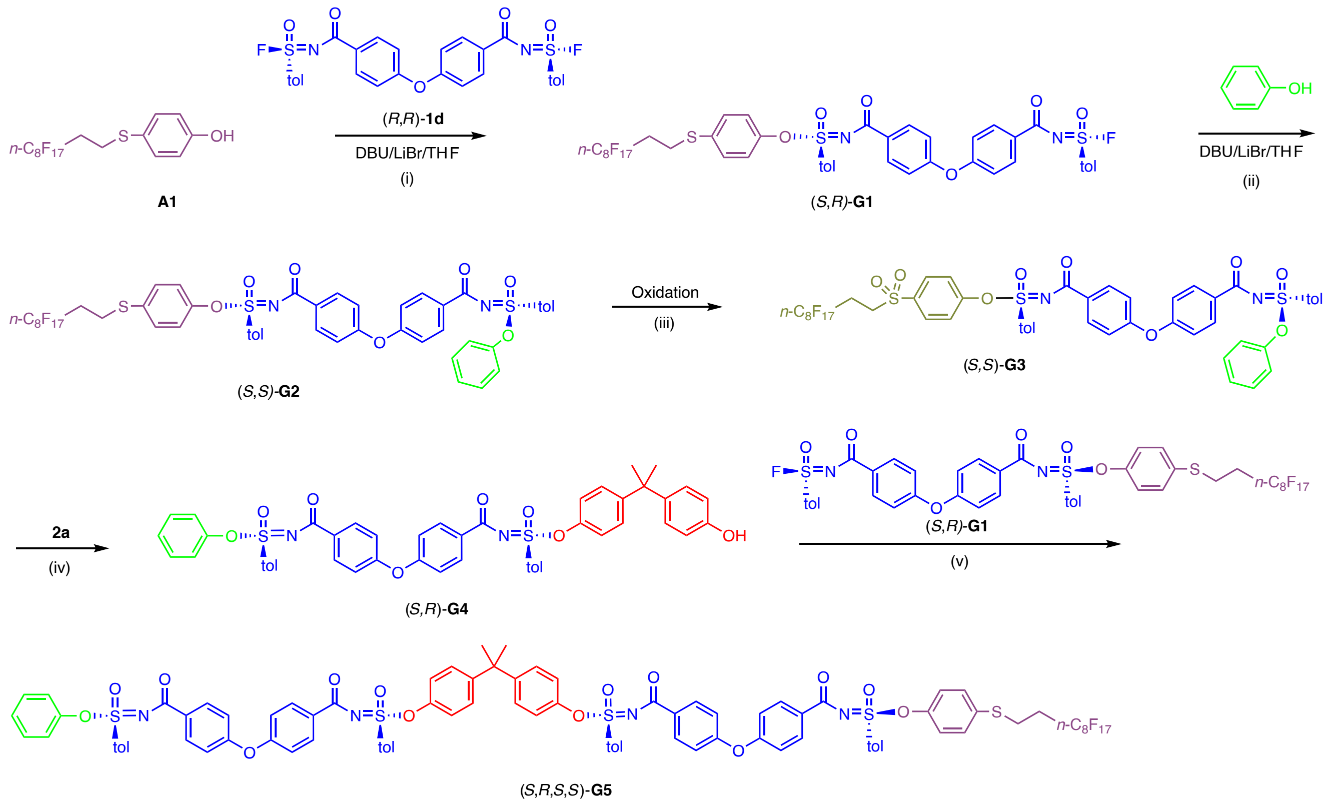

Fig. 5 | Synthetic routes of pentamer G5 with the *S*(ha)*R*(ple)*SS* configuration. Reaction conditions: (i) **A1** (1 equiv.), **1d** (3 equiv.), DBU (1.5 equiv.), LiBr (3 equiv.), THF, r.t., 2 h; (ii) **G1** (1 equiv.), phenol (1.2 equiv.), LiBr (1.5 equiv.), DBU (1.2 equiv.), THF, r.t., 2 h; (iii) **G2** (1 equiv.), ammonium molybdate tetrahydrate (0.1 equiv.), 30% H_2O_2 (18 equiv.), THF, r.t., 2 h; (iv) **G3** (1 equiv.), bisphenol A (5 equiv.), DBU (5 equiv.), THF, r.t., 2 h; (v) **G4** (1 equiv.), **G1** (1 equiv.), LiBr (1.6 equiv.), DBU (1.2 equiv.), THF, r.t., 3 h. SuFEx, sulfur–fluoride exchange reaction; SuPhenEx, sulfur–phenolate exchange reaction; THF, tetrahydrofuran; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; tol, *p*-tolyl.

in the FSPE purification, variability of this end of the molecule would further expand the flexibility of our approach. Here, it is good to point out the dual role that was needed for the S–O linkage of the fluorous tag: it should be stable under all the SuFEx reaction conditions used to prepare the oligomers, yet still be easily removable in an orthogonal manner afterwards. The stability was not only demonstrated by its use in the aforementioned syntheses, in which this moiety was maintained over and over again. The first attempt to remove it was made by treating the reaction products under harsher basic conditions than used in these syntheses. To this aim, heptamer **A7** was treated with 5 equiv. phenol (this excess was used to ensure substantial deprotonation of this molecule rather than the terminal phenol moiety on the **A7** heptamer) and 1.1 equiv. NaH. Monitoring the reaction progress by thin-layer chromatography (TLC), however, showed the formation of multiple spots, indicative of cleavage reactions at multiple sites, not only at the terminus leading to a multitude of small degradation compounds. To substitute this stably bound fluorous tag in a chemoselective manner under much milder SuPhenEx conditions, we then reasoned that an oxidative reaction could transform the poor sulfide–phenolate leaving group into a much better sulfone–phenolate leaving group[33,34]. First, we optimized the reaction conditions using trimer **A3** (Fig. 3b). After oxidizing the sulfur of the trimer using 30% H_2O_2 in the presence of ammonium molybdate tetrahydrate for 2 h at room temperature (r.t.), a SuPhenEx substitution was used to replace the now electron-deficient and easily leaving fluorous tag in **D1** by phenol, chosen as a representative phenolic moiety. The oxidation was evident by characteristic downfield shifts of multiple signals in the ^{1}H NMR spectra, and particularly from the downfield shift of the CH group linked to sulfur from 3.15–3.03 ppm to 3.35–3.27 ppm and the downfield shift of the CH group linked to the fluorine tag from 2.44–2.23 ppm to 2.74–2.53 ppm. Using DBU as a base, phenol-tagged trimer **E1** was obtained in a yield of 86% (27 mg, 0.032 mmol) within 2 h at room temperature. This demonstrates the high reactivity and chemoselectivity of this SuPhenEx reaction and opens up the road to further modification of the oligomer chains. (Note: the oxidation step is rather mild, and thus allows many different functionalities in the monomers, but easy-to-oxidize moieties like aldehydes, disulfides, or free thiols are to be avoided.)

As a next step in testing the versatility of this strategy, we focused on fluoro-tagged pentamer **D2**, obtained using such an oxidation step, which has four potentially SuPhenEx-reactive sites. When **D2** (35 mg, 0.0165 mmol) was reacted with phenol at r.t. it gently gave phenol-tagged pentamer **E2** (Fig. 3c) in a yield of 87% (23 mg, 0.0143 mmol), demonstrating that none of the internal S(VI) sites were reacting under these conditions. We finally applied this procedure to the sulfone-linked fluorous tag in heptamer **D3**, with six internal SuPhenEx-reactive sites, and chemoselectively exchanged only the fluorous tag for phenol, providing phenol-tagged heptamer **E3** (Fig. 3d) in a yield of 77% (18 mg, 7.62 µmol). Given the electronics of the SuPhenEx reaction, we hypothesize that this oxidized perfluoro tag can be replaced by any phenol, alcohol or amine[26,35,36] that is more electron-donating than the SO_2-substituted phenol produced after oxidation. Given the relatively high Hammett σ-value of the $-SO_2-$ moiety (0.72 for *para*-SO_2CH_3 (ref. 37)), which becomes only more electronegative with the attached fluoro tag), this basically means almost any of these nucleophiles.

To obtain some more quantitative information, we calculated the barrier for the SuPhenEx reaction of phenoxide on an analogue of compound IV (Fig. 1a) with –O-phenyl-*p*-SCH_3 or –O-phenyl-*p*-SO_2CH_3 replacing the green S–Ph in IV. We used ωB97XD/def2QZVPP//ωB97XD/6-311+G(d,p) density functional theory calculations, together with an SMD

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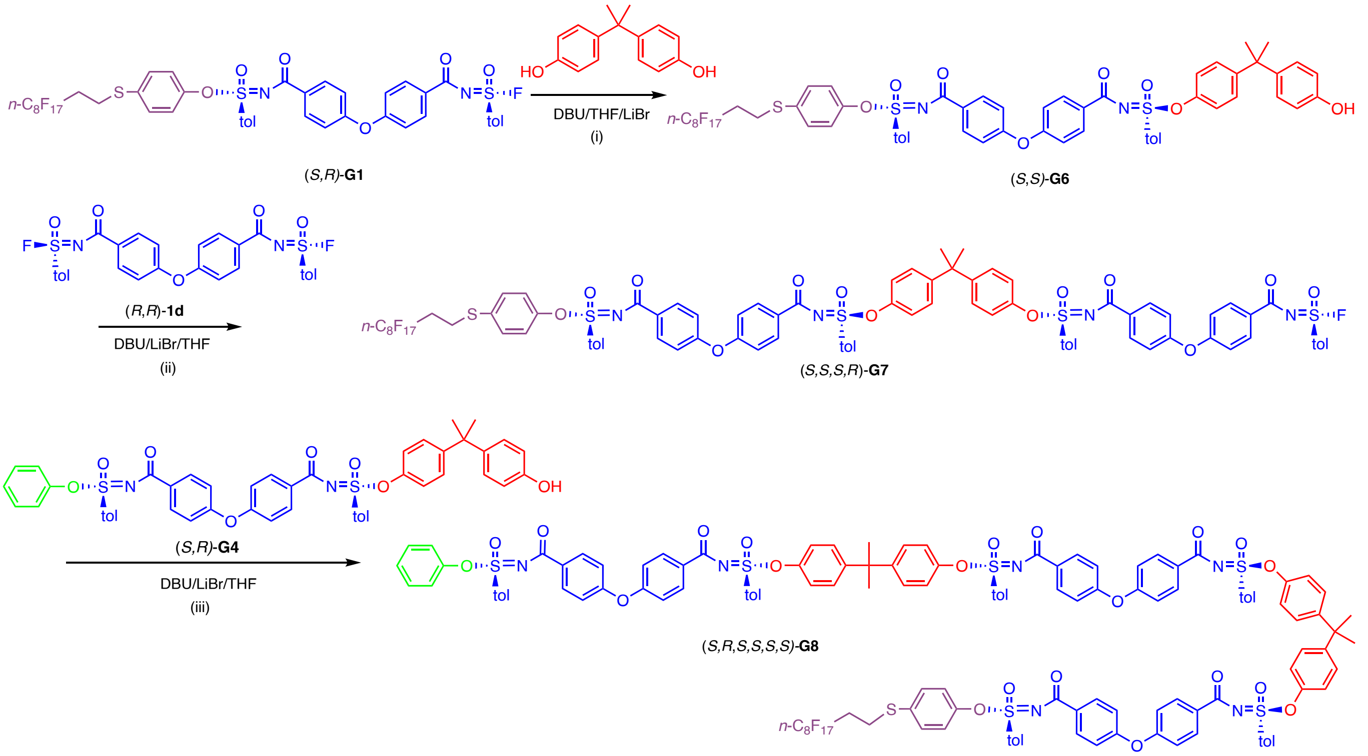

Fig. 6 | Synthetic route towards heptamer G8 with the *S,R,S,S,S,S* configuration. Reaction conditions: (i) **G1** (1 equiv.), bisphenol A (5 equiv.), DBU (5 equiv.), LiBr (2 equiv.), THF, r.t., 30 min; (ii) **G6** (1 equiv.), **1d** (3 equiv.), LiBr (4 equiv.), DBU (1.5 equiv.), THF, r.t., 2 h; (iii) **G7** (1 equiv.), **G4** (1.1 equiv.), DBU (1.5 equiv.), LiBr (2 equiv.), THF, r.t., 2 h. THF, tetrahydrofuran; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; tol, *p*-tolyl.

solvation model to mimic THF. In line with experiment, the barrier for loss of an –O-phenyl-*p*-SO_2CH_3 anion is indeed significantly lower, namely 3 kcal mol^{-1}, than for loss of an –O-phenyl-*p*-SCH_3 anion ($\Delta G^{\#}$ calculated to be 11 versus 14 kcal mol^{-1}). This calculated difference supports the experimental observation that, under mild reaction conditions, the oxidation of the sulfur turns only this moiety into a leaving group and no discernible cleavage of the chain by the SuPhenEx reaction on the internal part of the oligomer chain is observed (Supplementary Section 11).

The efficiency of the SuPhenEx reaction also allows a final step in this synthesis after 'waking up' the dormant sulfide linker: rather than a terminal (mono-)phenol, one can also react a (fluoro-tagged) oligomer with a free phenolic moiety. In this manner, the fluorous-tag phenol can be considered as a protecting group for the SuPhenEx reaction, to be replaced by other phenols when necessary. This strategy also allows divergent routes to grow long oligomeric chains in a divergent manner and thus more efficiently (Fig. 4). First, the phenol-capped trimer **E1** (30 mg, 35.3 μmol, 1.1 equiv.) was coupled with the fluoro-tagged tetramer **A4** (60 mg, 32.0 μmol) through a SuFEx reaction, resulting in the synthesis of heptamer **F1** with an isolated yield of 96% (83 mg, 30.6 μmol). Subsequently, the perfluoro-tag phenol on heptamer **F1** was activated through an oxidation reaction, followed by coupling with the fluorous-tag trimer **A3** via a SuPhenEx reaction. This yielded nonamer **F3** with an isolated yield of 83% (19 mg, 5.48 μmol). Finally, the perfluoro-tag phenol on nonamer **F3** was activated via oxidation and coupled with pentamer **E2** to yield thirteen-mer **F5** (26 mg, 5.8 μmol) with an isolated yield of 67%. For this reaction, a more reactive 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) base was employed in place of DBU and the reaction was complete within 2 h at room temperature. The molecular weight reached 4.50 kDa, which is approximately three times that of previously reported oligosulfates[38]. Given the continuously good yields of the SuPhenEx coupling steps, we believe that if the oligomer **F5** could contain a latent fluorous-tag phenol, it would allow for further elongation of the oligomeric chain.

Chiral sequence-defined oligomers

Both the SuFEx and the SuPhenEx reactions were previously shown to be enantiospecific click reactions[24,26]. After developing a strategy for sequence definition, we aimed for the next step by adding chiral information to the oligomers. This required a few changes to our strategy: for non-chiral SuFEx reactions as used above, DBU can be used nicely as an easy to add, readily available base. However, as shown by both our work[24] and that of Bull and co-workers[39], capture of the fluoride anion formed from the SuFEx reaction is essential to prevent racemization by re-attack onto the S(VI)–F centre. Given the frequently small amounts of the reacting phenolate, rather than trying to prepare the phenolate in advance by using an accurately determined but tiny amount of NaH (as we had done previously), we exploited Bull's approach to capture a fluoride ion by the addition of excess lithium bromide. This caused the reaction to proceed in an enantiospecific manner to yield chiral sequence-defined oligomers. In addition, when a symmetric chiral di-SF was utilized as the monomer, the same configuration for the two chiral centres of the monomer would be obtained if only the SuFEx reaction was employed to grow chains. However, the combination of SuFEx and SuPhenEx reactions uniquely allows control of the configuration of each and every sulfur centre (Fig. 1a). To demonstrate the tunability of each chiral sulfur centre, we decided to design the configuration of the oligomer chain as *SRSS* (easily memorized as *S*(ha)*R*(ple)*SS*; Fig. 5). The fluoro-tagged phenol **A1** (114 mg, 0.2 mmol) reacted with chiral di-SF compound **1d** (341 mg, 0.6 mmol, 96% diastereomeric excess (d.e.)) in the presence of DBU (44.7 μl, 0.3 mmol) as the base and lithium bromide (3 equiv.) as the fluoride anion scavenger. Product **G1** (*S,R*) was obtained with a yield of 81% (182 mg, 0.162 mmol) and virtually unchanged 96% d.e., demonstrating both high reactivity and the enantiospecificity of the coupling reaction. Subsequently, **G1** (100 mg, 0.089 mmol) underwent a SuFEx reaction with phenol, producing (*S,S*)-**G2** with a yield of 80% (85 mg, 0.071 mmol) and 94% d.e. Following this, the sulfur atom of the fluoro-tagged phenol on **G1** was oxidized by H_2O_2 as described

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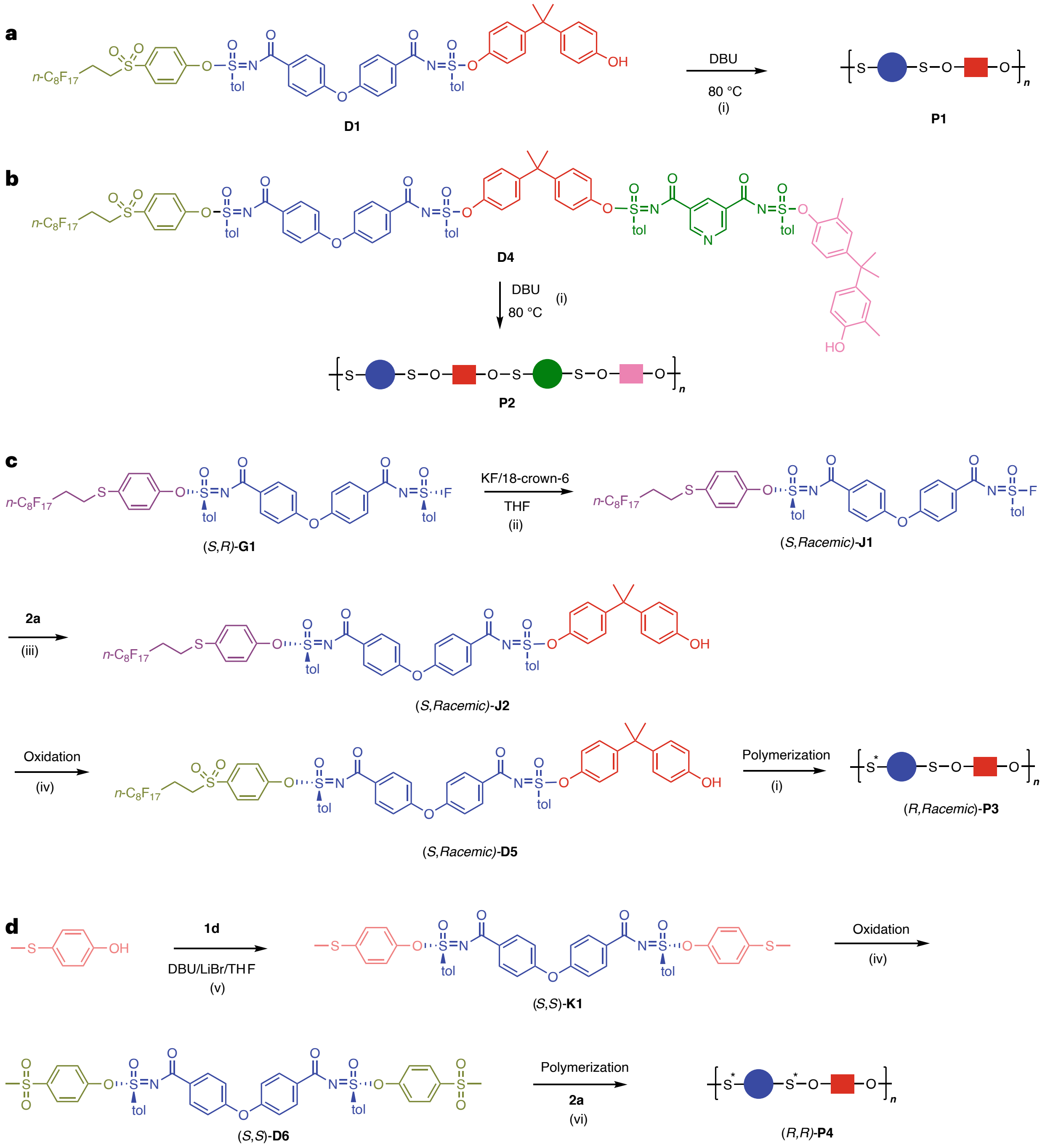

Fig. 7 | Synthesis of tail-to-head polymers by SuPhenEx. a, Polymer **P1** from **D1**. **b**, Polymer **P2** from **D4**. **c**, Polymer *(R, Racemic)*-**P3** from (*S, Racemic*)-**D5**. **d**, Polymer (*R*,*R*)-**P4** from (*S*,*S*)-**D6**. Reaction conditions: (i) Oxidized monomer (**D1, D4** or **D5**, 1 equiv.), DBU (1.1 equiv.), MeCN/DMF (1:1), 80 °C, 48 h; (ii) **G1** (1 equiv.), KF (2.2 equiv.), 18-crown-6 (3.3 equiv.), THF, r.t., 2 h; (iii) **J1** (1 equiv.), bisphenol A (5 equiv.), THF, r.t., 2 h; (iv) Monomers (**J2** or **K1**, 1 equiv.), ammonium molybdate tetrahydrate (0.1 equiv.), 30% H_2O_2 (18 equiv.), THF, r.t., 2 h; (v) **1d** (1 equiv.), 4-(methylthio)phenol (2.2 equiv.), LiBr (3 equiv.), DBU (2.2 equiv.), THF, r.t., 6 h; (vi) **D6** (1 equiv.), **2a** (1 equiv.), DBU (2.2 equiv.), MeCN/DMF, 80 °C, 2 days. SuPhenEx: sulfur–phenolate exchange reaction; THF, tetrahydrofuran; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DMF, *N*,*N*-dimethylformamide; tol, *p*-tolyl.

before and the resulting sulfone moiety substituted by **2a** through a SuPhenEx reaction, resulting in the product (*S*,*R*)-**G4** with a yield of 83% (23 mg, 0.027 mmol) and 94% d.e. Finally, (*S*,*R*)-**G4** (21 mg, 24.7 µmol) reacted with **G1** (33 mg, 29.5 µmol), producing (*S*,*R*,*S*,*S*)-**G5** with a yield of 73% (35 mg, 17.5 µmol). In order to identify the diastereospecificity of the SuFEx reaction in the last step, the reaction was repeated without LiBr, producing a partially racemized (*S*,*R*,*S*/*R*,*S*)-**G5**. Peaks of two diastereomers were separated using chiral HPLC and only 3% total reduction of stereochemistry was observed during SuFEx coupling, which was less than 1% of racemization at each sulfur centre. In this it should be noted that reaching this (*S*,*R*,*S*,*S*) configuration for the oligosulfonimidate is not dependent on the stereochemistry of the starting di-SF: had the reaction started with the different configuration of the di-SF monomer, stereoinversion using SuPhenEx reactions would have paved the way towards the same compound.

After demonstrating that the configuration of chiral sulfurs could be adjusted on demand, we next aimed to further extend the chiral oligomer chain length to demonstrate the generality of this synthetic

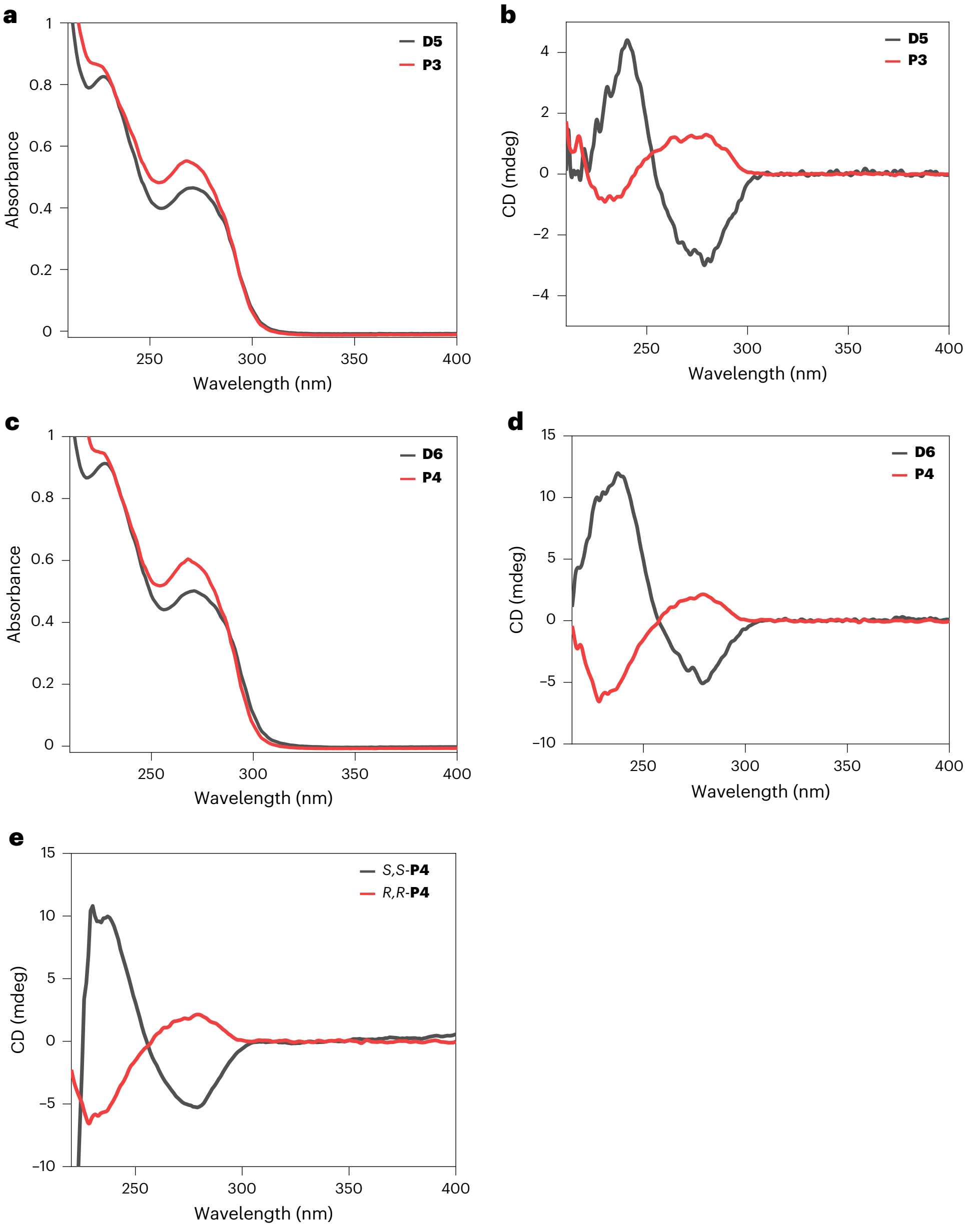

Fig. 8 | Ultraviolet–visible absorption and CD spectra. a, Ultraviolet–visible absorption spectra of **D5** and polymer **P3**. **b**, CD spectra of **D5** and polymer **P3**. **c**, Ultraviolet–visible absorption spectra of **D6** and polymer **P4**. **d**, CD spectra of **D6** and polymer **P4**. **e**, CD spectra of (*S*,*S*)-**P4** (black line; data from ref. 40) and (*R*,*R*)-**P4** (red line).

approach. Therefore, the synthetic route towards the (*S*,*R*,*S*,*S*,*S*,*S*)-**G8** heptamer was designed (Fig. 6). (*S*,*R*)-**G1** (88 mg, 0.079 mmol, 1 equiv.) reacted with excess equiv. of bisphenol A to yield (*S*,*S*)-**G6** (86 mg, 0.065 mmol, 82%, 96% d.e.). Subsequently, (*S*,*S*)-**G6** (60 mg, 45 µmol) reacted with chiral di-SF compound **1d** (77 mg, 135 µmol, 96% d.e., 3 equiv.) to give (*S*,*S*,*S*,*R*)-**G7** (58 mg, 31 µmol) with a yield of 68%. Finally, (*S*,*S*,*S*,*R*)-**G7** (20 mg, 10.7 µmol) coupled with (*S*,*R*)-**G4** (10 mg, 11.8 µmol, 94% d.e.), produced (*S*,*R*,*S*,*S*,*S*,*S*)-**G8** with a yield of 86%. In order to establish the diastereoselectivity of the last synthetic steps, partially racemized products (*S*,*S*,*S*/*R*,*S*/*R*)-**G7** and (*S*,*R*,*S*/*R*,*S*,*S*,*S*)-**G8** were synthesized and used to identify HPLC peaks corresponding to the racemization products. In this way we were able to confirm that the late-stage SuFEx reactions proceeded with maximally 1% racemization at each of the sulfur centres that are involved in the corresponding SuFEx reactions. Note that we employed **1d** with a d.e. of 96% as the starting material; we believe an even higher d.e. of the chiral oligomers can be obtained by increasing the d.e. of **1d**, for example through crystallization prior to use.

Sequence-controlled sulfonimidate polymers

To further expand the utility of the dormant property of the fluorous-tag phenol part on the oligomer chain, we finally aimed to induce SuPhenEx polymerization of sequence-defined oligomers to obtain sequence-controlled tail-to-head-type polymers. As a proof-of-concept (Fig. 7a), trimer **D1** (10 mg) in 100 µl anhydrous acetonitrile/anhydrous *N*,*N*-dimethylformamide (DMF) (1:1) was polymerized at 80 °C for 48 h in the presence of DBU (1.1 equiv.) as the base. Polymer **P1** was obtained as a white powder in a nearly quantitative yield (number-average molecular weight: $M_n = 62$ kDa; polydispersity index: $Đ = 1.36$) (Supplementary Section 7). To demonstrate that more complicated polymers could be made in this fashion, a tetramer with four different units was employed in which the reacting phenol was sterically hindered by an *ortho*-methyl moiety (tetramer **D4**, 10 mg). Even for such a polymerization, **P2** was obtained as a yellow–white powder with a nearly quantitative yield (M_n = 28 kDa; $Đ$ = 1.62) (Supplementary Section 7). To also demonstrate that sequence-controlled tail-to-head polymerization could proceed in an enantiospecific manner, an oxidized trimer (*S, Racemic*)-**D5** was designed and utilized as the monomer (Fig. 7c). This retained only the chirality of the sulfur atom as the SuPhenEx reactive site, while intentionally making the other chiral sulfur atom, which was not involved in the reaction, racemic, to eliminate its influence on any chiroptical measurements. When **G1** was exposed to a solution of KF in THF, the fluoride anion would attack in a racemizing fluoride exchange onto the end site of the sulfur centre. This racemization process was monitored by chiral HPLC and the results demonstrated that equilibrium could be reached after 2 h to obtain (*S, Racemic*)-**J2** (chiral HPLC figures in Supplementary Section 7). After that, (*S, Racemic*)-**J2** was substituted by **2a** and subsequently treated with H_2O_2 to obtain **D5** (15 mg, 11 μmol) with a yield of 48% over three steps. The polymer **P3** was prepared under the same conditions as **P1** and obtained as a white powder with a yield of 80% (M_n = 39 kDa; $Đ$ = 1.6) (Supplementary Section 7). From the results of circular dichroism (CD) measurements (Fig. 8b), an obvious absorption peak opposite to that of **D5** was observed, demonstrating that the head-to-tail polymerization indeed takes place with inversion of the configuration of the central S(VI) moiety.

In the aforementioned head-to-tail chiral polymerization, only one sulfur atom served as the SuPhenEx reactive site involved in the polymerization, thereby inverting the configuration of only one sulfur(VI) centre during the polymerization. We next aimed to investigate the enantiospecificity of the polymerization with two sulfur atoms as SuPhenEx reactive sites to further increase the tunability of the polymerization. (*S,S*)-**K1** (Fig. 7d) was synthesized by a SuFEx reaction of **1d** (60 mg, 0.105 mmol, 1 equiv., >99% d.e.) and 4-(methylthio)phenol (33 mg, 0.235 mmol, 2.2 equiv.) and was obtained with a yield of 84% (72 mg, 0.089 mmol) and virtually unchanged >99% enantiomeric excess (e.e.). This shows a promising tendency that with the higher enantiopurity of starting materials, the high enantiopurity of the products could be obtained. After an oxidation reaction using H_2O_2, (*S,S*)-**D6** (10 mg, 11 μmol, 1 equiv., >99% e.e.) reacted with **2a** (3 mg, 13 μmol, 1.1 equiv.) to produce polymer **P4** as a white powder (8 mg, 97%, M_n = 37 kDa; $Đ$ = 1.6) (Supplementary Section 7). CD measurements (Fig. 8d), clearly show an absorption peak opposite to that of **D6**, demonstrating that the symmetric polymerization takes place with a double stereoinversion. It is worth noting that the combination of SuFEx and SuPhenEx, allows to obtain a chiral polymer and its enantiomeric polymer by using only one configuration of a chiral di-SF monomer (prepared by a four-step synthesis), which efficiently shortens the overall synthetic efforts. We combined the reported CD curve (*S,S*)-**P4** (ref. 40) and our currently prepared (*R,R*)-**P4** in one figure (Fig. 8e). These CD data show opposite absorption peaks, confirming the success of such an approach. Moreover, the success of this polymerization demonstrates that the SuPhenEx reaction also worked for the sulfonyl-linked phenol caps with other alkyl groups (here CH_3), and is, as hypothesized, not limited to the perfluoro tag used above. Therefore this readily and greatly expands the series of potential substrates for caps on the oligomer chain. Moreover, chiral SuFEx-based polymers with control over the configuration of each S(VI) centre can be easily obtained in this manner, paving the way to polymer synthesis with excellent control over the stereocentres in sequence-controlled polymers.

Conclusions

A highly flexible synthetic strategy was developed for the stepwise iterative synthesis of oligosulfonimidates via SuFEx and SuPhenEx reactions. The whole sequence, including the cap, two types of building block and the configuration of each sulfur centre can be fine tuned in great detail, both regarding the sequence and the chirality of each sulfur atom. As a key feature we use here a perfluoro-tagged phenol as a dual-purpose cap: it not only greatly simplifies purification processes but also possesses dormant characteristics as it can be turned from a stable end cap to an excellent leaving group by a simple oxidation step that does not harm the rest of the oligomer. By leveraging this dormant feature, a sequence-defined thirteen-mer (MW = 4.50 kDa) was successfully synthesized through a convergent method and sequence-controlled sulfonimidate polymers were synthesized by a tail-to-head-type polymerization strategy. Finally, chiral oligosulfonimidates and polysulfonimidates with different configurations can be obtained by adjusting the configurations of the monomers and the method of polymerization. We expect that these synthetic methods will further pave the way for digital data storage and thus are a significant contribution to materials science[41].

Methods

General procedure for purifying products by FSPE

Fluorous silica gel (40 g)[29,30] was packed into a column and treated with 100 ml DMF, followed by 200 ml 80% MeOH/H_2O. Subsequently, the concentrated reaction mixture (maximum 2–3 g per loading) was dissolved in 1–5 ml dichloromethane (DCM) and loaded onto the column. Initially, 80% MeOH/H_2O was used to wash out non-fluorous tag compounds (for example monomers taken in excess). Subsequently THF or ACN were employed to wash out any fluorous-tagged compounds. If needed, the product was further purified by normal-phase flash chromatography.

General procedure for chain growth via reaction with a di-SF monomer

An oligomer with phenol-reactive sites (see details below) and DBU (1.5 equiv.) were placed in an oven-dried one-dram vial, dissolved in DCM or THF (see details in the Supplementary Information) and the reaction mixture was stirred for 10 min. Afterwards, the mixture was added with a syringe pump at a rate of 0.05 ml min^{-1} to another 15 ml glass vial containing the di-SF monomer (**1a**–**c**, 5 equiv.) in DCM. The reaction mixture was stirred for 30 min to 2 h and the reaction progress was monitored by TLC. Then, the mixture was quenched with water, the organic phase was extracted and the aqueous phase was further extracted with DCM three times. The resulting organic phases were combined and the solvent was evaporated under reduced pressure. The residue was purified by FSPE and the product was further purified by normal-phase flash chromatography.

General procedure for chain growth via reaction with a diphenol monomer

In an oven-dried one-dram vial, a bisphenol monomer (5 equiv.) and DBU (5 equiv.) were dissolved in THF and the reaction mixture was stirred for 10 min. Afterwards, the oligomer with an SF-reactive site (see details in the Supplementary Information) in THF was added with a syringe pump at a rate of 0.05 ml min^{-1}. The reaction mixture was stirred for 30 min to 2 h and the reaction progress was monitored by TLC. After completion, the reaction mixture was evaporated under reduced pressure and the residue was purified by FSPE. The product was further purified by normal-phase flash chromatography.

General procedure for the oxidation of sulfur on the fluorous tag

In a one-dram vial, an oligomer containing a fluorous tag (**A3, A5** or **A7**, 1 equiv., see details below) was dissolved in THF (0.17 M). Subsequently, ethanol (1/3 volume of THF) was added to the mixture, followed by the dropwise addition of ammonium molybdate tetrahydrate (0.1 equiv.) in 30% hydrogen peroxide (18 equiv.). The reaction mixture was stirred for 2 h and TLC was used to monitor the reaction progress. After that, water was added to quench the reaction mixture and DCM was used to extract the aqueous layer three times. The resulting organic layers were combined and evaporated under reduced pressure. Formed products (**D1**–**3**) were obtained as white solids and were further used without additional purification.

General procedure for the substitution of the fluorous tag with phenol

In an oven-dried one-dram vial, oxidized intermediate (**D1**–**3**, 1 equiv., see details in the Supplementary Information) and phenol (10 equiv.) were dissolved in THF (0.15 M). Subsequently, DBU (4 equiv.) in THF (0.5 M) was added to the reaction mixture. The reaction mixture was stirred at room temperature for 2 h and TLC was used to monitor the progress of the reaction. After that, the solvent was removed under reduced pressure. The crude product was purified by normal-phase flash chromatography to yield products **E1**–**E3** as white solids.

General procedure for polymerization by SuPhenEx reactions

The polymerization was performed inside an argon-filled glovebox (MBRAUN MB 20 G-LMF gas purifier with H_2O values of <0.1 ppm). In a 2 ml Biotage microwave glass vial equipped with a magnetic stir bar, the oxidized oligomer (**D1, D4** or **D5**, 1 equiv.) was dissolved in a mixture of 0.05 ml anhydrous acetonitrile and 0.05 ml anhydrous DMF with vigorous stirring. Then, DBU (1.1 equiv.) was added and the reaction mixture was stirred at 80 °C for 48 h. After that, 0.1 ml DMF was added. The vial was shaken to facilitate dissolution and the resulting solution was slowly poured into 50 ml MeOH while continuously stirring. Precipitation occurred and stirring was continued for an additional 10 min. After allowing the formed precipitate to settle for 10 min, the methanol layer was removed and a minimal amount of DMF was added to redissolve the precipitate. This cycle of precipitation, sedimentation and dissolution was repeated four times. The resulting white powder/fibrous material was transferred into a 4 ml glass vial and dried at 50 °C under reduced pressure for a minimum of 12 h.

Data availability

All relevant data generated and analysed during this study, which include experimental and spectroscopic data, are included in this Article and its Supplementary Information.

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Author contributions

F.M.M. and H.Z. conceived and designed the experiments. B.C., F.M.M. and H.Z. supervised the project. Y.H. designed and performed all small molecule syntheses and was helped by M.S. for some monomer syntheses. S.P.P. performed the polymerizations, X-ray photoelectron spectroscopy, gel permeation chromatography and CD measurements. H.Z. performed the theoretical calculations. Y.H., F.M.M. and H.Z. analysed all the data. Y.H. wrote the first draft of the manuscript and F.M.M. and H.Z. revised the manuscript. All authors discussed the results and commented on and agreed with the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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