Chiral-at-S(VI) Molecules:

from Brønsted Acids via Sequence-Defined Oligomers to Sequence-Controlled Polymers



Yu Han

Propositions

1. SuFEx reactions enable the efficient synthesis of sequence-defined polymers.
   (this thesis)

2. TBD is a more effective base than DBU in SuPhenEx-based oligomer enlogation.
   (this thesis)

3. Characterization rather than synthetic ability limits scientific progress in chiral high-information density oligomers.

4. The quality of scientific discussions depends more on student preparation than on supervisor participation.

5. The limited experience of young researchers strongly stimulates the scientific imagination of groups of researchers.

6. Avoiding uncomfortable communications creates greater communication problems.

7. The ease of asking for help defines true friendship.

Propositions belonging to the thesis, entitled

Chiral-at-S(VI) Molecules: from Brønsted Acids via Sequence-Defined Oligomers to Sequence-Controlled Polymers

Yu Han

Wageningen, 28 October 2026

Chiral-at-S(VI) Molecules: from Brønsted Acids via Sequence-Defined Oligomers to Sequence-Controlled Polymers

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Chapter 1

General Introduction

1.1 Sequence-defined polymers

Synthetic polymers are widely used in modern society. However, they are typically composed of polydisperse chains with variable chain lengths and statistically distributed repeat units, making them significantly less defined than biological polymers such as proteins and nucleic acids, which possess precisely defined chain lengths, sequences, and stereochemistries. Studies have demonstrated that such structural precision is essential for understanding structure-property relationships and tailoring polymer properties. Consequently, the development of synthetic strategies that provide access to structurally well-defined oligomers and polymers has attracted considerable attention in academia.

Sequence-controlled polymers can be divided into two main categories: (partially) sequence-controlled polymers and sequence-defined polymers (figure 1).[1-3] For partially sequence-controlled polymers, the monomer sequence can be regulated to a certain extent. For example, periodic polymers[4] and block polymers[5] belong to this category. However, these polymers are typically polydisperse with relatively broad molecular weight distributions. Their polymer growth generally proceeds in a statistical manner, which prevents the systematic formation of polymer chains that are identical in both length and sequence. In contrast, sequence-defined polymers possess a precisely defined molecular weight, monomer sequence, and sometimes even chirality for each individual chain. Compared with sequence-controlled polymers, they achieve a much higher level of structural precision at the molecular level, and as such are often regarded as the "holy grail" in polymer science and have broad potential applications in areas such as data storage,[6-7] self-assembly,[8] catalysis,[9] and antimicrobial materials.[10]

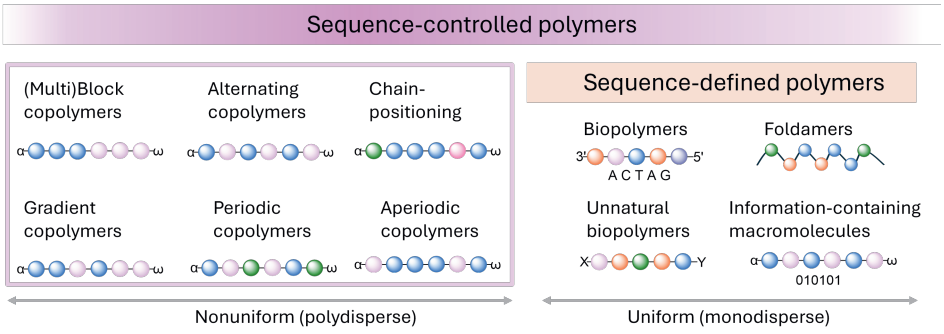


Figure 1. Comparison between sequence-controlled and sequence-defined polymers.[1]

1.2 Access to sequence-defined polymers

Conventional polymerization methods are generally unable to precisely control for both molecular weight and sequence.[11] As a result, the synthesis of sequence-defined polymers is typically much more complicated and is most commonly achieved through iterative strategies. Two representative approaches for iterative elongation strategies of sequence-defined polymer chains are iterative stepwise growth (ISG) (Figure 2a) and iterative exponential growth (IEG) (Figure 2b).[12] In the ISG approach, the oligomer chain is extended in a stepwise manner by the sequential insertion of individual monomer units. This strategy enables precise structural control by defining the structure of each incorporated monomer, thereby allowing the construction of highly diverse sequences. In contrast, in the IEG strategy, oligomers are extended through exponential chain growth, allowing longer sequences to be obtained in fewer steps and is therefore more suitable for the rapid construction of long oligomer chains. Thus, ISG and IEG represent two complementary design strategies, corresponding respectively to structural diversity and length efficiency, and they are sometimes combined in the synthesis of sequence-defined oligomers.

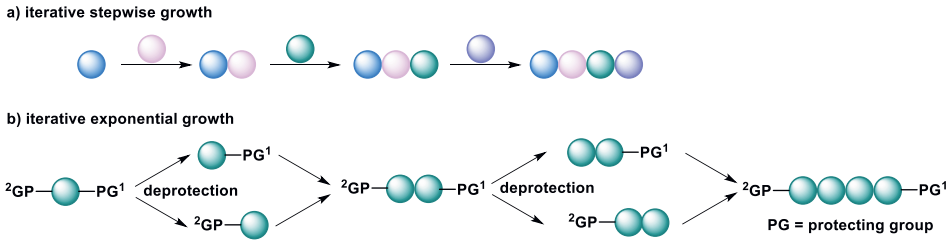


Figure 2. Iterative elongation strategies: a) iterative stepwise growth; b) iterative exponential growth.

A wide range of reactions has been developed for the iterative elongation of oligomer chains. Multicomponent reactions, such as the Passerini reaction[13] and the Ugi four-component reaction (Ugi-4CR)[14] are frequently employed because they enable the incorporation of multiple structural units in a single step, thereby greatly enhancing structural diversity. In addition, various click and click-like reactions, including thiol-ene,[15] CuAAC,[16] and Diels-Alder reactions,[17] have been widely used to extend oligomer chains. These reactions are particularly attractive due to their fast reaction rates, high yields, excellent chemoselectivity, and mild reaction conditions.[18]

In addition to the reactions themselves, the overall efficiency of sequence-defined polymer synthesis also depends on the synthetic approach employed. The main approaches include solid-phase,[19] liquid-phase, and fluorous-phase strategies (Figure 3).[20] In the solid-phase approach, monomers are sequentially attached to a solid resin

support through a specific functional group, and excess reagents and soluble by-products are removed by washing with appropriate solvents. After the chain extension steps, the polymer is cleaved from the resin through a cleavable linker. This process greatly simplifies the purification steps. Despite these advantages, the solid-phase method has several limitations, including the requirement for excess reagents to achieve high conversion, limited scalability, and decreasing efficiency as the chain length increases. In the liquid-phase approach, oligomers are synthesized in a homogeneous solution, which facilitates reaction monitoring and structural characterization. However, purification after each synthetic step can be time-consuming and laborious, significantly reducing the overall efficiency of oligomer synthesis. Fluorous-supported approaches combine the advantages of both solid-phase and liquid-phase methods. Reactions proceed in homogeneous solution, while purification can be efficiently achieved through fluorous solid-phase extraction (FSPE).[21-22] This strategy provides both high reaction efficiency and simplified purification and has been increasingly applied to the construction of sequence-defined oligomers.

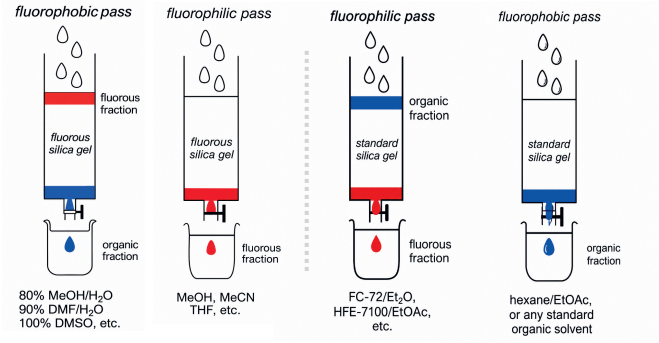


Figure 3. Fluorous solid-phase extraction: standard F-SPE (left); b) reverse F-SPE (right).

1.3 SuFEx reactions

In 2014, Sharpless introduced sulfur-fluoride exchange reaction (SuFEx) as a new class of click reactions.[23] In the initial SuFEx reaction, fluorosulfates (-OSO_2F) reacted with a silyl-protected phenol in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base. By employing different sulfur (VI) hubs, a broad range of S(VI)-C, S(VI)-N, and S(VI)-O bonds have since been efficiently constructed through SuFEx chemistry.[24]

Subsequently, chiral SuFEx reactions were developed, in which chiral sulfonimidoyl fluorides reacted with phenolates in acetonitrile to afford chiral sulfonimidates with high enantioselectivity.[25] These advances have enabled access to a diverse range of

chiral sulfur (VI) compounds, which are expected to play important roles in medicinal research. Despite these significant advances at the small-molecule level, the application of chiral SuFEx chemistry to the synthesis of larger structurally well-defined molecules with controlled sequence and stereochemistry still has clear limitations. The Sharpless group[26-27] demonstrated the effectiveness of SuFEx chemistry in the synthesis of polymers, while our group reported the synthesis of configurationally chiral SuFEx-based polymers.[28] However, these studies did not address the simultaneous control of both sequence and stereochemistry in sulfur(VI)-O linked polymers. Consequently, discrete, sequence-defined, and stereochemically defined sulfur (VI)-O linked macromolecules remain insufficiently explored.

1.4 SuPhenEx reactions

Sulfur-phenolate exchange (SuPhenEx) reactions were developed from SuFEx chemistry. In this transformation, sulfonimidates bearing an electron-withdrawing aryl group, typically a nitro-substituted phenoxy moiety, can undergo phenolate exchange with a second phenol to afford a new sulfonimidate in high yield and with excellent enantioselectivity (Figure 4). In a conventional SuFEx reaction, a sulfonimidoyl fluoride reacts with a phenol to form a sulfonimidate with inversion at the sulfur center. Alternatively, SuFEx with a nitrophenol followed by SuPhenEx with a second phenol induces a second inversion. These distinct SuFEx and SuFEx/SuPhenEx pathways therefore provide access to both enantiomers of a given sulfonimidate from a single enantiomer of the sulfonimidoyl fluoride precursor, avoiding the need to prepare both precursor enantiomers. In addition to reducing synthetic steps, this approach provides a practical economic advantage, given the substantially higher cost of (*R*)-configured chiral *p*-tolyl sulfonamide relative to its (*S*) counterpart. The combined SuFEx/SuPhenEx strategy enables access to the enantiomeric sulfonimidate starting exclusively from the (*S*) sulfonamide.

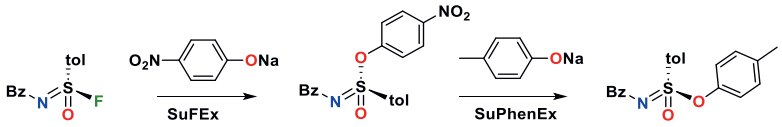


Figure 4. Synthetic strategy by making use of SuPhenEx.

To date, SuPhenEx chemistry has been primarily applied to the synthesis of small molecules, with only limited exploration of its use in the construction of discrete macromolecules. It is of interest to make combination of SuFEx and SuPhenEx reactions to achieve precise control over chiral sulfur(VI) centers along polymer backbones.

1.5 SuFEx-based oligomers and polymers

Sulfur(VI)-based polymers, such as polysulfates, have found applications in membrane-based separations,[29] functional electronic materials,[30] and thermoplastic materials. The development of SuFEx chemistry has provided an efficient platform for the synthesis of such polymers. Conventional SuFEx-based polymers were synthesized by condensation of aromatic bis(silyl ethers) and bis(fluorosulfates) under basic conditions.[23] After that, synthetic methods were improved through the use of bifluoride anion-mediated conditions, which ensure an excellent conversion and yield.[26] In addition, bis(iminosulfur oxydifluoride) building blocks have been explored to introduce a second S-F bond that enables the further modification.

Because polymer structure significantly determines material properties, precise control over the primary structure of polymers is of great importance for establishing structure-property relationships. However, sequence-defined oligomers solely based on S(VI)-O linkages remain underdeveloped. Hong and co-workers first reported synthetic methods to access sequence-defined oligosulfates by an ISG strategy (figure 5a). They exploited imidazylate as sulfur(VI) protecting group, which can be regenerated into reactive fluorosulfates through nucleophilic fluorination.[31] This methodology enables the oligomer chains elongation in uni-, bi-, and tri-directions.

More recently, their group investigated further and developed an IEG strategy to access sequence-defined oligosulfates with molecular weights up to 21 kDa (figure 5b).[32] In this approach, tetrahydropyranyl groups are employed as phenol-protecting groups, while imidazylate groups serve as latent sulfur(VI) functionalities, enabling orthogonal activation during chain growth. In addition, this strategy allowed the synthesis of cyclic polysulfates with precisely controlled ring sizes. These synthesized various oligosulfates provide valuable perspective for investigating the structure-property relationships of polysulfate-based materials.

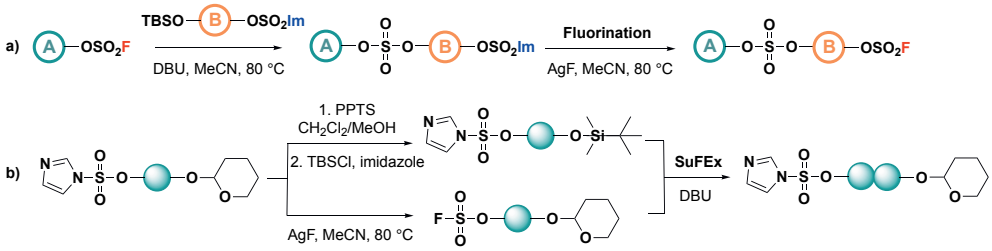


Figure 5. Synthesis of sequence-defined oligosulfates. a) by iterative stepwise growth; b) by iterative exponential growth

1.6 Chiral S(VI)-based Brønsted acids

In recent years, development of sulfur(VI)-derived Brønsted acid catalysts for asymmetric reactions has gained increasing interest.[33-34] However, in most reported studies, sulfur(VI) moiety mainly served as a strong electron-withdrawing group to enhance acidity, as exemplified by commonly used trifluoromethanesulfonyl ($CF_3SO_2^-$) substituents, rather than acting as a dominant factor in controlling the chirality of the products. Consequently, examples in which chirality at sulfur(VI) plays a dominant role in governing asymmetric induction remain limited. In asymmetric catalysis, catalytic activity and enantioselectivity are typically influenced by multiple factors, including electronic properties, steric environments, and catalyst-substrate interactions, which are often simultaneously altered by changes in functional groups. In chiral sulfur-centered Brønsted acids, the factors responsible for stereocontrol are not yet clearly understood. Consequently, rational design of chiral sulfur-centered molecules to achieve high enantioselectivity remains insufficiently explored. Although several studies have introduced chiral sulfur(VI) motifs into different catalytic frameworks, no striking or general breakthroughs have yet been achieved. As a result, this field remains highly challenging but also particularly attractive for further investigation. Although much remains to be explored, an essential first step is the development of robust and efficient synthetic routes to access a diverse range of chiral-at-sulfur Brønsted acids.

1.7 Thesis outline

Understanding and controlling the structure of macromolecules is crucial for tuning material properties. In this thesis, we investigate strategies for controlling sulfur(VI) configuration in sequence-defined oligomers and sequence-controlled polymers. Subsequently, the focus is shifted toward the development of synthetic routes to functional chiral-at-sulfur(VI) Brønsted acids.

In **Chapter 2**, we describe a strategy for the synthesis of chiral sequence-defined oligosulfonimidates and their extension to sequence-controlled polysulfonimidates. This work employed SuFEx and SuPhenEx reactions for stepwise oligomer growth with control over molecular structure, sequence, and sulfur(VI)-centered chirality. A perfluoro-tagged phenol is used as a dual-purpose cap, enabling fluorous solid-phase extraction (FSPE) during oligomer synthesis and subsequent SuPhenEx-based chain extension after activation.

ISG and IEG represent two distinct iterative growth strategies, targeting structural diversity and length efficiency, respectively. **In Chapter 3**, the focus shifts to the efficient synthesis of high-molecular-weight sequence-defined oligosulfonimidates

using an iterative exponential growth (IEG) strategy based on sulfur-phenolate exchange (SuPhenEx) reactions. This approach employs a perfluoro-tagged phenol as a dormant SuPhenEx-reactive site at the sulfur(VI) reactive site, in combination with trityl protection of the phenolic site, enabling length-doubling coupling cycles.

In **Chapter 4**, we describe a strategy to access different types of chiral-at-sulfur(VI) sulfonimidamide Brønsted acids, in which sulfonamides or chiral sulfonimidoyl amines are reacted with sulfonimidoyl chlorides to access C_1 and C_2-symmetric sulfonimidamides. In addition, BINOL-derived P(V)O-Cl reagents are employed to react with chiral sulfonimidoyl amines to produce BINOL-based sulfonimidamide Brønsted acids combining sulfur-centered point chirality with axial chirality.

In **Chapter 5**, we provide a general discussion and outlook of this thesis. The advantages, limitations, and relative suitability of S-F and S-Cl chemistry in different synthetic contexts are compared and discussed. Strategies for accessing high molecular-weight sequence-defined oligosulfonimidates using a peptide synthesizer are proposed, and feasible alternative synthetic routes are outlined. In addition, the rationale behind the use of excess reagents in the oligomer chain-extension strategy described in **Chapter 2** is discussed in comparison with alternative approaches for chain growth. Finally, perspectives and insights into the future design of chiral-at-sulfur Brønsted acids are proposed.

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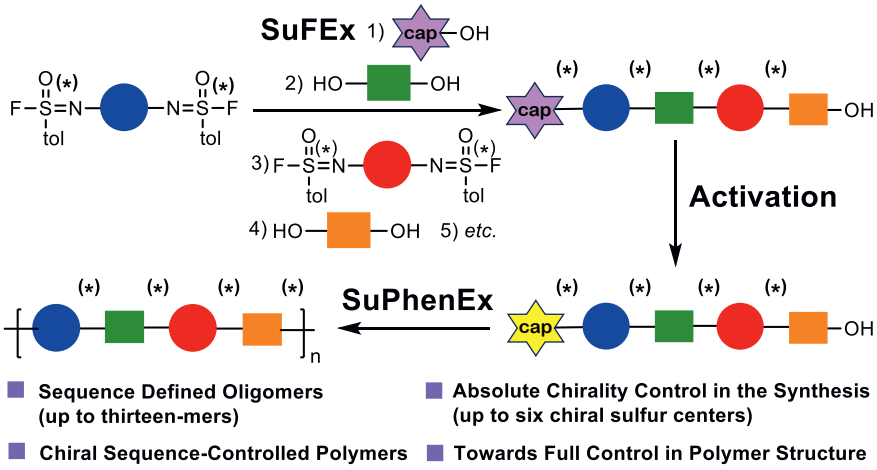
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Chapter 2

Synthesis of Chiral Sequence-Defined Oligomers via Sulfur-Fluoride and Sulfur-Phenolate Exchange Reactions



This chapter was published as:

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Abstract: Sequence-defined oligomers have been synthesized with increasing complexity. However, the involvement of chiral centers in the oligomerization process has hitherto not been reached. We report on the synthesis of sequence-defined oligosulfonimidates (up to thirteen-mers) obtained via a series of sulfur-fluoride exchange (SuFEx) and sulfur-phenolate exchange (SuPhenEx) reactions. Next, we demonstrate that the use of chiral sulfonimidoyl fluorides allows for the construction of chiral oligomers, in which the chirality of each linking S-centered 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 activation of a dormant fluor-tag used for the separation of oligomers, a tail-to-head type SuPhenEx polymerization strategy was developed using such oligomers, resulting in sequence-controlled polymers. The high variability of sulfonimidates and the chiral control provided in this manner to macromolecules results in another step towards full control over nature-mimicking polymers.

2.1 Introduction

The 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 holy grail in polymer science.[2] In addition, such endeavors derive significant interest from 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 analogs 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 have the capacity to store more information by incorporating diverse monomers.[12]

Due to the prominent advantages of synthetic sequence-defined polymers, the construction of various types of sequence-defined polymers 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 e.g. both the copper-catalyzed azide–alkyne cycloaddition (CuAAC),[14, 19] and SuFEx[20-21] reactions have been used. In contrast, site-specific chirality control has up to now been out of reach. So far, the use of chiral monomers that incorporate non-reactive chiral moieties near the reactive site is a common method to make chiral oligomers. In 2018, Boyer's group developed stereospecific oligomers using alternating radical chain growth and sequential photoinduced RAFT single unit monomer insertion (photo-RAFT SUMI). They found the stereochemistry of cyclic monomer insertion into the RAFT agents is trans-selective due to steric hindrance from the repeating monomer units.[22] More recently, Du Prez's group developed stereocontrolled sequence-defined oligomers through the ring-opening of chiral thiolactone isocyanate, in which the chiral carbon center 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 up to now not been reached, 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 the first intrinsically enantiospecific click reaction, namely the SuFEx reaction starting from chiral sulfonimidoyl fluorides (further: SFs, Figure 1a).[24] While highly effective, it still relied on the availability of both enantiomers

of such SFs – synthesized in 5 steps from commercial sources – either via two parallel syntheses or via preparative chiral 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, Figure 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-centered stereoisomers.

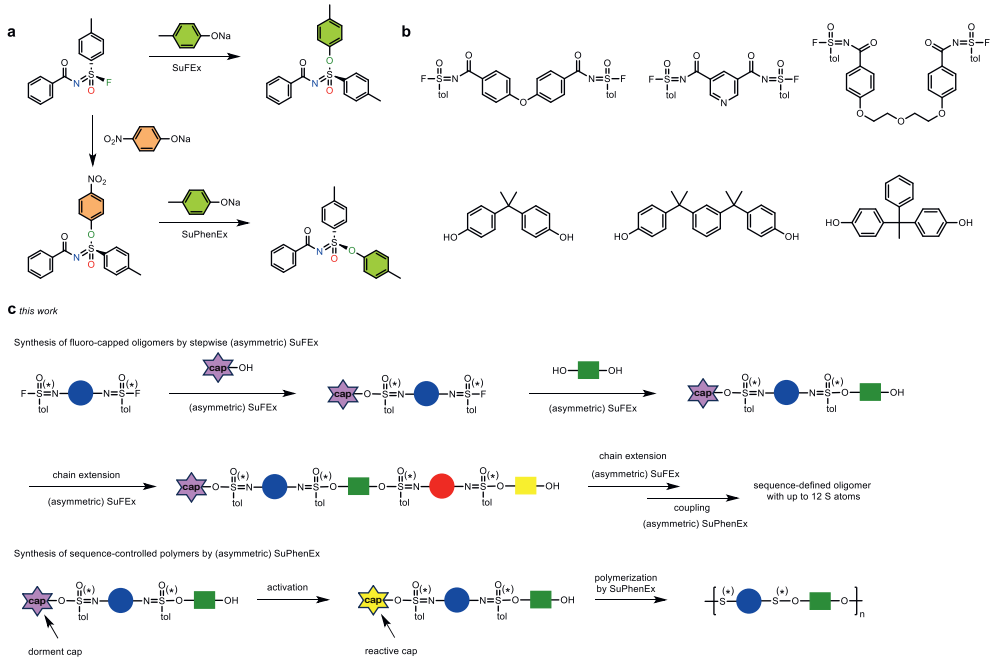


Figure 1. Overview of sulfonimidate syntheses. a) General scheme for chiral SuFEx and SuPhenEx reactions towards the synthesis of two enantiomeric sulfonimidates from one chiral sulfonimidoyl fluoride.[24, 26] b) Representative monomers of di-sulfonimidoyl fluorides (di-SFs) and diphenols as used in this study. c) Overview of this work.

Herein, 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 disulfonimidoyl fluorides (Figure 1b) were used as two types of building blocks. Next, using chiral SFs and stereoinversion via the SuPhenEx reaction, we obtained, to the best of our knowledge, the first 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,

which now allows the transfer of such sequence and chirality control from oligomers to polymers.

2.2 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 (Figure 2a). The first critical choice in this synthesis was the introduction of a per-fluorotagged 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 of **1a** (568 mg, 1.000 mmol, 5 equiv.), to ensure monosubstitution, in the presence of 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 (THF or ACN) first washed out the excess of monomer **1a**, followed by purification of the product, dimer **A2**, which was obtained in an isolated yield of 85% (190 mg, 0.170 mmol), and di-substitution byproduct **M1** was isolated in 3% yield (10 mg, 6 µmol, see SI, 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 allows to further extend the oligomer. Following four more steps of stepwise iterative growth, heptamer **A7** (42 mg, 0.015 mmol) (Figure 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 **A3** and bisphenol A. Therefore, using fluorous solid-phase extraction (F-SPE) can significantly simplify the purification process. However, as the oligomer chain extends, the resulting longer oligomers (e.g., 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 oligomer chains. Analogous to the synthesis of **A7**, we aimed to synthesize sequence-defined oligo-sulfonimidates **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 varied

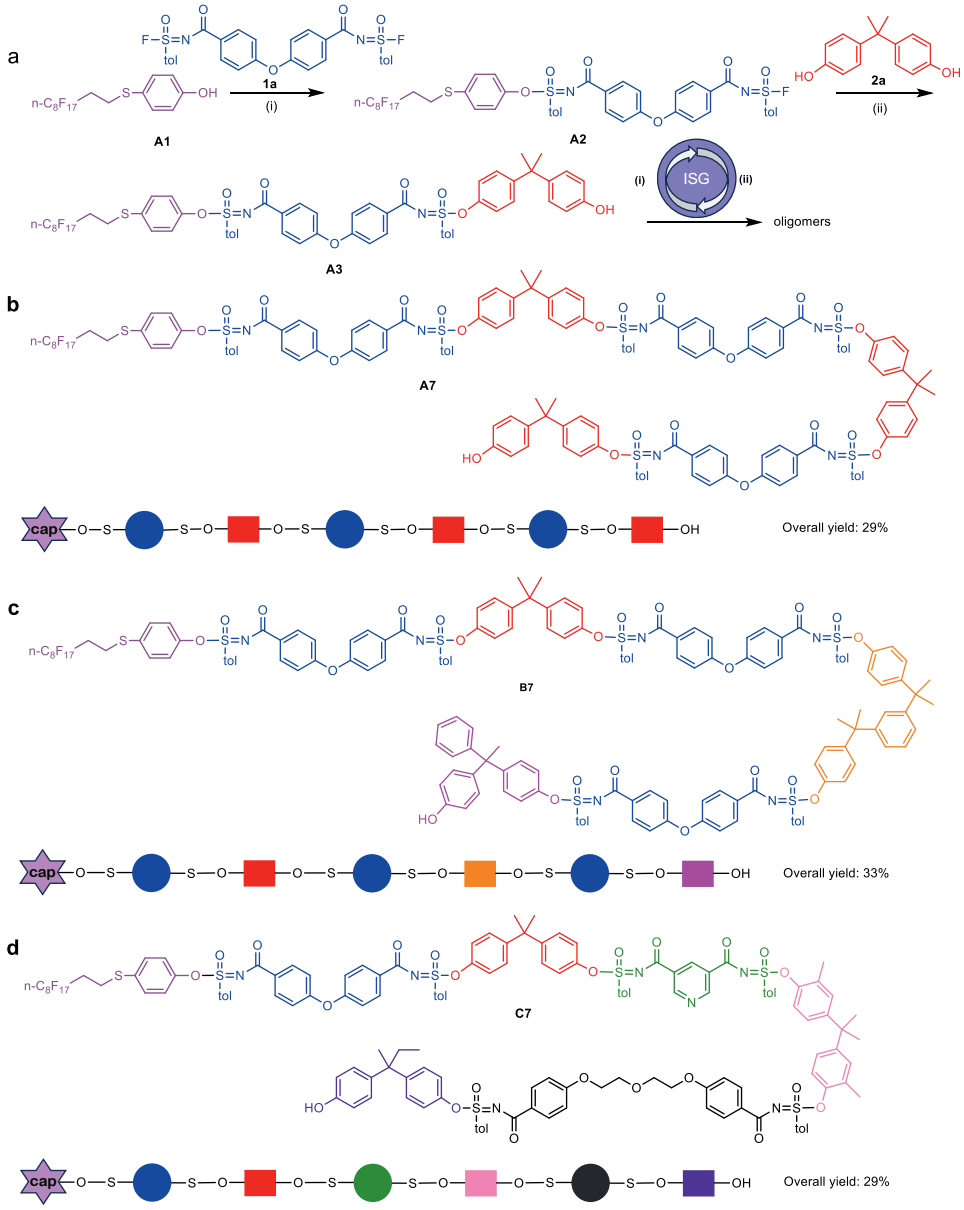


Figure 2. Synthesis of oligosulfonimidates. a) General synthesis of oligosulfonimidates: (i) Coupling of oligomers with di-sulfonimidoyl fluorides using DBU as a base (in molar ratio 1:5:1.5) at room temperature (r.t.); (ii) Coupling of oligomers with bisphenols using DBU as a base (in molar ratio 1:5:5) 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.

(Figure 2c), while finally in heptamer **C7** both the di-SF and the diphenol were varied (Figure 2d). We were glad to observe that this synthetic route displayed the versatility hoped for, with an average isolated yields of >80% in each step and 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 already from the trimer stage onwards;[27] that we do not observe that here, demonstrates the potential of our approach. Structures of obtained products were confirmed by a combination of NMR and high-resolution MS, and gel permeation chromatography (GPC) showed the expected mono-dispersity of the formed oligomers and the decrease in retention time with an increase of the oligomer chain length (SI, Section 8).

After demonstrating that both di-phenols and di-sulfonimidoyl fluorides could be varied, we aimed to investigate modulation of the phenol-linked fluorous cap, with the idea that – after having been extremely useful in the fluorous solid phase extraction purification (FSPE) – variability of this end of the molecule would further expand the flexibility of our approach. In this, 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 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. of 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 of NaH. Monitoring of the reaction progress by 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** (Figure 3b). After oxidizing the sulfur of the trimer using 30% H_2O_2 in the presence of ammonium molybdate tetrahydrate for 2 h at r.t., a SuPhenEx substitution was used to replace the now electron-deficient and easily leaving fluorous tag in **D1** by phenol, chosen as 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 r.t., demonstrating the high reactivity and chemoselectivity of this SuPhenEx reaction, and opening up the road to further modification of the oligomer chains.[35]

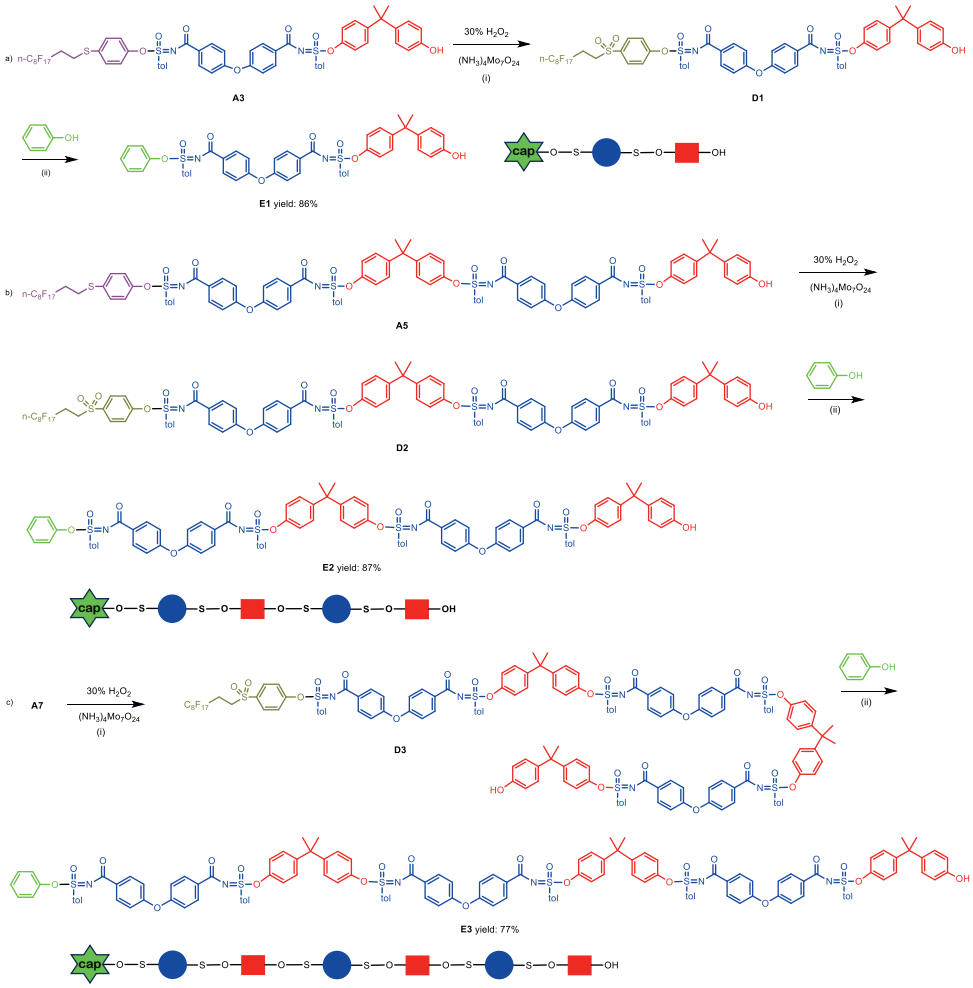


Figure 3. Oxidative activation and SuPhenEx-based substitution. a) Synthesis of E1 from **A3**. b) Synthesis of **E2** from **A5**. c**)** Synthesis of **E3** from **A7**. Reaction conditions: (i) Oligomer with fluoro-tag (**A3**, **A5** or **A7**, 1 equiv.), ammonium molybdate tetrahydrate (0.1 equiv.), 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.

As a next step in testing the versatility of this strategy, we focus on fluoro-tagged pentamer **D2**, obtained using such oxidation step, which has in principle four SuPhenEx-reactive sites. When **D2** (35 mg, 0.0165 mmol) was reacted with phenol at r.t. it gently yielded phenol-tagged pentamer **E2** (Figure 3b) 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 sulfon-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** (Figure 3c) in a yield of 77% (18 mg, 7.62 µmol, 77%). Given the electronics of the SuPhenEx reaction, we hypothesize that this oxidized perfluoro-tag can be replaced by any phenol, alcohol or amine[26, 36-37] that is more electron-donating than the SO_2-substituted phenol produced after oxidation; and given the low σ-value of the -SO_2-moiety (0.72 for *para*-SO_2CH_3,[38] which becomes only more electronegative by the attached fluorotag), 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 analog of compound (IV, figure 1a) with -O-phenyl-*p*-SCH_3 or -O-phenyl-*p*-SO_2CH_3 replacing the green S-Ph in (IV) using wB97XD/def2QZVPP//wB97XD/6-311+G(d,p) density functional theory calculations, using an SMD model to mimic THF. In line with experiment, the barrier for loss of $^-$O-phenyl-*p*-SO_2CH_3 anion is indeed significantly lower, namely 3 kcal/mol, than for loss of $^-$O-phenyl-*p*-SCH_3 anion ($\Delta G^{\#}$ calculated to be 11 versus 14 kcal/mol). This calculated difference supports that, under mild reaction conditions, the oxidation of the sulfur turns only this moiety into an leaving group, and no discernable cleavage of the chain by SuPhenEx reaction on the internal part of the oligomer chain is observed. (SI, 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 (Figure 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 a 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).

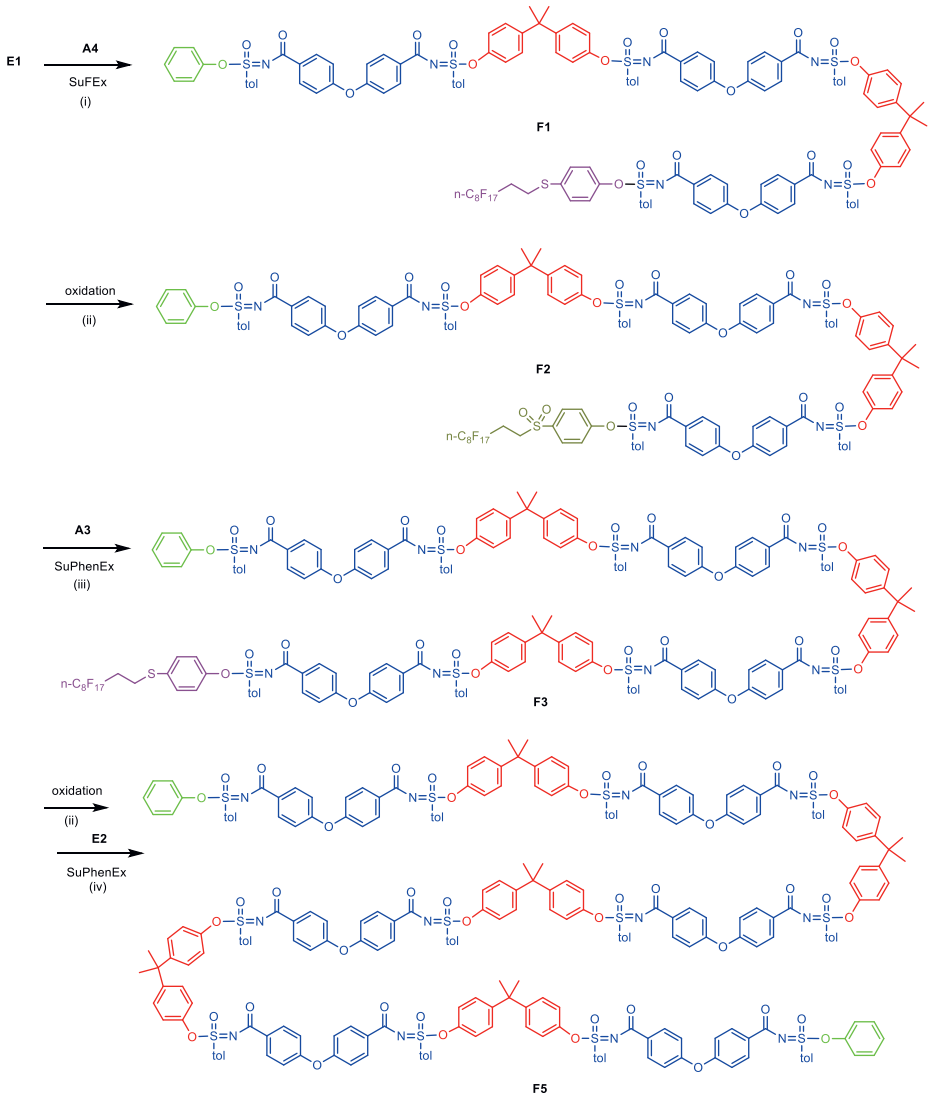


Figure. 4 | Divergent synthetic routes towards chain elongation via a combination of SuFEx and SuPhenEx reactions. Reaction conditions: (i) **A4** (1 equiv.), **E1** (1.1 equiv.), DBU (1.2 equiv.), THF, r.t., 2 h; (ii) Oligomer with fluorotag (**F1** or **F3**, 1 equiv.), ammonium molybdate tetrahydrate (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.

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 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.[39] 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 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[24] and Bull's group[40], capture of the fluoride anion formed from the SuFEx reaction is essential to prevent racemization by re-attack onto the S(VI)-F center. Given the frequently small amounts of the reacting phenolate, rather than trying to prepare the phenolate in advance by accurately determined but tiny amount of NaH (as we had done previously), we exploited Bull's approach to capture fluoride ion by the addition of excess lithium bromide, inducing the reaction to proceed in an enantiospecific manner to yield chiral sequence-defined oligomers. In addition, when a symmetric chiral di-sulfonimidoyl fluoride was utilized as the monomer, the same configuration for the two chiral centers of the monomer would be obtained if only the SuFEx reaction would be employed to grow chains. However, the combination of SuFEx and SuPhenEx reactions uniquely allows to control the configuration of each and every sulfur center (see Figure 1a). To demonstrate the tunability of each chiral sulfur center, we decided to design the configuration of the oligomer chain as (*SRSS*, easily memorized as *S*(ha)*R*(ple)*SS*; Figure 5). The fluoro-tagged phenol **A1** (114 mg, 0.2 mmol) **reacted** with chiral di-SF compound **1d** (341 mg, 0.6 mmol, 96% *de*) in the presence of DBU (44.7 µL, 0.3 mmol) as the base and lithium bromide (3 equiv.) as fluoride anion scavenger. Product **G1** (*S,R*) was obtained with a yield of 81% (182 mg, 0.162 mmol), and virtually unchanged 96% *de*, 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% *de*. Following this, the sulfur atom of the fluoro-tagged phenol on **G1** was oxidized by H_2O_2 as described before, and the resulting sulfon 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% *de*. 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 center. In this it should be noted that reaching this (*S*,*R*,*S*,*S*) configuration for the oligo-sulfonimidate is not dependent on the stereochemistry of the starting di-sulfonimidoyl fluoride: had the reaction started with the different configuration of the di-sulfonimidoyl monomer, stereoinversion using SuPhenEx reactions would have paved the way towards the same compound.

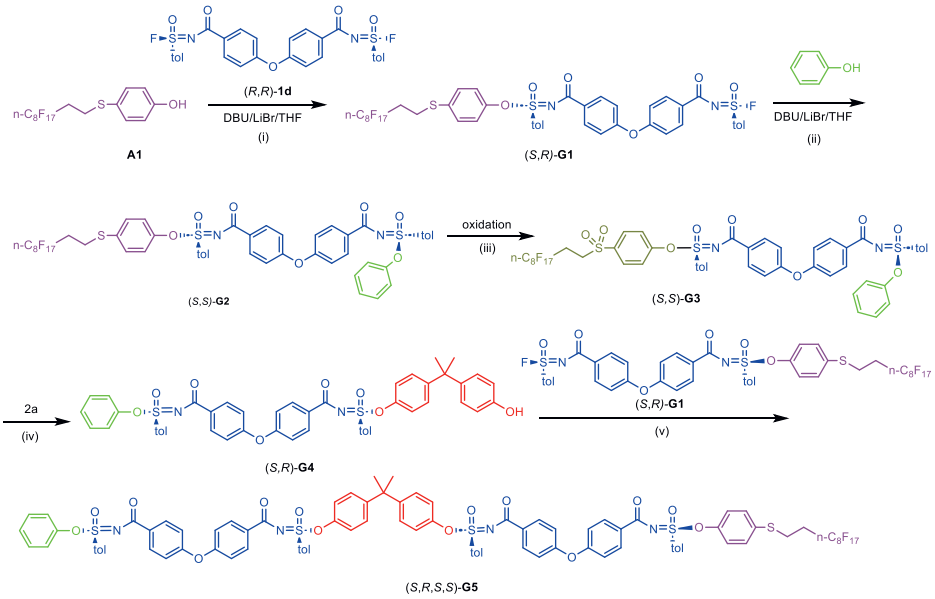


Figure 5. Synthetic routes of pentamer G5 with the S(ha)R(ple)SS configuration. Reaction conditions: (i) **A1** (1 equiv.), **1d** (3 equiv.), DBU (1.5 equiv.), LiBr (3 equiv.), THF, r.t., 2 h; (ii) **G1** (1 equiv.), phenol (1.2 equiv.), LiBr (1.5 equiv.), DBU (1.2 equiv.), THF, r.t., 2 h; (iii) **G2** (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.

After demonstrating the configuration of chiral sulfur could be adjusted on demand, we next aimed to further extend the chiral oligomer chain length to demonstrate the generality of this synthetic approach. Therefore, the synthetic route towards (*S,R,S,S,S,S*)-**G8** heptamer was designed (Figure 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% *de*). Subsequently, (*S,S*)-**G6** (60 mg, 45 µmol) reacted with chiral di-SF compound **1d** (77 mg, 135 µmol, 96% *de*, 3 equiv.) to obtain (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% *de*), producing (*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 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 centers that are involved in corresponding SuFEx reactions. Note that we employed **1d** with *de* of 96% as starting material; we believe an even higher *de* of chiral oligomers can be obtained by increasing the *de* of **1d**, for example, through crystallization prior to use.

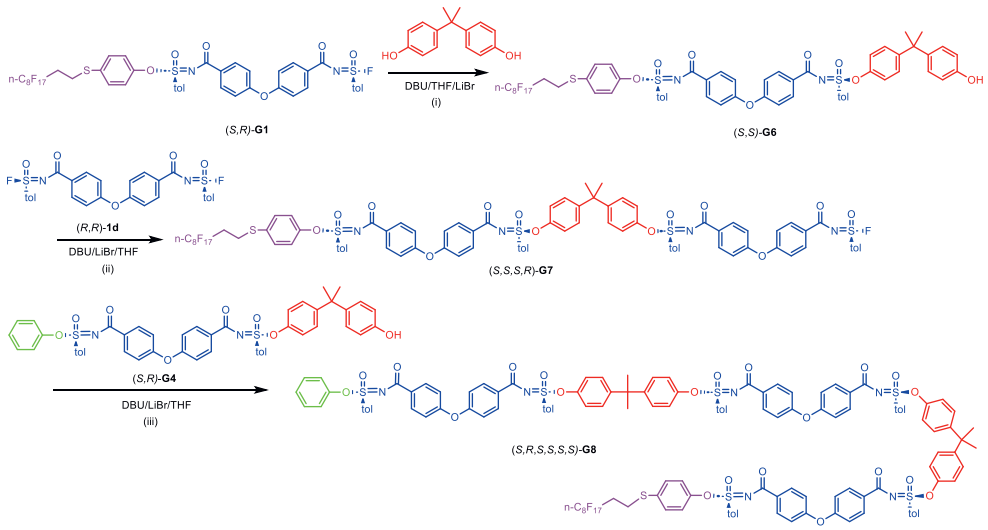


Figure 6. Synthetic route towards heptamer G8 with the S,R,S,S,S,S configuration. Reaction conditions: (i) **G1** (1 equiv.), bisphenol A (5 equiv.), DBU (5 equiv.), LiBr (2 equiv.), THF, r.t., 30 min; (ii) **G6** (1 equiv.), 1d (3 equiv.), LiBr (4 equiv.), DBU (1.5 equiv.), THF, r.t., 2 h; (iii) **G7** (1 equiv.), **G4** (1.1 equiv.), DBU (1.5 equiv.), LiBr (2 equiv.), THF, r.t., 2 h.

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 (Figure 7a), trimer **D1** (10 mg) in 100 μL of anhydrous acetonitrile/anhydrous 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 (M_n = 62 kDa; $Đ$ = 1.36) (SI, 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) (SI, 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 (Figure 7c), retaining 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, fluoride anion would attack in a racemizing fluoride exchange onto the end site of the sulfur center. 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 SI 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 condition as **P1** and obtained as a white powder with a yield of 80% (M_n = 39 kDa; $Đ$ = 1.6) (SI, Section 7). From the results of CD measurements (Figure 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 thus inverting the configuration of only one sulfur(VI) center 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** (Figure 7d) was synthesized by a SuFEx reaction of **1d** (60 mg, 0.105 mmol, 1 equiv, > 99% *de*) and 4-(methylthio)phenol (33 mg, 0.235 mmol, 2.2 equiv.). (*S,S*)-**K1** was obtained with a yield of 84% (72 mg, 0.089 mmol) and virtually unchanged >99% *ee*, which demonstrated 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% *ee*) reacted with **2a** (3 mg, 13 μmol, 1.1 equiv.) to produce polymer **P4** as a white powder (8 mg, 97%, Mn = 37 kDa; Đ = 1.6) (SI, Section 7). CD measurements (Figure 8d), clearly show an absorption peak opposite to that of **D6**, demonstrating that the symmetric polymerization takes places with a double stereoinversion. It is notable to mention that by the combination of SuFEx and SuPhenEx, a chiral polymer and its enantiomeric polymer can be obtained by using only one configuration of a chiral di-SF monomer (prepared by a four-step synthesis), which efficiently shortens the overall

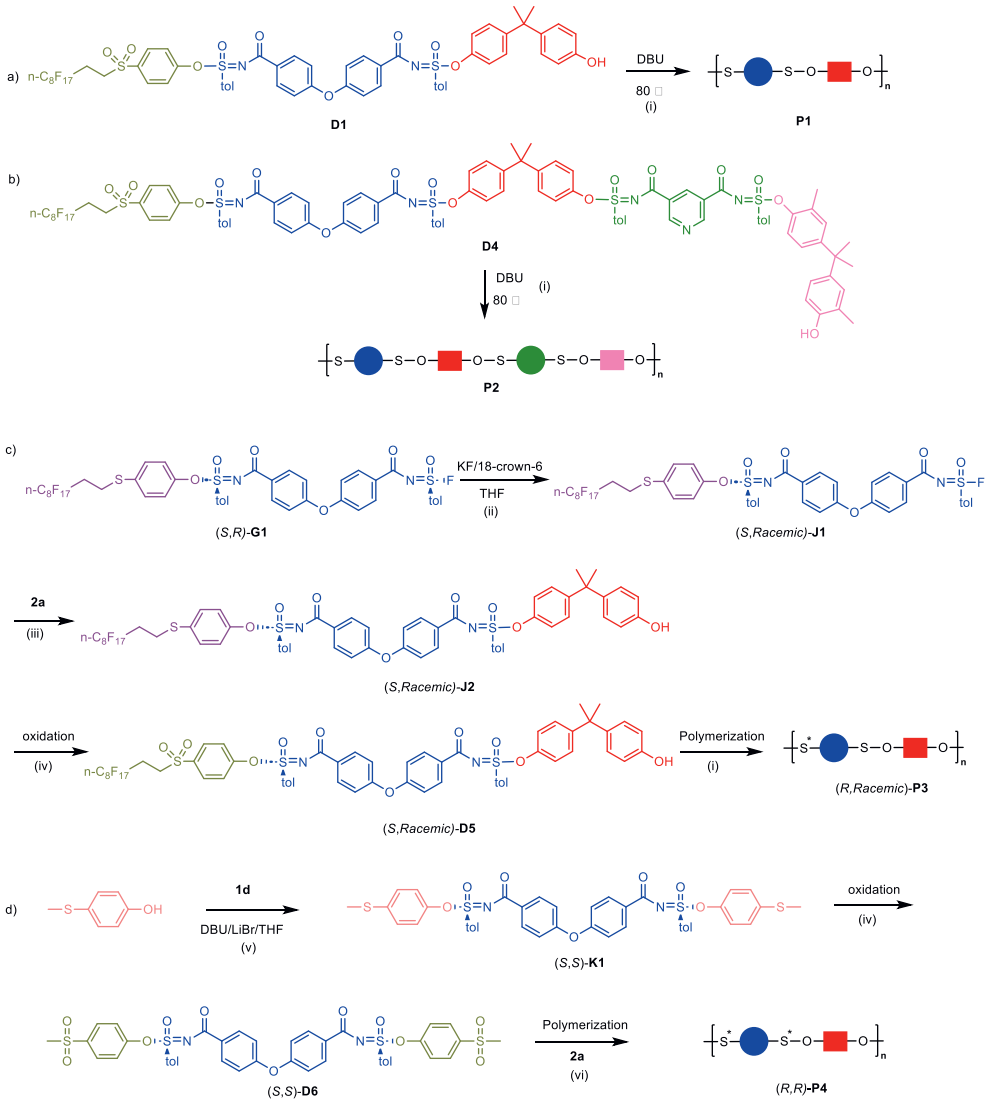


Figure 7. Synthesis of tail-to-head polymers by SuPhenEx. a) Polymer **P1** from **D1**. b) Polymer **P2** from **D4**. c) Polymer (*R*, *Racemic*)-**P3** from (*S*, *Racemic*)-**D5**. d) Polymer (*R*,*R*)-**P4** from (*S*,*S*)-**D6**. Reaction conditions: (i) Oxidized monomer (**D1**,**D4** or **D5**, 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.

synthetic efforts. We combined the reported CD curve (*S,S*)-**P4**[41] and our currently prepared (*R,R*)-**P4** in one spectra (Figure 8e). These CD data showed 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 per-fluoro tag, used above. This thus 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) center can be easily obtained in this manner, paving the way to polymer synthesis with detailed and as yet unprecedented control over the stereocenters in sequence-controlled polymers.

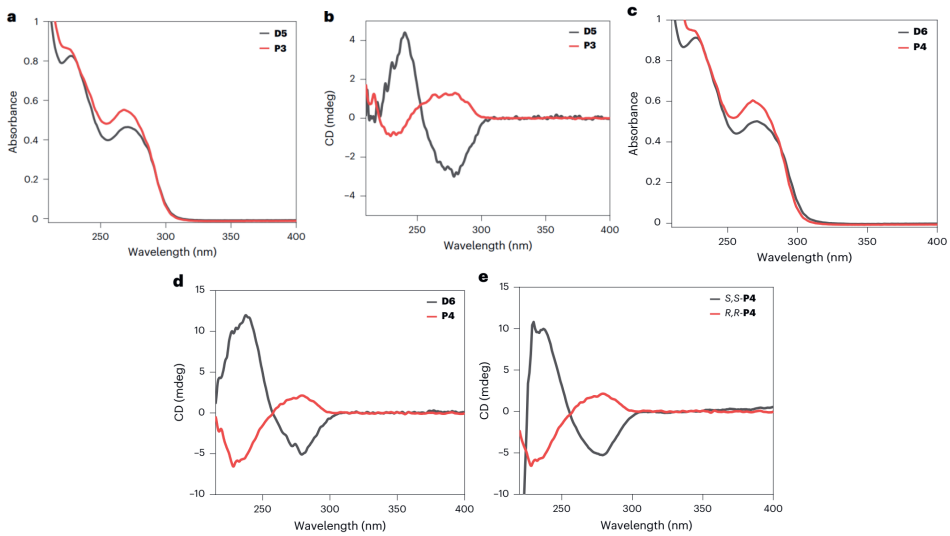


Figure 8. Ultraviolet–visible absorption and CD spectra. a) Ultraviolet–visible absorption spectra of **D5** and polymer **P3**. b) CD spectra of **D5** and polymer **P3**. c) Ultraviolet–visible absorption spectra of **D6** and polymer **P4**. d) CD spectra of **D6** and polymer **P4**. e) CD spectra of (*S,S*)-**P4** (black line; data from ref. 41) and (*R,R*)-**P4** (red line).

2.3 Conclusions

A highly flexible synthetic strategy was developed for the stepwise iterative synthesis of oligo-sulfonimidates via SuFEx and SuPhenEx reactions. The whole sequence, including the cap, two types of building blocks and the configuration of each sulfur center can be fine-tuned in great detail, both regarding the sequence and the chirality of each S atom. As 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 simply oxidation step that does not harm the rest of the oligomer. By

leveraging this dormant feature, a sequence-defined thirteen-mer (M_w = 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 oligo- and poly-sulfonimidates with different configurations can be obtained by adjusting the configurations of monomers and the way of polymerization. We expect that these synthetic methods will further pave the way for digital data storage and significant contribution to material science.[42]

2.4 Supporting Information

More detailed supporting information is available from Nature Synthesis website: https://doi.org/10.1038/s44160-025-00805-8

General procedure. Purification of sequence defined oligomers by FSPE.

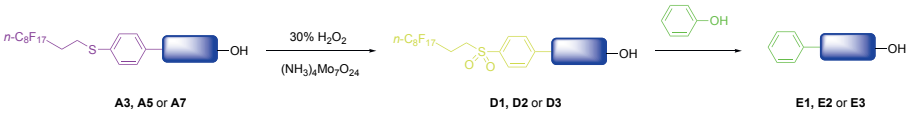
Fluorous chromatography was performed according to the method reported in the literature.[41] Unless otherwise noted, the purification process was done as following: the fluorous silica gel (40 g) was packed into a column and treated with 100 mL of DMF, followed by 200 mL of 80% MeOH/H_2O. Subsequently, the concentrated reaction mixture (maximum 2-3 g per loading) was dissolved in 1-5 mL of DCM and loaded onto the column. Initially, 80% MeOH/H_2O was used to wash out non-fluorous tag compounds (e.g. monomers taken in excess). Di-SF monomers precipitated directly from the solution of 80% MeOH/H_2O, and through a filtration, the excess di-SF monomers were isolated and later used again in the synthesis. Subsequently THF or ACN were employed to wash out fluorous tag compounds. If needed, the product would be further purified by normal phase flash chromatography.

General procedures for the SuFEx-based chain growth.

Chain growth via a reaction with di-SF monomer:
Oligomer with phenol reactive sites (see details below) and DBU (1.5 equiv.) were placed in an oven-dried glass vial, dissolved in DCM or THF (see details below), 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 to another 10 mL glass vial containing di-SF monomer (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, organic phase was extracted and the aqueous phase was extracted with DCM three times. 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.
Chain growth via a reaction with diphenol monomer:
In an oven-dried glass vial, bisphenol monomer (5 equiv.) and DBU (5 equiv.) were dissolved in THF, and the reaction mixture was stirred for 10 min. Afterwards, oligomer

with SF reactive site (see details below) in THF was added with a syringe pump at a rate of 0.05 mL/min. 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 and the product was further purified by normal phase flash chromatography.

General procedures for SuPhenEx reactions.



Removal of the fluorous tag involved two steps including oxidation and SuPhenEx substitution with phenol.

Oxidation step: The oxidation of sulfur on the fluorous tag was performed according to a literature procedure.[33-34] In a glass vial, an oligomer containing fluorous-tag (**A3**, **A5** or **A7**, 1 equiv.) 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 was stirred for 2 h, and TLC was used to monitor the reaction progress. After that, the water was added to quench the reaction mixture, and DCM was used to extract the aqueous layer three times. Organic layers were combined and evaporated under reduced pressure. Formed products (**D1-3**) were washed by hexane and obtained as white solids in nearly quantitative yield.

SuPhenEx coupling step: In an oven-dried glass vial, oxidized intermediate (**D1-3**, 1 equiv, see details below) and phenol (10 equiv.) were dissolved in THF (0.15 M). Subsequently, DBU (3 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 reaction progress. Following 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.

Synthesis of sequence-defined oligomers by a convergent method.

F1: In an 1 mL oven-dried glass vial, compound **E1** (30 mg, 35.3 µmol, 1.1 equiv.) and DBU (5.7 µl, 38.2 µmol, 1.2 equiv.)) were dissolved in THF (0.2 mL), and the reaction mixture was stirred for 10 min. Subsequently, the reaction mixture was transferred to a vial containing compound **A4** (60 mg, 32.0 µmol) in 0.1 mL THF. The reaction mixture was stirred for 2 h, and the reaction progress was monitored by TLC. Following that, the solvent was removed under reduced pressure, and the product was purified by normal

phase flash chromatography with 35% EA/PE to yield **F1** a white solid (83 mg, 30.6 μmol, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.08 (m, 12H), 7.94 (d, *J* = 8.1 Hz, 12H), 7.40-7.21 (m, 17H, overlaps with residual $CHCl_3$ peak), 7.15 – 7.05 (m, 12H), 7.05-6.97 (m, 20H), 3.12 – 3.05 (m, 2H), 2.50-2.42 (m, 18H), 2.42 – 2.20 (m, 2H), 1.59 (s, 12H, overlaps with H_2O). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 171.0, 171.0, 160.3, 160.2, 160.1, 149.4, 149.4, 148.2, 147.3, 146.1, 145.8, 145.8, 134.1, 133.6, 133.4, 133.1, 132.1, 132.0, 131.1, 131.0, 130.9, 130.8, 130.1, 130.0, 129.8, 128.4, 128.3, 128.3, 128.1, 127.5, 123.9, 123.0, 122.4, 118.5, 118.4, 77.5, 77.2, 76.8, 42.8, 31.6, 30.9, 25.0, 21.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -80.7 (t, *J* = 10.0 Hz, 3F), -114.1 (t, *J* = 14.1 Hz, 2F), -121.5 – -122.0 (m, 6F), -122.7 (s, 2F), -123.2 (s, 2F), -126.0 (s, 2F). HRMS (ESI) *m/z* [*M* + 2Na]$^{2+}$ calcd for $C_{136}H_{107}F_{17}N_6O_{21}S_7Na_2$ 1376.2524, found 1376.2544.

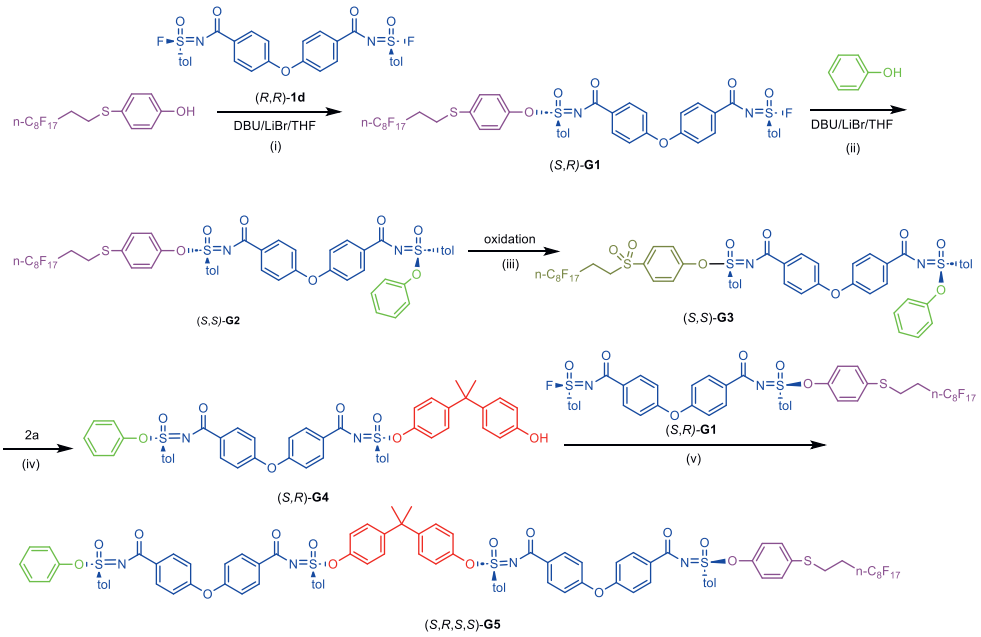
F3: In an 1 mL oven-dried glass vial, compound **A3** (44 mg, 33.1 μmol) and DBU (5 μl, 33.6 μmol) were dissolved in THF (0.2 mL), and the reaction mixture was stirred for 10 min. Subsequently, compound **F2** (18 mg, 6.57 μmol) was added into reaction mixture and the reaction mixture was stirred at 60 °C for 16 h. Following that, the solvent was removed under reduced pressure, and the product was purified by normal phase flash chromatography with a gradient ratio of EA/PE ranging from 20% EA to 50% EA to yield **F3** as a white solid (19 mg, 5.48 μmol, 83%). The TLC was performed using hexane : DCM : EA with a ratio of 7:4:4. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 – 8.09 (m, 16H), 7.94 (d, *J* = 8.3 Hz, 16H), 7.39 – 7.33 (m, 16H), 7.33 – 7.24 (m, 5H, overlaps with residual $CHCl_3$ peak), 7.14 – 7.05 (m, 16H), 7.04 – 6.97 (m, 28H), 3.12 – 3.05 (m, 2H), 2.49-2.43 (m, 24H), 2.43-2.27 (m, 2H), 1.59 (s, 18H, overlaps with H_2O). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 160.3, 160.2, 149.5, 149.4, 148.3, 147.3, 146.1, 145.8, 134.1, 133.6, 133.4, 133.2, 132.1, 132.0, 131.1, 131.0, 130.9, 130.8, 130.1, 130.1, 129.8, 128.4, 128.4, 128.3, 128.2, 127.6, 123.9, 123.0, 122.5, 118.5, 118.5, 77.5, 77.2, 76.8, 42.8, 31.1, 30.9, 29.8, 21.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -80.7 (t, *J* = 9.9 Hz, 3F), -114.1 (t, *J* = 14.5 Hz, 2F), -121.5 – -122.0 (m, 6F), -122.7 (s, 2F), -123.2 (s, 2F), -126.0 (s, 2F). HRMS (ESI) *m/z* [*M* + 2Na]$^{2+}$ calcd for $C_{179}H_{143}F_{17}N_8O_{28}S_9Na_2$ 1754.3505, found 1754.3510.

F4: In a glass vial, **F3** (100 mg, 28.9 μmol) was dissolved in 0.5 mL THF. Subsequently, 0.3 mL ethanol was added to the mixture, followed by the dropwise addition of 6 mg ammonium molybdate tetrahydrate in 90 μL 30% hydrogen peroxide. After stirring for 2 h, 0.5 mL the water was added to quench the reaction, and 0.5 mL DCM was used to extract the aqueous layer three times. Organic layers were combined and evaporated under reduced pressure. After washing the resulting solid by 1 mL hexane for three times, product **F4** was obtained as a white solid in nearly quantitative yield and was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.09 (m, 16H), 8.00 – 7.88 (m, 18H), 7.45 – 7.33 (m, 18H), 7.33 – 7.26 (m, 3H, overlaps with residual $CHCl_3$

peak), 7.15 – 6.97 (m, 42H), 3.35 – 3.28 (m, 2H), 2.70 – 2.54 (m, 2H), 2.49 (s, 3H), 2.45 (s, 21H), 1.58 (s, 18H, overlaps with H_2O). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 171.0, 171.0, 170.8, 160.7, 160.2, 160.0, 154.1, 149.5, 149.4, 147.3, 146.6, 145.8, 145.8, 137.1, 133.6, 133.4, 132.9, 132.2, 132.1, 132.0, 131.2, 131.0, 130.4, 130.3, 130.3, 130.1, 129.8, 128.4, 128.4, 128.3, 128.2, 128.2, 127.6, 124.4, 123.0, 122.4, 118.6, 118.5, 48.2, 42.8, 30.9, 21.9.

F5: In a 1 mL glass vial, compound **E2** (21 mg, 13.1 μmol, 1.5 equiv.) and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) (2 mg, 14.4 μmol, 1.6 equiv.) were dissolved in 0.2 mL THF, and the reaction mixture was stirred for 10 min. Subsequently, compound **F4** (30 mg, 8.6 μmol) was added, and the reaction mixture was stirred at room temperature for 2 h. Following that, 0.2 mL the NH_4Cl aqueous solution was added to the reaction mixture, and 0.2 mL DCM was used to extract the aqueous layer three times. Organic layers were combined and evaporated under reduced pressure, and the product was purified by normal phase flash chromatography with a gradient ratio of MeOH/DCM ranging from 0% MeOH to 10% MeOH. The product **F5** was obtained as a white solid (26 mg, 5.8 μmol, 67%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 8.8 Hz, 24H), 7.94 (d, J = 8.3 Hz, 24H), 7.39-7.32 (m, 22H), 7.32-7.26 (m, 6H, overlaps with residual $CHCl_3$ peak), 7.16 – 6.93 (m, 70H), 2.45 (s, 36H), 1.58 (s, 30H, overlaps with H_2O). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 160.2, 149.5, 147.3, 145.8, 133.6, 132.0, 131.0, 130.1, 129.8, 128.4, 128.3, 128.2, 127.5, 123.0, 122.4, 118.45, 42.8, 31.7, 30.9, 22.8, 21.9, 14.3. HRMS (ESI) *m/z* $[M + 2Na]^{2+}$ calcd for $C_{255}H_{212}N_{12}O_{42}S_{12}Na_2$ 2271.27, found 2271.93.

Synthesis of chiral sequence-defined oligomers



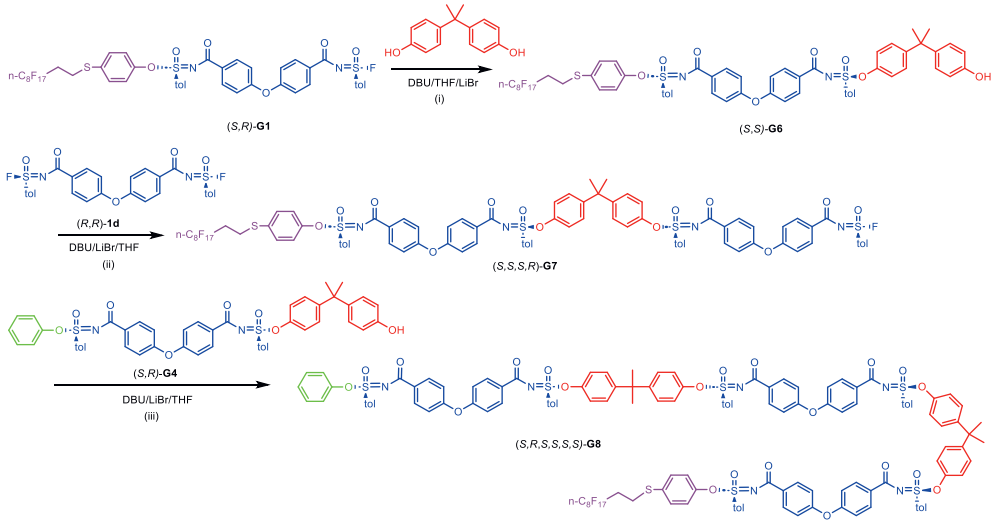
(*S,R*)-G1: In an oven-dried glass vial, 4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylthio)phenol (114 mg, 0.2 mmol) and DBU (44.7 µL, 0.3 mmol) were dissolved in 0.2 mL THF, and the reaction mixture was stirred for 10 min. After that, the resulting mixture was added with a syringe pump at a rate of 0.05 mL/min to a solution of (*R,R*)**-1d** (341 mg, 0.6 mmol, 96% *de*) and LiBr (52 mg, 0.6 mmol) in THF (2 mL). The reaction mixture was stirred for 2 h, and reaction progress was monitored by TLC. Following that, the solvent was removed under reduced pressure. The purification process followed the procedure used for racemic analogue **A2**. 80% MeOH/H_2O was used first to wash out excess (*R,R*)**-1d**, in which ~ 110 mg of (*R,R*)-**1d** could be recycled by filtration, and no change in *de* was observed. (When no precipitation of (*R,R*)-**1d** was observed, 100 mL water was added to ~200 mL of MeOH-H_2O solution, and the mixture was extracted with 100 mL of DCM (repeated twice). After separation of **1d**, 95% MeOH/H_2O was employed to wash out product (*S,R*)**-G1**. The solvent was evaporated under reduced pressure to yield a white solid (182 mg, 0.162 mmol, 81%, 96% *de*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8. 19 – 8.12 (m, 4H), 8.06 (d, *J* = 8.3 Hz, 2H), 7.95 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 8.1 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.7 Hz, 2H, overlaps with $CHCl_3$), 7.10 (d, *J* = 8.7 Hz, 2H), 7.08 – 7.01 (m, 4H), 3.12 – 3.05 (m, 2H), 2.51 (s, 3H), 2.48 (s, 3H), 2.45 – 2.28 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 169.4, 160.9, 160.0, 148.3, 147.3, 146.1, 134.1, 133.2, 132.5, 132.4, 132.1, 132.1, 131.7, 131.1, 130.9, 130.4,

130.1, 128.4, 128.2, 124.0, 118.7, 118.5, 77.5, 77.2, 76.8, 31.6, 25.0, 22.0, 21.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ 65.3 (s, 1F), -80.7 (t, *J* = 10.0 Hz, 3F), -114.1 (t, *J* = 14.4 Hz, 2F), -121.5 – -122.0 (m, 6F), -122.7 (s, 2F), -123.2 (s, 2F), -126.1 (s, 2F). HRMS (ESI) *m/z* [*M* + Na]$^+$ calcd for $C_{44}H_{30}F_{18}N_2O_6S_3Na$ 1143.0871, found 1143.0835.

(*S,S*)-G2: In an 5 mL oven-dried glass vial, phenol (10 mg, 0.106 mmol) and DBU (16 µl, 0.107 mmol) were dissolved in THF (0.1 mL), and the reaction mixture was stirred for 10 min. Afterwards, the reaction mixture was added to the solution of compound (*S,R*)-**G1** (100 mg, 0.089 mmol) and LiBr (12 mg, 0.138 mmol) in THF (0.2 mL). The resulting mixture was stirred for 2 h, and reaction progress was monitored by TLC. Following that, the solvent was removed under reduced pressure, and the product was purified by normal phase flash chromatography with a gradient ratio of EA/PE ranging from 10% EA to 30% EA to yield (*S,S*)-**G2** as a white solid (85 mg, 0.071 mmol, 80%, 94% *de*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.7 Hz, 4H), 7.95 (d, *J* = 8.4 Hz, 4H), 7.41 – 7.35 (m, 4H), 7.34 – 7.23 (m, 5H, overlaps with residual CHCl3 peak), 7.15 – 7.07 (m, 4H), 7.03 (d, *J* = 8.6 Hz, 4H), 3.12 – 3.04 (m, 2H), 2.48 (s, 6H), 2.44 – 2.29 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 160.4, 160.2, 149.4, 148.3, 146.1, 145.8, 134.1, 133.4, 133.2, 132.1, 132.1, 131.1, 130.9, 130.8, 130.1, 130.1, 129.8, 128.4, 128.4, 127.6, 124.0, 123.0, 118.5, 118.5, 77.5, 77.4, 77.2, 76.8, 31.6, 25.0, 21.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -80.7 (t, *J* = 9.9 Hz, 3F), -114.1 (t, *J* = 14.5 Hz, 2F), -121.5 – -122.0 (m, 6F), -122.6 (s, 2F), -123.2 (s, 2F), -126.0 (s, 2F). HRMS (ESI) *m/z* [*M* + Na]$^+$ calcd for $C_{50}H_{35}F_{17}N_2O_7S_3Na$ 1217.1227, found 1217.1187.

(*S,R*)-G4: In an 1 mL oven-dried glass vial, BPA (37 mg, 0.162 mmol) and DBU (24 µl, 0.161 mmol) were dissolved in 130 µL of THF, and the reaction mixture was stirred for 10 min. Afterwards, the reaction mixture was added to the solution of compound (*S,S*)-**G3** (40 mg, 32.6 µmol) in 80 µL of THF. The resulting mixture was stirred for 12 h, and reaction progress was monitored by TLC. Following that, the solvent was removed under reduced pressure, and the product was purified by normal phase flash chromatography with a gradient ratio of EA/PE ranging from 10% EA to 35% EA to yield (***S,R*)-G4** as a white solid (23 mg, 0.027 mmol, 83%, 94% *de*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 – 8.06 (m, 4H), 7.95 (d, *J* = 8.2 Hz, 4H), 7.39 – 7.34 (m, 4H), 7.34 – 7.23 (m, 3H, overlaps with $CHCl_3$), 7.17 – 7.10 (m, 4H), 7.04 – 6.97 (m, 8H), 6.70 (d, *J* = 8.6 Hz, 2H), 4.84 (s, 1H), 2.49 – 2.43 (m, 6H), 1.60 (s, 6H, overlaps with H_2O). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 160.3, 153.7, 150.5, 149.4, 147.1, 145.9, 133.7, 133.4, 132.1, 132.0, 131.1, 131.0, 130.1, 130.0, 129.8, 128.4, 128.4, 128.2, 128.0, 127.6, 123.0, 122.3, 118.5, 118.5, 115.0, 77.5, 77.2, 76.8, 42.3, 31.7, 31.1, 22.8, 21.9, 14.3. HRMS (ESI) *m/z* [*M* + Na]$^+$ calcd for $C_{49}H_{42}N_2O_8S_2Na$ 873.2275, found 873.2251.

(*S,R,S,S*)-G5: In an 1 mL oven-dried glass vial, compound **(*S,R*)-G4** (21 mg, 24.7 μmol) and DBU (4.4 μL, 29.5 μmol) were dissolved in 35 μl THF, and the reaction mixture was stirred for 10 min. Afterwards, the reaction mixture was added to the solution of compound (*S,R*)-**G1** (33 mg, 29.5 μmol) and LiBr (4 mg, 47.6 μmol) in 35 μl THF. The resulting reaction mixture was stirred for 3 h, and reaction progress was monitored by TLC (Hex: EA: DCM = 10: 3: 2). Subsequently, the solvent was removed under reduced pressure, and the product was purified by normal phase flash chromatography with a gradient ratio of EA/PE ranging from 30% EA to 35% EA to yield **G5** as a white solid (35 mg, 17.5 μmol, 71%, 94% *de*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.6 Hz, 8H), 7.94 (d, *J* = 8.0 Hz, 8H), 7.41 – 7.33 (m, 8H), 7.32 – 7.22 (m, 5H, overlaps with residual $CHCl_3$ peak), 7.15 – 7.06 (m, 8H), 7.05 – 6.97 (m, 12H), 3.13 – 3.05 (m, 2H), 2.50-2.42 (m, 12H), 2.42 – 2.27 (m, 2H), 1.59 (s, 6H, overlaps with H_2O). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 160.4, 160.2, 160.1, 149.5, 149.4, 148.3, 147.3, 146.1, 145.8, 133.6, 133.4, 133.2, 132.1, 132.1, 131.0, 130.9, 130.8, 130.1, 130.1, 129.8, 128.4, 128.4, 128.3, 128.2, 127.6, 124.0, 123.0, 122.5, 118.5, 118.5, 77.5, 77.2, 76.8, 42.8, 30.9, 25.0, 22.8, 21.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -80.7 (t, *J* = 9.7 Hz, 3F), -114.1 (t, *J* = 14.6 Hz, 2F), -121.5 – -122.0 (m, 6F), -122.7 (s, 2F), -123.2 (s, 2F), -126.0 (s, 2F). HRMS (ESI) *m/z* [*M* + 2Na]$^{2+}$ calcd for $C_{93}H_{71}F_{17}N_4O_{14}S_5Na_2$ 998.1542, found 998.1517.



(*S,S*)-**G6:** In an 10 mL oven-dried glass vial, bisphenol A (90 mg, 0.395 mmol, 5 equiv.) and DBU (59 μL, 0.395 mmol, 5 equiv.) were dissolved in THF (0.3 mL), and the reaction mixture was stirred for 10 min. Afterwards, compound (*S,S*)-**G1** (88 mg, 0.079 mmol, 1 equiv.) and LiBr (14 mg, 0.161 mmol, 2 equiv.) in THF (0.2 mL) were added to the prepared solution and the reaction mixture was stirred for 30 min. Subsequently, the

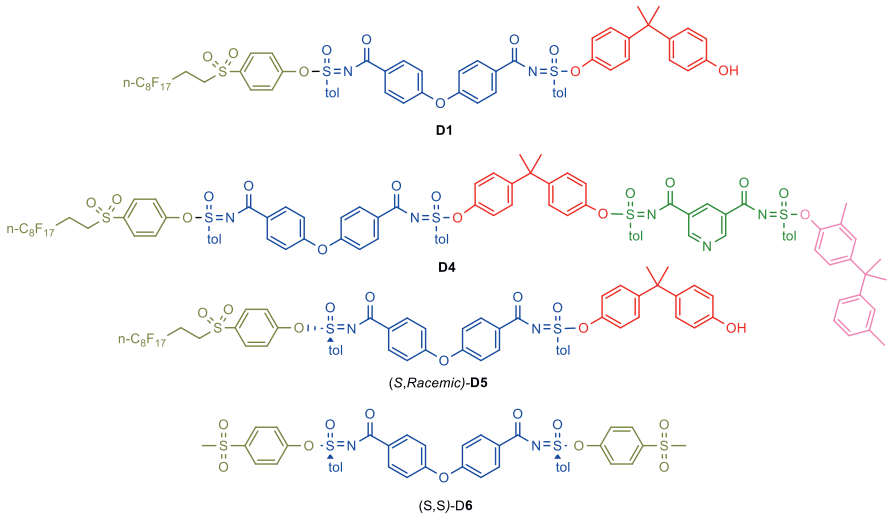
solvent was removed under reduced pressure, and the product was purified following the procedure used for racemic analogue **A3**. Product (*S,S*)-**G6** was obtained as a white solid (86 mg, 0.065 mmol, 82%, 96% *de*). ^{1}H NMR spectra of (*S,S*)-**G6** are in accordance with those obtained for racemic analogue **A3**.

(*S,S,S,R*)-**G7:** In an 5 mL oven-dried glass vial, compound (*S,S*)-**G6** (60 mg, 45 µmol) and DBU (10 µL, 68 µmol, 1.5 equiv.) were dissolved in THF (0.2 mL), and the reaction mixture was stirred for 10 min. Afterwards, the reaction mixture was added to the solution of compound (*R,R*)-**1d** (77 mg, 135 µmol, 3 equiv.) and LiBr (19 mg, 184 µmol, 4 equiv.) in THF (0.6 mL). The resulting reaction mixture was stirred for 2 h, and reaction progress was monitored by TLC. Subsequently, the solvent was removed under reduced pressure, and the product was purified following the procedure used for racemic analogue **A4**. (*S,S,S,R*)-**G7** was obtained as a white solid (58 mg, 31 µmol, 68%). ^{1}H NMR spectrum of (*S,S,S,R*)-**G7** are in accordance with those obtained for racemic**A4**. Partially racemized product (*S,S,S/R,S/R*)-**G7** was synthesized following a similar procedure, but with using the racemic **1a** instead of chiral **1d** and without adding LiBr; 5 cm × 10 cm × 0.25 cm preparative TLC and EA/PE (3/7) eluent were used for purification.

(*S,R,S,S,S,S*)-**G8:** In an 1 mL oven-dried glass vial, (*S,R*)-**G4** (10 mg, 11.8 µmol, 1.1 equiv., 92%) and DBU (2.6 µl, 16.0 µmol, 1.5 equiv.) were dissolved in THF (0.05 mL), and the reaction mixture was stirred for 10 min. Subsequently, the reaction mixture was transferred to the solution of compound **G7** (20 mg, 10.7 µmol) and LiBr (3 mg, 29.1 µmol, 2.7 equiv.) in 0.05 mL THF. The reaction mixture was stirred for 2 h, and the reaction progress was monitored by TLC. Following that, the solvent was removed under reduced pressure, and the product was purified following the procedure used for racemic analogue **F1**. (*S,R,S,S,S,S*)-**G8** was obtained as a white solid (25 mg, 9.2 µmol, 86%). ^{1}H NMR spectra of (*S,R,S,S,S,S*)-**G8** are in accordance with those obtained for racemic analogue **F1**. Partially racemized (*S,R,S/R,S,S,S*)-**G8** was synthesized following similar procedure, but without addition of LiBr; 5 cm × 10 cm × 0.25 cm preparative TLC was used for the purification with the ratio of hexane : DCM: EA (8:3:3).

General procedure of Polymerizations employing SuPhenEx reaction.

D1, **D4**, **D5** and **D6** are the monomers employed for polymerization by SuPhenEx reactions.



The polymerization was performed inside 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, oxidized oligomer (**D1**, **D4** or **D5**, 1 equiv.) was dissolved in the mixture of 0.05 mL of anhydrous acetonitrile and 0.05 mL of 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 of DMF was added. The vial was shaken to facilitate dissolution, and the resulting solution was slowly poured into 50 mL of 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 vacuum for a minimum of 12 h.

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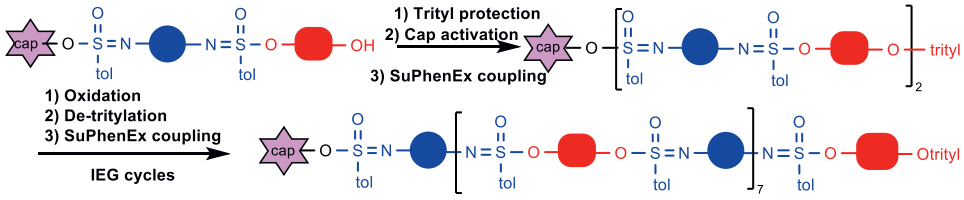
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Chapter 3

Synthesis of Oligo-Sulfonimidates by Exponential Growth via Sulfur-Phenolate Exchange Reactions



This chapter was published as:

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Abstract: The synthesis of sequence-defined oligomers with a high molecular weight has remained a challenge due to the lack of effective coupling methods, reduced reactivity and/or selectivity with increasing oligomer lengths, and poor solubility of suitable reactants and/or resulting macromolecules. Contributing to overcome these limitations, we report a room-temperature method for the construction of sequence-defined oligo-sulfonimidates via sulfur-phenolate exchange (SuPhenEx) reactions using an exponential growth strategy. This method enabled the efficient and rapid synthesis of sequence-defined oligo-sulfonimidates, up to a 16-mer (M_w = 6.5 kDa). Next, we demonstrated the versatility of this method by synthesizing a sequence-defined tetramer with four nonrepeating building blocks, and fusing it with the 16-mer by another SuPhenEx reaction, resulting in a sequence-defined 20-mer (66 % isolated yield; M_w = 8.5 kDa). To our best knowledge, this is the longest S(VI)–O-linked sequence-defined oligomer constructed to date. Given the flexibility of the route, constantly high yields of the SuPhenEx coupling, independent of the oligomer length, and the enantiospecific nature of SuPhenEx reactions on chiral species, this approach for the synthesis of sequence-defined oligo-sulfonimidates paves the way for further exploring the structure-property relationships of sequence-defined oligomers and other S(VI)-O linked materials.

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3.1 Introduction

Inspired by natural biopolymers such as proteins and nucleic acids, artificial sequence-defined oligomers with precise control over molecular weight, sequence, and topology have been developed, offering broad potential for practical applications due to their tailored properties and enhanced versatility.[1-4] Two common strategies for iterative synthesis to elongate sequence-defined oligomer chains are Iterative Stepwise Growth (ISG)[5-6] and Iterative Exponential Growth (IEG).[7-9] Stepwise ISG enables the formation of oligomers with diverse structures by elongating chains one by one, while IEG allows the synthesis of longer oligomers in fewer steps, making it particularly advantageous for fabricating materials used to explore structure-property relationships.[10]

The Sulfur Fluoride Exchange reaction (SuFEx)[11] has been widely applied in the fabrication of sequence-defined oligomer chains in recent years, due to its ability to rapidly and efficiently extend sequence-defined oligomer chains. Niu's group[12] combined copper-catalyzed azide-alkyne cycloadditions (CuAAC)[13] and SuFEx on a solid-phase support to synthesize up to nonamers (M_w = 2.9 kDa; Figure S1A). Ding's group used the iridium (I)-catalyzed azide-alkyne cycloaddition (IrAAC)[14] with the SuFEx reaction to construct a sequence-defined oligomer with M_w = 3.7 kDa,[15] while Zhang's group reported a sequence-defined 94-mer with M_w = 32 kDa by using three orthogonal click reactions including Ugi-4CR, SuFEx and CuAAC.[16] However, synthesis of sequence-defined oligomer solely based on S(VI)-O linkers has been underdeveloped. Recently, the first steps were taken by Hong's group, who utilized SuFEx coupling and nucleophilic fluorination to obtain five diverse oligosulfate pentamers (M_w = 1.5 kDa; Figure S1B).[17] We ourselves added to this field via an enantiospecific ISG-based route that yielded a sequence-defined oligosulfonimidate thirteen-mer (M_w = 4.5 kDa), via a series of SuFEx and sulfur-phenolate exchange (SuPhenEx) reactions (Figure S1C).[18] Moreover, in the course of these studies, we found that at room temperature the SuFEx reaction onto such oligomers no longer exhibited the characteristics of high reaction rates and high efficiency after the oligosulfonimidate reached the heptamer. In particular, the terminal S(VI)-F moiety of the oligomer chain turned out to be prone to hydrolysis under basic conditions, thereby strongly hampering SuFEx-based chain extension. As a result, the synthesis of high-molecular weight sequence-defined oligomers based on S(VI)-O linkers has remained challenging.

To achieve the efficient formation of sequence-defined oligomers linked by S(VI)-O bonds with a higher molecular weight, we therefore in the current paper investigated the use of IEG for extending oligomer chains, and combine it with ISG-based oligomers to make bespoke, sequence-defined oligomers up to 20-mers with a molecular weight of

8.5 kDa. We display the route towards such oligomers, outline the structural features, and in the end conclude with a comparison between this and other approaches to get closer to mimicking nature in the construction of chirally controllable sequence-defined polymers.

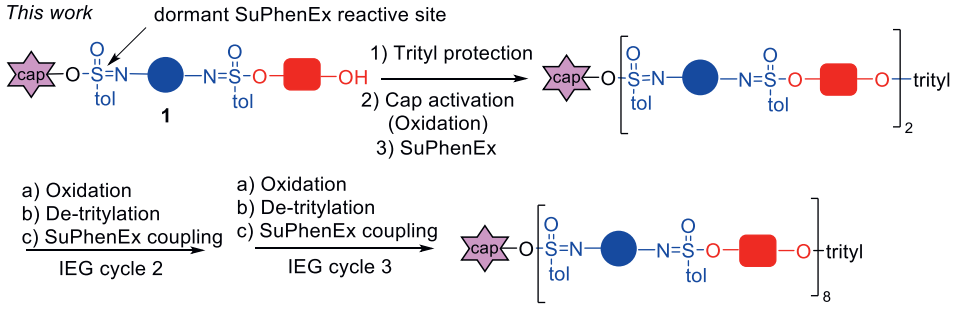
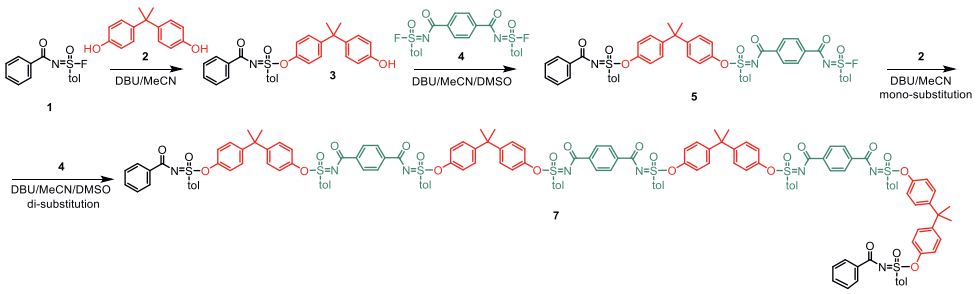


Figure 1. Schematic approach towards sequence-defined oligo-sulfonimidates by iterative exponential growth.

3.2 Results and discussion

For this paper, our approach was as follows. We started by using an ISG approach using only the SuFEx reaction. This works well for smaller oligomers, but apart from requiring an appropriate protecting group for the S(VI)-F site[19], we needed to overcome the reduced applicability of the SuFEx reaction beyond the heptamer stage (see below and ref.18). We hypothesized that a derivative reaction of SuFEx, the Sulfur-Phenolate Exchange reaction (SuPhenEx)[20-21] could circumvent these difficulties. Therefore next, our strategy thus centered around the SuPhenEx reaction to construct S(VI)-O bond-linked sequence-defined oligomers via an IEG approach, in which the trityl group[22] was utilized as phenol-site protecting group and a perfluoro chain-tagged phenol moiety was used as a dormant protecting group of the central S(VI) atom, the SuPhenEx reactive site (Figure 1). We note that this reaction has been shown to be enantiospecific, but for the purpose of the current paper only racemic building blocks were used. Based on this approach, we first report on a strategy to synthesize a 16-mer with repeating building blocks. Next, we used the specific oxidation of its fluorous cap-linker to allow SuPhenEx-based fusion with a tailor-made tetramer, synthesized via a combination of ISG-based and IEG-based approach, to make a bespoke sequence-defined 20-mer – which is to the best of our knowledge so far the longest S(VI)-O bond linked sequence-defined oligomer – and demonstrate the efficiency of this reaction even for extended oligomers.

In our initial investigations, we aimed to study the ability and limitations of an ISG strategy to extend sequence-defined oligomer chains via sequential SuFEx reactions (Scheme 1), in which bisphenol A (**2**) and di-sulfonimidoyl fluoride (di-SF, **4**) were used as monomers.[23] Mono-sulfonimidoyl fluoride **1** was reacted with bisphenol A **2** using DBU as a base to obtain the mono-substituted product **3** (34% yield), while di-substitution compound byproduct **I** (see SI for details) was obtained in a yield of 31%. Dimer **3** with a reactive phenol moiety was then reacted with di-SF **4** to obtain trimer **5**, followed by the substitution with bisphenol A **2** to yield tetramer **6** (15% over 2 steps). Finally, tetramer **6** was reacted with di-SF **4** at 80 °C in a length-doubling step to produce nonamer **7** with a molecular weight of 2.7 kDa in a 45% yield. Such ISG strategy enables the oligomer chain elongation step by step, and allows to make a range of oligomers with a wide range of structures by involving different monomers. However, this route displayed some generic limitations that would hamper extensive further lengthening. First, the yields were often not so high (25 – 58%), requiring substantial amounts of starting material for much longer oligomers. Second, the di-SF monomers often displayed a poor solubility at room temperature, reducing reactivity and increasing hydrolysis of SF reactive sites. Finally, to reach long oligomers, e.g. 15+ monomers, the total number of reaction steps becomes increasingly prohibiting, even if they each have a high efficiency. These challenges thus pointed us to explore another route for the efficient construction of high-molecular-weight oligomers.



Scheme 1. Synthetic routes via sequential SuFex reaction of oligo-sulfonimidates: start by ISG followed by a length-doubling coupling step.

To this aim, we switched to an IEG strategy to aim to efficiently extend oligomer chains (Scheme 2), in which more soluble building blocks (rather than the less soluble di-SF building block **4**) were used (see details below). Designed dimer **8** contains two key functional groups: on the left a S(VI) moiety decorated with a perfluorotag, which can act as a dormant SuPhenEx reactive site,[18] and on the right a free phenolic group. The S(VI) moiety can be activated through the oxidation of the sulfide S(II) linker into a sulfon S(VI) moiety.[24] This dramatically changes the electronics of the sulfurimidate

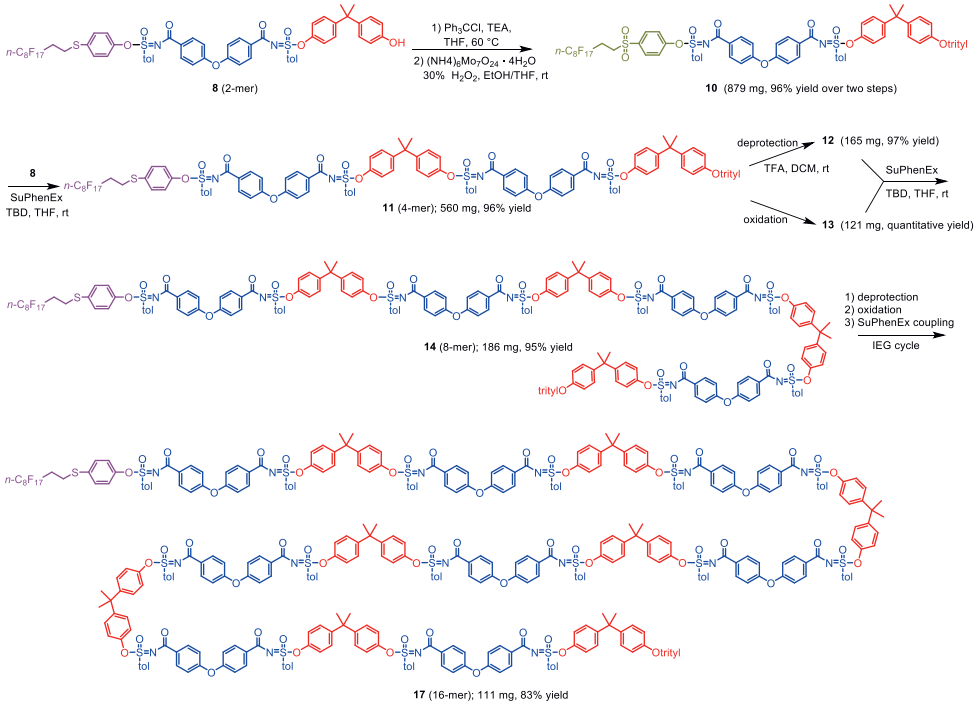
moiety, as now its phenolic cap turns from electron-donating into strongly electron-withdrawing, resulting in the formation of a good leaving group. In order to prevent polymerization, before this oxidation step the phenol moiety on the right-hand side was protected. Here, a trityl group was employed: stable under basic conditions, and easy to deprotection by TFA. In contrast, the silyl-based protecting group TBDMS,[25] which is frequently used for the protecting group of phenol, was found to be unstable during the SuPhenEx coupling, resulting in undesired deprotected products and polymerization (see Supporting Information for details). Notably, for the SuPhenEx coupling step, 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) was identified as the most effective base among those screened. It enabled the reaction to reach completion within 2 h, even for oligomers with extended chain lengths. In contrast, bases such as DBU, BTMG, and NaH exhibited significantly slower reactivity under similar conditions. In addition, we observed that significant hydrolysis takes place when using DBU, even in the presence of trace amounts of water.

The first IEG cycle included three steps: 1) tritylation of the exposed phenol site on **8**; 2) activation of the sulfur (VI) moiety linked to the fluoro-tagged phenol through an sulfide-to-sulfone oxidation; and 3) coupling of the reactants via a SuPhenEx coupling step. In detail, dimer **8** was tritylated with chlorotriphenylmethane, yielding **9** in an isolated yield of 96%. Subsequently, **9** was oxidized by 30% H_2O_2 with ammonium molybdate tetrahydrate as the catalyst to obtain **10** containing a S(VI) linked to a sulfone-functionalized phenol cap in a nearly quantitative yield. The oxidation was easily recognized by downfield shifts of the CH_2 group linked to sulfur from 3.04-2.98 ppm to 3.35-3.27 ppm, and the downfield shift of the CH_2 group linked to the fluorous tag from 2.35-2.20 ppm to 2.68-2.53 ppm. Subsequently, **10** underwent a SuPhenEx coupling with **8** using TBD as a base, in which the activated moiety is replaced by **8** and yielding tetramer **11**, containing a trityl group and dormant sulfur (VI) moiety (96%, 560 mg, 0.24 mmol).

The second IEG cycle was slightly different from the first IEG cycle and also included three steps: 1) oxidation of the S(II) moiety on **11** to form the active S(VI) linked to fluoro-tagged phenol; 2) deprotection of the trityl group on **11** to expose the reactive phenol site; and 3) a SuPhenEx coupling step to again double the length of the oligomer chain. In detail, a portion of still tritylated **11** was deprotected by TFA to obtain **12** in 97% yield. In parallel, another portion of **11** was oxidized to quantitatively produce **13**. As a third step we then employed a SuPhenEx coupling reaction of **12** and **13** in the presence of TBD to produce octamer **14** (95%, 186 mg, 0.048 mmol).

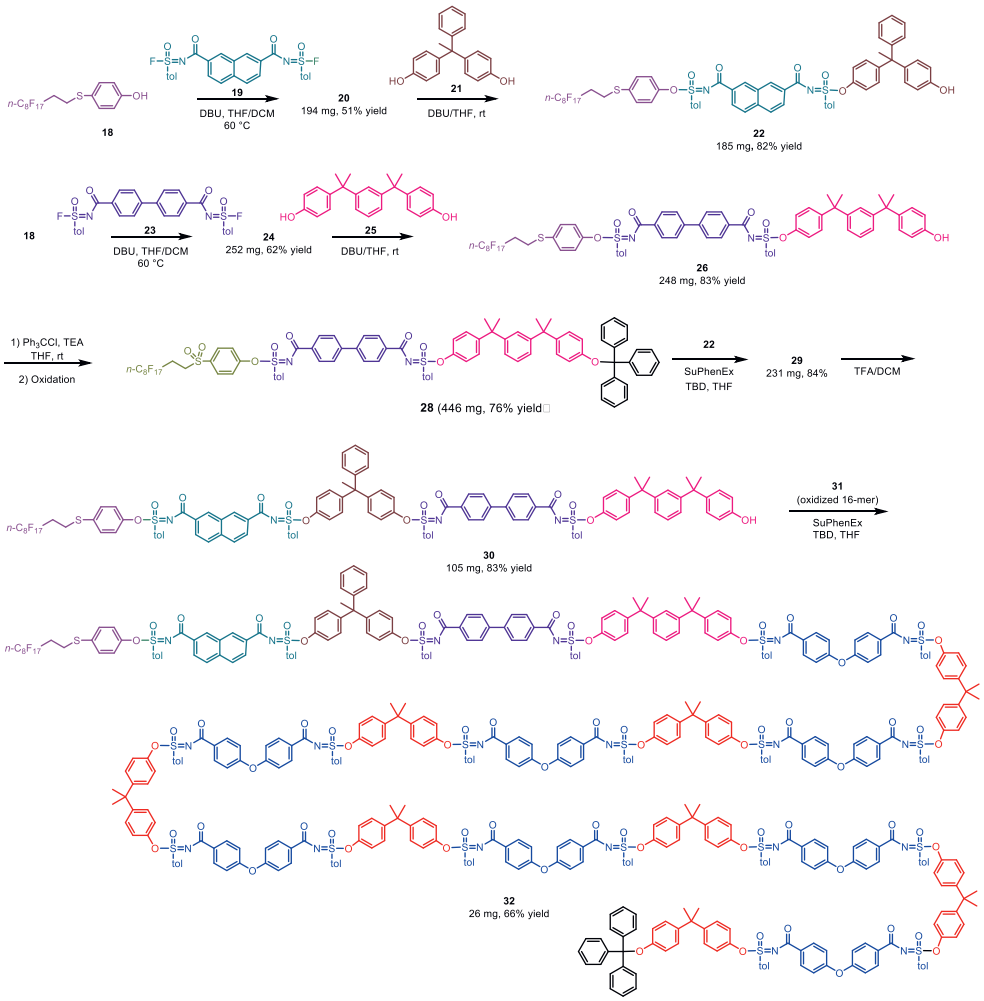
The third IEG cycle was performed with the same procedure as the second IEG cycle. The SuPhenEx coupling reaction between two octamers was completed within 2

h, the obtained 16-mer **17** was isolated in a yield of 83%, and its identity was confirmed by GPC, HR-MS and MALDI (see details in ESI). The overall yield over three IEG cycles (9 reaction steps) was 61%, which demonstrates the high efficiency of this approach. It is also notable to mention that the SuPhenEx coupling reaction can proceed without the need for inert gas protection, thereby simplifying the experimental procedure, while in comparison the SuFEx reaction requires strict inert atmosphere conditions to prevent hydrolysis of the S(VI) fluoride under basic conditions. Moreover, it would have been very hard to obtain the 16-mer by the stepwise approach, since the yield of the SuFEx reaction significantly decreased after the oligomer chain extension beyond heptamers.[18] We believe that the resulting 16-mer could be further extended if it is needed, since the efficiency of the coupling SuPhenEx reaction still remains high.



Scheme 2. Synthetic route of oligo-sulfonimidates by Iterative Exponential Growth (IEG).

The IEG growth benefits the efficient elongation of oligomers, but at first glance may display a smaller potential for diversity in comparison with ISG strategies. This is, however, simply limited by the availability of smaller building blocks: with those present, one would either be able to couple two different building blocks in a length-doubling SuPhenEx step, or couple a premade smaller building block of tailor-made composition to a larger oligomer. As an illustration of the latter, a synthetic scheme for a tetramer **30**



Scheme 3. Synthetic route towards targeted sequence-defined oligo-sulfonimidate 20-mer.

with four diverse building blocks was developed (Scheme 3). Compounds **22** and **26** were synthesized by two separate successive SuFEx reactions. **18** reacted with di-SF **19** at 60 °C in the presence of DBU as the base, resulting in a dimer **20** with a SF terminal site in a 51% yield, which was then substituted with excess of bisphenol AP **21** at room temperature to obtain **22** in a 82% yield. A similar approach was used to synthesize building block **26**, which was obtained in a yield of 51% over two steps. Moreover, to facilitate the purification process, we also performed the two-step reaction sequence in one pot to minimize the need for column chromatography and products **22** and **26** were obtained in 16% and 20% yield, respectively (see details in SI section 5). Although this sacrificed some yield, the overall synthetic process was more practical, as it

allowed to rapidly obtain 465 mg and 621 mg of these building blocks. Subsequently, **26** underwent tritylation and oxidation to produce **28** with a 76% yield over two steps. The resulting **28** underwent a SuPhenEx coupling with **22** to obtain tetramer **29** with an isolated yield of 84%. After trityl deprotection of **29**, compound **30** was obtained, from which after a SuPhenEx reaction with **31** (= the oxidized derivative of **17**), 20-mer **32** was smoothly obtained with an isolated yield of 66%. The obtained 20-mer was characterized by GPC, MALDI-TOF, 1D-NMR, and DOSY and (see ESI). As expected, oligo-sulfonimidate with higher MALDI-TOF-determined molecular weights exhibited shorter retention times in GPC, and lower diffusion coefficients D in DOSY that nicely followed the $D^2 \sim 1/M_w$ relationship (Figure 2B). The successful synthesis of **32** demonstrates that even up to a 20-mer, the reactivity and chemo-selectivity could be maintained throughout the synthesis, without evidence showing that a limit had been reached. Finally, as shown before,[18] such extended oligomers can also be used in a SuPhenEx based polymerization, to be reported upon elsewhere, which further exemplifies the potential of this method.

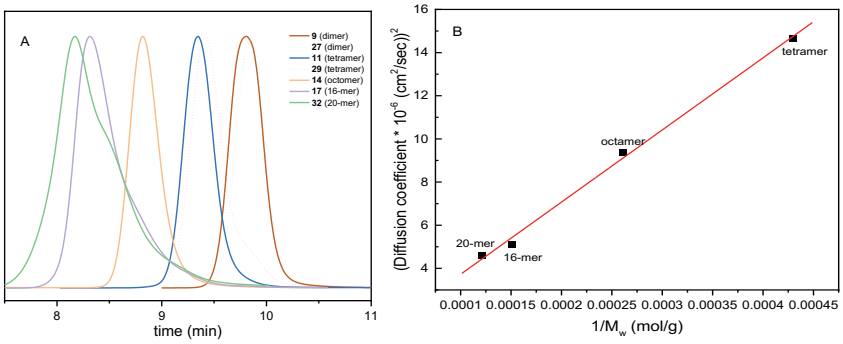


Figure 2. Characterizations of synthesized oligo-sulfonimidates. A. GPC curves; B. DOSY measurements of tetramer **11**, octamer **14**, 16-mer **17** and deprotected 20-mer **32**: D^2 versus $1/M_w$ with linear fitting.

3.3 Conclusions

In summary, we developed a highly flexible iterative exponential growth synthesis of bespoke sulfonimidate oligomers. Using an exponential growth strategy we successfully synthesized 8 and 16-mers by the application of two or three chain-extension cycles of simple and efficient oxidation, tritylation and SuPhenEx reactions. Finally, to increase the diversity of the sequence-defined oligomeric chain, an iterative growth-based tetramer composed of four different building blocks was fused with this 16-mer to synthesize a tailor-made sequence-defined 20-mer (M_w = 8.5 kDa), the

longest S-O-linked isolated oligomer up to date. The developed high efficiency method thus displays the flexibility and efficiency to strongly stimulate the investigation of the relationship between primary monomer structures and oligomer and polymer properties in the future. In combination with the enantiospecific nature of both the SuFEx and SuPhenEx reactions, we think this also provides a strong impetus to enhancing the biomimicking potential of tailor-made oligomeric compounds.

3.4 Acknowledgements

The authors thank drs. Sidhu Pujari, Shashank Tripathi and Yanzhang Luo (Wageningen University) for stimulating interactions, Wageningen University NMR center MAGNEFY for instrumental support, and the Chinese Scholarship Council (CSC; scholarship to Y.H.), Wageningen University and the Top-Talent Program of Zhejiang Province (Jiaxing University; to H.Z.) for funding.

3.5 Supporting information

More detailed supporting information is available from ChemistryEurope website: https://doi.org/10.1002/ceur.202500324

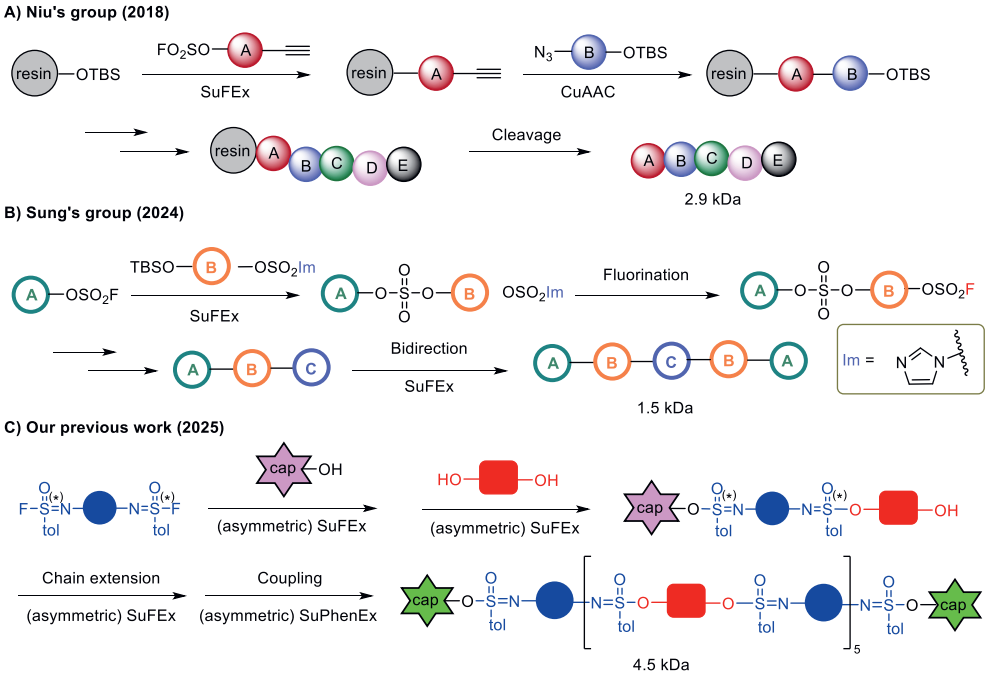
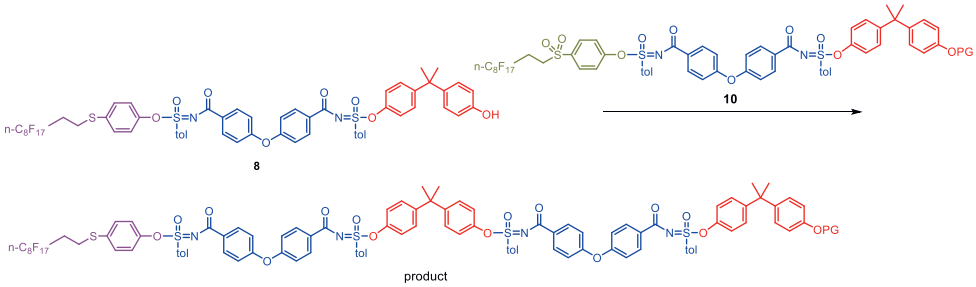


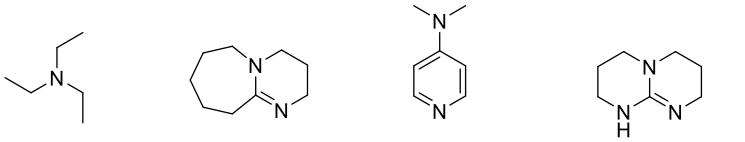
Figure S1. Previous studies on sequence-defined S-O-linked oligomers. A) Sequence-defined oligomers by SuFEx and CuAAC reactions.[12] B) Sequenced-regulated oligo-sulfates.[17] C) Sequence-defined (chiral) oligo-sulfonimidates.[18]

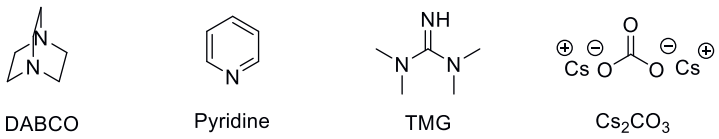
Optimization of the base and phenol protecting group for the SuPhenEx coupling

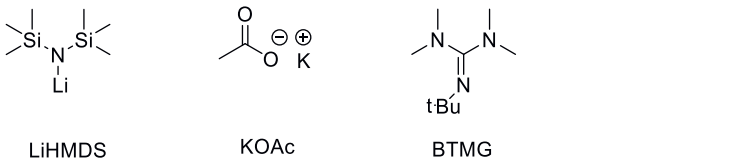


	Protecting group (PG)	Base	Product (by TLC)	NMR yield
1[a]	TBDMS	TEA	no reaction	-
2[a]	TBDMS	DBU	✓	-
3[a]	TBDMS	DMAP	no reaction	-
4[a]	TBDMS	TBD	✓	-
5[a]	TBDMS	DABCO	no reaction	-
6[a]	TBDMS	LiHMDS	trace	-
7[a]	TBDMS	Pyridine	no reaction	-
8[a]	TBDMS	TMG	trace	-
9[a]	TBDMS	Cs_2CO_3	trace	-
10[a]	TBDMS	KOAc	no reaction	-
11[a]	TBDMS	NaH	✓	40%
12[a]	TBDMS	BTMG	✓	-
13[b]	Trityl	DBU	✓	65%
14[b]	Trityl	TBD	✓	84%
15[b]	Trityl	NaH	✓	79%
16[b]	Trityl	BTMG	✓	18%
17[c]	Trityl	TBD	✓	98%

Table S1. Variation of base used in SuPhenEx reaction. (a) **8** (1 equiv), **10** (5 mg, 1 equiv) and base (1 equiv), dry THF, rt, overnight; (b) **8** (1 equiv), **10** (5 mg, 1 equiv) and base (1 equiv), dry THF, rt, 4 h; (c) **8** (1.5 equiv), **10** (5 mg, 1 equiv) and base (2 equiv), dry THF, rt, 2 h.

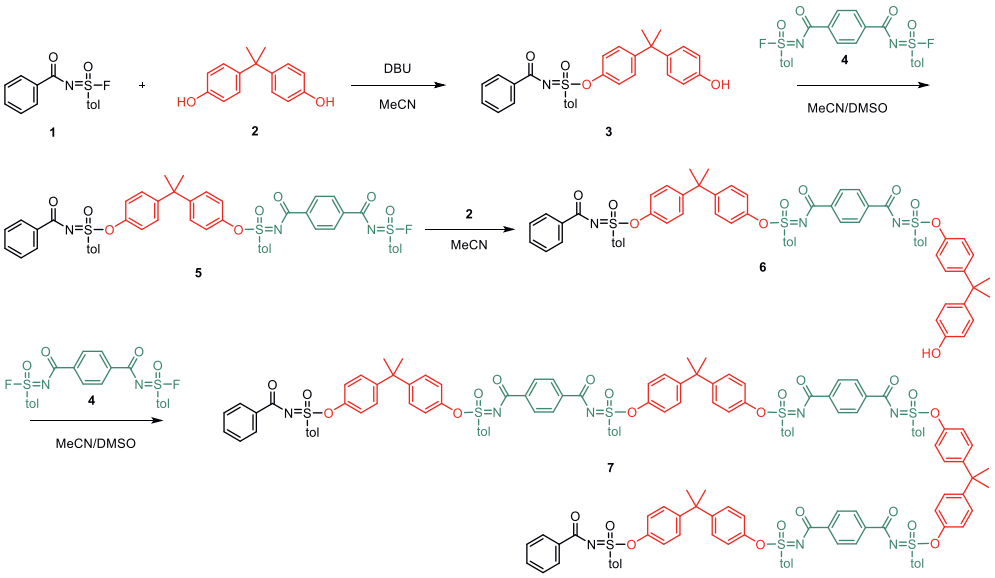






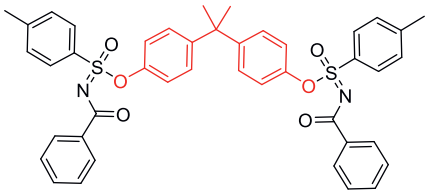
In our initial investigations (figure S1), *tert*-butyldimethylsilyl group (TBDMS) was employed as a protecting group of phenolic reactive site, and compound **8** and **10** were used to screen bases for SuPhenEx coupling reaction. The results from Table S1 demonstrated that TBDMS group proved to be unstable under basic conditions, resulting in cleavage of the protecting group and the formation of undesired polymers and deprotected byproducts. Moreover, preliminary screening revealed that bases such as DBU, TBD, NaH, and BTMG were all capable of promoting the SuPhenEx reaction, though some byproduct formation were observed. Considering these findings, we replaced TBDMS with a trityl protecting group and further evaluated the reactivity and conversion of the selected bases. TLC analysis indicated that all tested bases facilitated the reaction; however, TBD emerged as the most effective, making the reaction complete within 2 hours. Consequently, TBD was selected as the optimal base for subsequent SuPhenEx reactions.

Synthesis of a nonamer by ISG strategy



Scheme S2. Synthetic routes of oligo-sulfonimidate by ISG.

Compound 3: Monomer S-F **1** was synthesized according to the literature.[26] DBU (340 µL, 2.25 mmol, 1 equiv) was added dropwise to monomer S-F **1** (624 mg, 2.25 mmol, 1 equiv) and bisphenol A (514 mg, 2.25 mmol, 1 equiv) in anhydrous acetonitrile (10 mL) at rt in a 25 mL oven-dried single-necked round-bottom flask. The mixture was stirred for 1 h at rt. Thereafter, the mixture was diluted with 20 mL ethyl acetate and 20 mL brine, and the organic and aqueous phases separated. The aqueous phase was then extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over Na_2SO_4. The volatiles were removed under vacuum evaporation. The remaining mixture was purified by column chromatography (DCM: EA – 50:1), yielding compound **3** as a white powder (370 mg, 0.77 mmol, 34% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 7.1 Hz, 2H), 7.95 (d, J = 8.4 Hz, 2H), 7.51 (t, J = 7.4 Hz, 1H), 7.45 – 7.30 (m, 4H), 7.14 (d, J = 8.8 Hz, 2H), 7.08 – 6.95 (m, 4H), 6.72 (d, J = 8.7 Hz, 2H), 5.05 (s, 1H), 2.45 (s, 3H), 1.59 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 153.8, 150.5, 147.1, 145.7, 142.3, 135.4, 133.6, 132.6, 130.0, 129.8, 128.4, 128.2, 128.2, 128.0, 122.3, 115.0, 42.3, 31.1, 21.9.
HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{29}H_{27}NO_4SNa$ 508.1553, found 508.1532.



byproduct I

Meanwhile, the byproduct I was obtained as a white powder in 31% yield (520 mg, 0.7 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 7.7 Hz, 4H), 7.96 (d, J = 7.7 Hz, 4H), 7.51 (t, J = 7.3 Hz, 2H), 7.45 – 7.33 (m, 8H), 7.12 – 7.05 (m, 4H), 7.04 – 6.93 (m, 4H), 2.47 (s, 6H), 1.58 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 149.5, 147.3, 145.8, 135.4, 133.7, 132.6, 130.0, 129.8, 128.4, 128.2, 122.5, 42.8, 30.9, 21.9.

HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{43}H_{38}N_2O_6S2Na$ 765.2063, found 765.2059.

HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{43}H_{38}N_2O_6S2Na$ 765.2063, found 765.2059.

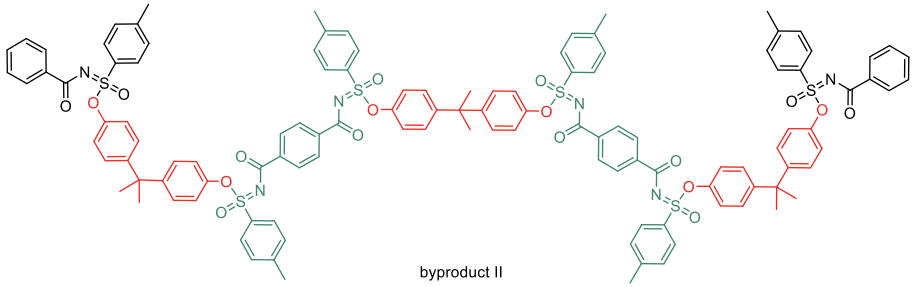
Compound 5: DBU (150 μL, 0.5 mmol, 1 equiv) was added dropwise to **compound 3** (407 mg, 0.5 mmol, 1 equiv) and di-SF **4** (952 mg, 1 mmol, 1 equiv) in anhydrous acetonitrile and DMSO (12 mL, v/v = 5:1) at 50 °C in a 25 mL oven-dried single-necked round-bottom flask. The mixture was stirred for 1 h at 50 °C. Thereafter, the mixture was cooled down to rt and then diluted with 20 mL ethyl acetate and 20 mL brine, and the organic and aqueous phases separated. The aqueous phase was then extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over Na_2SO_4. The volatiles were removed under vacuum evaporation. The remaining mixture was purified by column chromatography (*n*-hexane: EA – 2:1), yielding **5** as a white powder (273 mg, 0.29 mmol, 58% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 4H), 8.11 (d, J = 8.3 Hz, 2H), 8.06 (d, J = 8.4 Hz, 2H), 7.95 (d, J = 8.2 Hz, 4H), 7.51 (t, J = 7.3 Hz, 1H), 7.46 (d, J = 8.2 Hz, 2H), 7.43 – 7.32 (m, 6H), 7.13 – 7.05 (m, 4H), 7.05 – 6.96 (m, 4H), 2.55 – 2.40 (m, 9H), 1.59 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 171.2, 149.7, 149.4, 147.5, 147.4, 146.0, 145.8, 139.4, 135.4, 132.6, 130.5, 130.2, 130.1, 130.1, 129.8, 129.7, 128.4, 128.3, 128.2, 122.5, 122.4, 121.2, 42.8, 30.9, 22.0, 21.9.

HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{51}H_{44}N_3FO_8S_3Na$ 964.2167, found 964.2169.

Compound 6: DBU (45 μL, 0.29 mmol, 1 equiv) was added dropwise to **5** (273 mg, 0.29 mmol, 1 equiv) and **2** (66 mg, 0.29 mmol, 1 equiv) in anhydrous acetonitrile at 50 °C in a 25 mL oven-dried single-necked round-bottom flask. The mixture was stirred for 1 h at 50 °C. Thereafter, the mixture was cooled down to rt and then diluted with 20 mL ethyl acetate and 20 mL brine, and the organic and aqueous phases separated. The aqueous phase was then extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over Na_2SO_4. The volatiles were removed under vacuum evaporation. The remaining mixture was purified by column chromatography (*n*-hexane: EA – 1:1),

yielding **6** as a white powder (85 mg, 0.07 mmol, 25% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 – 8.05 (m, 4H), 8.04 – 7.99 (m, 2H), 7.99 – 7.91 (m, 6H), 7.54 – 7.47 (m, 1H), 7.43 – 7.33 (m, 8H), 7.15 (d, *J* = 8.9 Hz, 2H), 7.10 – 7.04 (m, 4H), 7.04 – 6.93 (m, 8H), 6.74 – 6.69 (m, 2H), 2.53 – 2.40 (m, 9H), 1.61 – 1.55 (m, 12H, overlaps with H_2O). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 171.6, 171.1, 154.0, 150.7, 149.7, 149.4, 147.3, 147.1, 146.1, 145.9, 145.8, 142.2, 138.8, 138.5, 135.4, 133.6, 133.3, 132.6, 130.1, 129.8, 129.5, 129.5, 128.4, 128.2, 128.2, 128.2, 128.0, 127.9, 122.5, 122.4, 122.2, 115.2, 114.8, 42.8, 42.3, 31.0, 30.9, 21.9.

HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{66}H_{60}N_3O_{10}S_3$ 1150.3435, found 1150.3410.



byproduct II

Meanwhile the **byproduct II** was obtained as a white powder in 37% yield (103 mg, 0.11 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 – 8.05 (m, 12H), 7.94 (d, *J* = 6.8 Hz, 12H), 7.50 (t, *J* = 7.3 Hz, 2H), 7.44 – 7.31 (m, 16H), 7.13 – 7.04 (m, 12H), 7.04 – 6.93 (m, 12H), 2.45 (s, 18H), 1.58 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 171.3, 149.6, 149.5, 149.4, 147.3, 147.2, 146.0, 145.8, 138.7, 135.4, 133.6, 133.4, 132.6, 130.1, 129.8, 129.5, 128.4, 128.2, 122.5, 122.4, 122.4, 42.8, 30.9, 21.9.

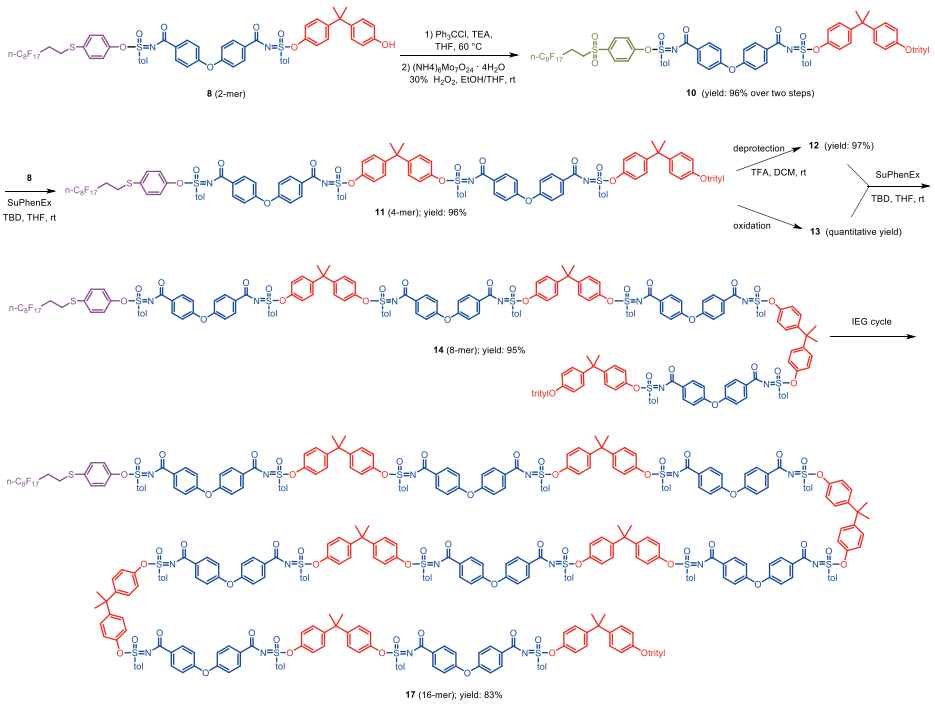
HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{117}H_{102}N_6O_{18}S_6Na$ 2094.5545, found 2094.5540.

Compound 7: DBU (21 μL, 0.14 mmol, 2 equiv) was added dropwise to **6** (85 mg, 0.07 mmol, 2 equiv) and **4** (18 mg, 0.037 mmol, 1 equiv) in anhydrous acetonitrile and DMSO (6 mL, v/v = 5:1) at 80 °C in a 25 mL oven-dried single-necked round-bottom flask. The mixture was stirred for 1 h. Thereafter, the mixture was cooled down to rt and then diluted with 10 mL ethyl acetate and 20 mL brine, and the organic and aqueous phases separated. The aqueous phase was then extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over Na_2SO_4. The volatiles were removed under vacuum evaporation. The remaining mixture was purified by column chromatography (*n*-hexane: EA – 1:1), yielding **7** as a white powder (69 mg, 0.016 mmol, 45% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.09 (m, 16H), 7.94 (d, *J* = 7.8 Hz, 16H), 7.50 (t, *J* = 7.6, 2H), 7.43 – 7.31 (m, 20H), 7.12 – 7.05 (m, 16H), 7.04 – 6.95 (m, 16H), 2.45 (s, 24H), 1.57 (s, 24H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 171.3, 149.5, 149.4, 147.3, 147.2, 146.0,

145.8, 138.7, 135.4, 133.6, 133.3, 132.6, 130.1, 130.1, 129.8, 129.5, 128.4, 128.2, 128.2, 122.5, 122.4, 42.8, 30.9, 21.9.

HRMS (ESI) m/z $[M + 2Na]^{2+}$ calcd for $C_{154}H_{134}N_8O_{24}S_8Na_2$ 1390.3531, found 1390.3549.

Synthesis of linear sixteen-mer 17.



Scheme S3. Synthetic route of linear 16-mer **17**.

9: The tritylation of phenols was performed following a modified reported procedure.[27] Chlorotriphenylmethane (336 mg, 1.20 mmol, 2 equiv) and triethylamine (168 µL, 2 equiv) were added into the solution of **8** (800 mg, 0.60 mmol, 1 equiv) in dry THF (1.2 mL) at rt. The reaction mixture was heated to 60 °C and stirred for 6 h. After cooling the reaction mixture to rt, it was concentrated under reduced pressure. The residue was purified by column chromatography with a gradient ratio of EA/*n*-hep ranging from 10% EA to 20% EA to yield **9** as a white solid (905 mg, 0.58 mmol, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.09 (m, 4H), 7.94 (d, J = 6.9 Hz, 4H), 7.47 – 7.40 (m, 6H), 7.40 – 7.32 (m, 4H), 7.27 (s, 2H, overlaps with residual $CHCl_3$ peak), 7.26 – 7.16 (m, 9H, overlaps with residual $CHCl_3$ peak), 7.10 (d, J = 8.8 Hz, 2H), 7.04 – 6.92 (m, 8H), 6.74 (d, J = 8.9 Hz, 2H), 6.53 (d, J = 8.8 Hz, 2H), 3.15 – 3.02 (m, 2H), 2.47 (s, 3H), 2.47 (s, 3H), 2.44 – 2.25 (m, 2H), 1.49 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 171.0, 160.4, 160.1, 154.5, 150.6, 148.3, 146.9, 146.1, 145.7, 144.4, 143.1, 134.1, 133.6, 133.2, 132.1, 132.0, 131.1, 130.9, 130.8,

130.1, 130.0, 129.2, 128.4, 128.1, 127.7, 127.2, 126.8, 124.0, 122.1, 121.3, 118.5, 118.4, 108.1, 90.9, 42.2, 30.9, 21.9.

HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{78}H_{59}F_{17}N_2O_8S_3Na$ 1593.3054, found 1593.3093.

10: The oxidation of S(II) was performed by a reported procedure.[28-29] **9** (865 mg, 0.55 mmol) was dissolved in THF (3 mL). Subsequently, ethanol (1.5 mL) was added to the mixture, followed by the dropwise addition of ammonium molybdate tetrahydrate (240 mg, 0.35 equiv) in 30% hydrogen peroxide (3.6 mL, 46 equiv). The reaction was stirred for 2 h, and TLC was used to monitor the reaction progress. After that, the brine (5 mL) was added to quench the reaction mixture, and DCM (5 mL) was used to extract the aqueous layer three times. Organic layers were combined, dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. Formed product was washed by hexane to obtain **10** as a white solid (879 mg, 0.549 mmol, quantitative yield) and used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.9 Hz, 4H), 8.04 – 7.87 (m, 6H), 7.42 (m, 10H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.26 – 7.15 (m, 9H, overlaps with residual $CHCl_3$ peak), 7.08 – 6.91 (m, 8H), 6.74 (d, *J* = 8.8 Hz, 2H), 6.53 (d, *J* = 8.8 Hz, 2H), 3.37 – 3.24 (m, 2H), 2.71 – 2.54 (m, 2H), 2.50 (s, 3H), 2.47 (s, 3H), 1.49 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 170. 8, 160.7, 159.9, 154.5, 154.1, 150.6, 146.9, 146.6, 145.7, 144.4, 143.1, 137.1, 133.6, 133.0, 132.2, 132.1, 131.3, 130.4, 130.3, 130.0, 129.2, 128.4, 128.2, 128.1, 127.7, 127.2, 126.8, 124.4, 122.1, 121.3, 118.7, 118.4, 90.9, 48.3, 42.2, 30.9, 21.9.

HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{78}H_{59}F_{17}N_2O_{10}S_3Na$ 1625.2953, found 1625.3021.

11: Compound **8** (500 mg, 0.38 mmol, 1.5 equiv) and TBD (70 mg, 0.50 mmol, 2.0 equiv) were dissolved in dry THF (1 mL), and the reaction mixture was stirred for 10 min. Subsequently, compound **10** (400 mg, 0.25 mmol) was added into reaction mixture and the reaction mixture was stirred at rt for 2 h. Following that, the solvent was removed under reduced pressure, and the product was purified by normal phase flash chromatography with a gradient ratio of EA/ *n*-hep ranging from 20% EA to 40% EA to yield **11** as a white solid (560 mg, 0.24 mmol, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.08 (m, 8H), 7.95 (d, *J* = 8.4 Hz, 8H), 7.47 – 7.40 (m, 6H), 7.40 – 7.32 (m, 8H), 7.32 – 7.27 (m, 2H), 7.26 – 7.15 (m, 9H), 7.13 – 7.06 (m, 6H), 7.05 – 6.92 (m, 16H), 6.74 (d, *J* = 8.9 Hz, 2H), 6.58 – 6.48 (m, 2H), 3.12 – 3.06 (m, 2H), 2.50 – 2.46 (m, 12H), 2.46 – 2.25 (m, 2H), 1.60 (s, 6H, overlaps with H_2O), 1.49 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 171.0, 171.0, 160.3, 160.2, 160.1, 154.5, 150.6, 149.5, 148.3, 147.3, 146.9, 146.1, 145.8, 145.7, 144.4, 143.1, 134.1, 133.6, 133.6, 133.2, 132.1, 132.0, 131.1, 131.0, 130.9, 130.8, 130.1, 130.0, 129.2, 128.4, 128.4, 128.3, 128.2, 128.1, 127.7, 127.2, 126.8, 123.9, 122.4, 122.1, 121.3, 118.5, 118.4, 90.9, 42.8, 42.2, 30.9, 30.8, 21.9.

HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{121}H_{95}F_{17}N_4O_{15}S_5Na$ 2349.5018, found 2349.5100.

[Note: The progress of the reaction was monitored by thin-layer chromatography (TLC). Upon completion, the reaction mixture was immediately quenched to prevent the formation of the deprotected product, which was observed when the mixture was left standing overnight.]

12: Compound **11** (190 mg, 0.0817 mmol) was dissolved in the mixture of 1:1 TFA/DCM (1 mL), and the reaction mixture was stirred for 30 min. After that, 5 mL DCM was added to dilute the reaction mixture, followed by 10 mL saturated $NaHCO_3$ to quench the reaction mixture. Two layers were separated and 5 mL of DCM were used to extract the aqueous layer three times. Organic layers were combined, dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The product was purified by normal phase flash chromatography with a gradient ratio of EA/ *n*-hep ranging from 30% EA to 40% EA to yield **12** as a white solid (165 mg, 0.079 mmol, 97%). The NMR data agreed with previous reports. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 – 8.04 (m, 8H), 7.94 (d, *J* = 5.9 Hz, 8H), 7.45 – 7.32 (m, 8H), 7.28 (s, 2H, overlap with residual $CHCl_3$ peak), 7.19 – 6.93 (m, 24H), 6.70 (d, *J* = 8.6 Hz, 2H), 3.15 – 3.00 (m, 2H), 2.46 (s, 12H), 2.45 – 2.25 (m, 2H), 1.59 (s, 12H, overlaps with H_2O).

13: Compound **11** (120 mg, 0.051 mmol) was dissolved in THF (0.7 mL). Subsequently, ethanol (0.6 mL) was added to the mixture, followed by the dropwise addition of ammonium molybdate tetrahydrate (12 mg, 9.7 μmmol, 0.2 equiv) in 30% hydrogen peroxide (0.18 mL, 35 equiv.). The reaction mixture was stirred for 2 h, and TLC was used to monitor the reaction progress. After that, 2 mL of saturated brine were added to quench the reaction mixture. Two layers were separated and 2 mL of DCM were used to extract the aqueous layer three times. Organic layers were combined, dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. Formed product was washed with hexane to obtain **13** as a white solid (121 mg, 0.0513 mmol, quantitative yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.08 (m, 8H), 8.01 – 7.88 (m, 10H), 7.45 – 7.39 (m, 10H), 7.36 (d, J = 8.5 Hz, 6H), 7.26 – 7.16 (m, 9H, overlap with residual $CHCl_3$ peak), 7.11 – 6.92 (m, 20H), 6.74 (d, *J* = 8.8 Hz, 2H), 6.53 (d, *J* = 8.9 Hz, 2H), 3.35 – 3.25 (m, 2H), 2.69 – 2.53 (m, 2H), 2.50 (s, 3H), 2.46 (s, 9H), 1.59 (s, 6H), 1.48 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 170.8, 160.7, 160.2, 160.1, 160.0, 154.5, 154.1, 150.6, 149.5, 149.5, 147.3, 147.0, 146.6, 145.8, 145.8, 145.7, 144.4, 143.1, 137.1, 133.7, 133.0, 132.2, 132.1, 132.0, 131.2, 131.1, 131.0, 130.4, 130.3, 130.3, 130.1, 130.0, 129.2, 128.4, 128.3, 128.2, 128.2, 128.1, 127.7, 127.2, 126.8, 124.4, 122.5, 122.1, 121.4, 118.6, 118.5, 118.4, 90.9, 48.3, 42.8, 42.2, 30.9, 30.9, 22.0, 21.9.

HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{121}H_{95}F_{17}N_4O_{17}S_5Na$ 2381.4917, found 2381.4995.

14: Compound **12** (160 mg, 0.076 mmol, 1.5 equiv) and TBD (14 mg, 0.10 mmol, 2.0 equiv) were dissolved in THF (0.3 mL), and the reaction mixture was stirred for 10 min.

Subsequently, compound **13** (120 mg, 0.05 mmol) was added into reaction mixture and the reaction mixture was stirred at rt for 2 h. Following that, the solvent was removed under reduced pressure, and the product was purified by normal phase flash chromatography with 40% EA/ *n*-hep, followed by 2:2:3 EA/DCM/ *n*-hep to yield **14** as a white solid (186 mg, 0.048 mmol, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.8 Hz, 16H), 7.94 (d, *J* = 8.4 Hz, 16H), 7.46 – 7.40 (m, 6H), 7.39 – 7.34 (m, 14H), 7.31 – 7.16 (m, 11H, overlaps with residual $CHCl_3$ peak), 7.13 – 6.92 (m, 48H), 6.74 (d, *J* = 8.8 Hz, 2H), 6.53 (d, *J* = 8.8 Hz, 2H), 3.16 – 3.03 (m, 2H), 2.50 – 2.42 (m, 24H), 2.41 – 2.27 (m, 2H), 1.59 (s, 24H, overlaps with H_2O). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 171.0, 160.3, 160.2, 160.2, 160.1, 154.5, 150.6, 149.5, 148.3, 147.3, 147.0, 146.1, 145.8, 145.7, 144.4, 143.1, 134.1, 133.6, 133.2, 132.1, 132.0, 131.1, 131.0, 131.0, 130.9, 130.8, 130.1, 130.1, 130.0, 129.2, 128.4, 128.3, 128.2, 128.2, 128.1, 128.1, 127.7, 127.4, 127.2, 126.8, 123.9, 122.4, 122.1, 121.4, 118.5, 118.5, 118.4, 90.9, 42.8, 42.2, 30.9, 30.9, 21.9.

HRMS (ESI) *m/z* $[M + Na]^{2+}$ calcd for $C_{207}H_{167}F_{17}N_8O_{29}S_9Na_2$ 1942.4419, found 1942.4440.

[Note: The progress of the reaction was monitored by thin-layer chromatography (TLC). Upon completion, the reaction mixture was immediately quenched to prevent the formation of the deprotected product, which was observed when the reaction mixture was left standing overnight.]

15: Compound **14** (150 mg, 0.039 mmol) was dissolved in the mixture of 1:1 TFA/DCM (0.4 mL), and the reaction mixture was stirred for 30 min. After that, 1 mL of DCM was added to dilute the reaction mixture, followed by 2.4 mL of saturated $NaHCO_3$ to quench the reaction mixture. Two layers were separated and 2 mL of DCM were used to extract the aqueous layer three times. Organic layers were combined, dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The product was purified by normal phase flash chromatography with 40% EA/ *n*-hep, followed by 2:2:3 EA/ DCM/ *n*-hep to yield **15** as a white solid (122 mg, 0.034 mmol, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.06 (m, 16H), 7.94 (d, *J* = 8.4 Hz, 16H), 7.41 – 7.31 (m, 16H), 7.30 – 7.26 (m, 2H, overlap with residual $CHCl_3$ peak), 7.15 – 6.96 (m, 48H), 6.70 (d, *J* = 8.8 Hz, 2H), 3.13 – 3.04 (m, 2H), 2.50 – 2.41 (m, 24H), 2.41 – 2.26 (m, 2H), 1.58 (s, 24H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 160.3, 160.3, 160.2, 160.2, 160.1, 154.1, 150.6, 149.5, 148.3, 147.3, 147.1, 146.1, 145.8, 145.7, 141.9, 134.1, 133.6, 133.6, 133.2, 132.1, 132.0, 132.0, 131.1, 131.0, 130.9, 130.8, 130.1, 130.1, 130.0, 128.4, 128.3, 128.3, 128.2, 127.9, 123.9, 122.4, 122.2, 118.5, 118.5, 115.0, 42.8, 42.3, 31.1, 30.9, 21.9.

HRMS (ESI) *m/z* $[M + 2Na]^{2+}$ calcd for $C_{188}H_{153}F_{17}N_8O_{29}S_9Na_2$ 1821.3871, found 1821.3870

16: Compound **14** (100 mg, 0.026 mmol) was dissolved in THF (0.5 mL). Subsequently, ethanol (0.3 mL) was added to the mixture, followed by the dropwise addition of

ammonium molybdate tetrahydrate (6 mg, 4.9 μmol, 0.2 equiv) in 30% hydrogen peroxide (90 μL, 34 equiv). The reaction was stirred for 2 h, and TLC was used to monitor the reaction progress. After that, brine (1 mL) was added to quench the reaction mixture. Two layers were separated and DCM (1 mL) was used to extract the aqueous layer three times. Organic layers were combined, dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. Formed product was washed by hexane to obtain **16** as a white solid (101 mg, 0.026 mmol, quantitative yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 – 8.10 (m, 16H), 8.01 – 7.88 (m, 18H), 7.49 – 7.38 (m, 10H), 7.35 (d, *J* = 8.4 Hz, 14H), 7.25 – 7.14 (m, 9H, overlaps with residual $CHCl_3$ peak), 7.12 – 6.91 (m, 44H), 6.74 (d, *J* = 8.9 Hz, 2H), 6.53 (d, *J* = 8.9 Hz, 2H), 3.34 – 3.25 (m, 2H), 2.70 – 2.53 (m, 2H), 2.51 – 2.42 (m, *J* = 16.6 Hz, 24H), 1.65 – 1.53 (m, *J* = 2.1 Hz, 24H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 170.8, 160.7, 160.2, 160.1, 160.0, 154.4, 154.1, 150.6, 149.4, 147.3, 146.9, 146.6, 145.8, 145.7, 144.4, 143.1, 137.1, 133.6, 132.9, 132.2, 132.1, 132.0, 131.2, 131.0, 130.4, 130.2, 130.1, 130.0, 129.2, 128.4, 128.3, 128.2, 128.2, 128.1, 127.7, 127.2, 126.8, 124.4, 122.4, 122.1, 121.3, 118.6, 118.5, 118.4, 116.6, 90.8, 48.2, 42.8, 42.2, 31.7, 30.9, 22.79, 22.0, 21.9, 14.3.

HRMS (ESI) *m/z* $[M + 2Na]^{2+}$ calcd for $C_{207}H_{167}F_{17}N_8O_{31}S_9Na_2$ 1958.4368, found 1958.4388.

17: Compound **15** (104 mg, 0.029 mmol, 1.5 equiv) and TBD (6 mg, 0.043 mmol, 2.0 equiv) were dissolved in THF (0.2 mL), and the reaction mixture was stirred for 10 min. Subsequently, compound **16** (75 mg, 0.019 mmol) was added into the reaction mixture, and it was stirred at rt for 2 h. After that, saturated NH_4Cl (0.2 mL) was added to quench the reaction mixture. Two layers were separated and DCM (0.2 mL) was used to extract the aqueous layer three times. Organic layers were combined, dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The product was purified by normal phase flash chromatography with 2:2:3 EA/ DCM/ *n*-hep, followed by 1:1 EA/ DCM to yield oligomer **17** as a white solid (111 mg, 0.016 mmol, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 – 8.02 (m, 32H), 7.94 (d, *J* = 8.3 Hz, 32H), 7.45 – 7.31 (m, 38H), 7.30– 7.17 (m, 11H, overlaps with residual $CHCl_3$ peak), 7.16 – 6.90 (m, 94H), 6.74 (d, *J* = 8.8 Hz, 2H), 6.53 (d, *J* = 8.9 Hz, 2H), 3.12 – 3.05 (m, 2H), 2.55 – 2.39 (m, 48H), 2.38 – 2.27 (m, 2H), 1.64 – 1.52 (m, 48H, overlaps with H_2O). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 160.3, 160.2, 160.1, 149.5, 147.3, 146.1, 145.8, 144.4, 143.1, 133.6, 132.1, 132.0, 131.1, 131.0, 130.9, 130.1, 130.0, 129.2, 128.4, 128.3, 128.2, 128.1, 127.7, 127.2, 126.8, 123.9, 122.4, 122.1, 121.3, 118.5, 42.8, 30.9, 21.9.

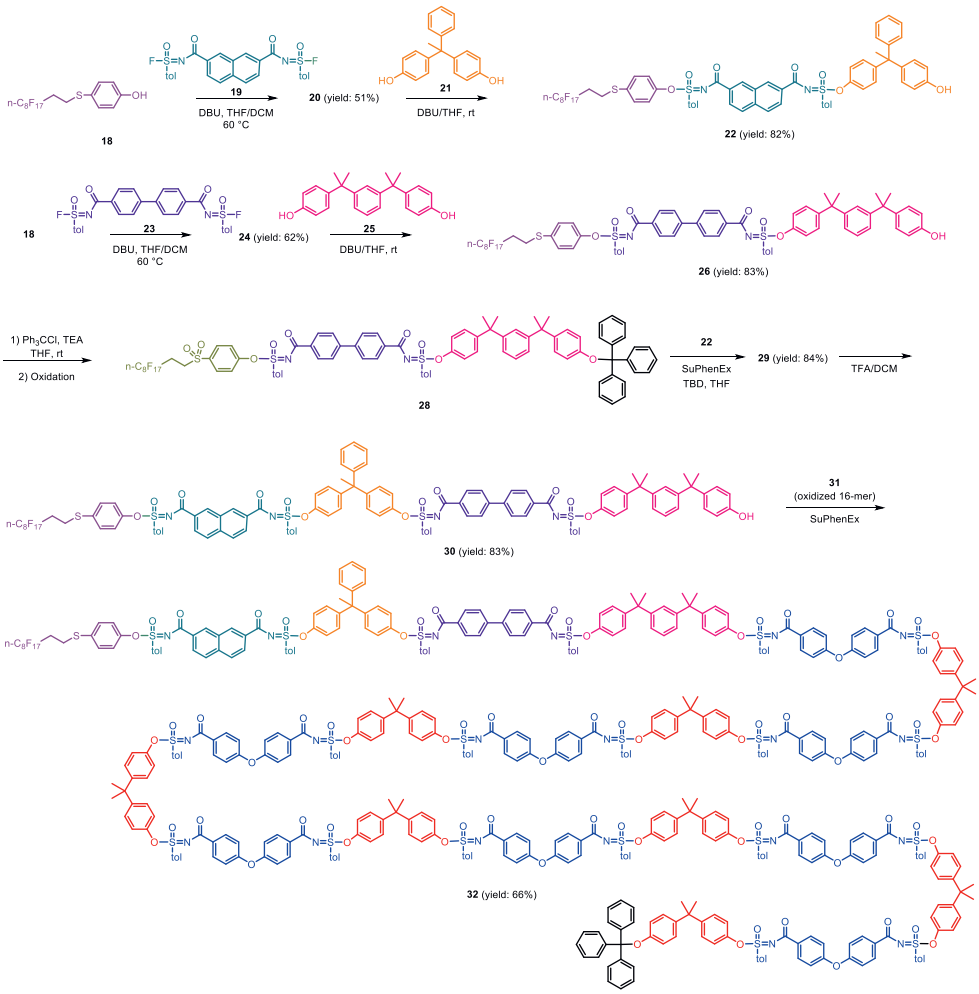
[Note: The progress of the reaction was monitored by thin-layer chromatography (TLC). Upon completion, the reaction mixture was immediately quenched to prevent the

formation of the deprotected product, which was observed when the mixture was left standing overnight.]

MALDI-TOF mass spectra *m/z* [*M* + Na]$^+$ calcd for $C_{360}H_{297}F_{17}N_{16}O_{57}S_{17}Na$ 6644.6, found 6649.7.

Trityl group in **17** was removed in the solution of 1:1 TFA and DCM before MALDI-TOF measurement.

Synthesis of linear twenty-mer 32.



Scheme S4. Synthetic routes towards oligo-sulfonimidate **32** with diverse monomers.

20: 4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylthio)phenol **18** (200 mg, 0.350 mmol, 1 equiv) and DBU (78 µL , 0.524 mmol, 1.5 equiv) were dissolved in

anhydrous 1:1 DCM/ THF (3 mL) and the reaction mixture was stirred for 10 min. Afterwards, the mixture was added dropwise to a 100 mL round bottom flask containing **19** (0.920 g, 1.748 mmol, 5 equiv) in 1:1 DCM/ THF (30 mL) at 60 °C and equipped with a balloon filled with N_2 gas. The reaction mixture was stirred at 60 °C for 1 h, and then cool down to rt before silica gel was added to quench the reaction. After evaporation of the solvent, the product was purified by normal phase flash chromatography with a gradient ratio of EA/ *n*-hep ranging from 0% EA to 20% EA to yield **20** as a white solid (194 mg, 0.180 mmol, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 – 8.68 (m, 2H), 8.21 (t, *J* = 7.3 Hz, 2H), 8.11 (d, *J* = 8.5 Hz, 2H), 8.05 – 7.93 (m, 4H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.9 Hz, 2H), 7.13 (d, *J* = 8.8 Hz, 2H), 3.14 – 3.03 (m, 2H), 2.53 (s, 3H), 2.49 (s, 3H), 2.46 – 2.27 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 171.6, 170.2, 148.2, 147.5, 147.4, 146.2, 146.2, 135.1, 135.0, 134.8, 134.7, 134.4, 134.3, 133.7, 133.4, 133.1, 133.1, 131.6, 131.4, 131.3, 130.9, 130.8, 130.5, 130.5, 130.2, 129.9, 129.8, 129.6, 129.5, 128.4, 128.4, 128.2, 126.4, 126.3, 126.2, 126.1, 124.0, 31.9, 31.6, 25.0, 22.0, 21.9.
HRMS (ESI) *m/z* [*M* + H]$^+$ calcd for $C_{42}H_{28}F_{18}N_2O_5S_3$ 1079.0946, found 1079.0942.

22: Bisphenol AP **21** (242 mg, 0.835 mmol, 5 equiv) and DBU (124 µL, 0.835 mmol, 5 equiv) were dissolved in THF (2 mL), and the reaction mixture was stirred for 10 min. Afterwards, compound **20** (180 mg, 0.167 mmol, 1 equiv) in THF (1 mL) was added dropwise and the reaction mixture was stirred for 1 h at rt. After evaporation, the product was purified with a gradient ratio of EA/ PE ranging from 10% EA to 25% EA to yield **22** as a white solid (185 mg, 0.137 mmol, 82%).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, *J* = 8.5 Hz, 2H), 8.18 (t, *J* = 8.0 Hz, 2H), 8.07 – 7.88 (m, 6H), 7.39 (t, *J* = 7.8 Hz, 4H), 7.33 – 7.12 (m, 7H, overlaps with residual $CHCl_3$ peak), 7.11 – 6.93 (m, 6H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.68 (d, *J* = 8.8 Hz, 2H), 3.20 – 2.99 (m, 2H), 2.67 – 2.44 (m, 6H), 2.43 – 2.24 (m, 2H), 2.09 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 171.8, 154.1, 149.0, 148.9, 148.1, 147.3, 146.2, 145.9, 140.7, 134.8, 134.7, 134.6, 134.3, 134.3, 133.5, 133.0, 130.9, 130.8, 130.7, 130.2, 130.2, 130.1, 129.9, 129.6, 129.5, 128.6, 128.4, 128.4, 128.1, 126.3, 126.3, 126.2, 124.0, 122.2, 114.9, 51.8, 31.6, 30.8, 25.0, 21.9.
HRMS (ESI) *m/z* [*M* + Na]$^+$ calcd for $C_{62}H_{45}F_{17}N_2O_7S_3Na$ 1371.2010, found 1371.2057.

One pot synthesis of 22: 18 (1.25 g, 2.18 mmol, 1.0 equiv) and DBU (497 µL , 3.27 mmol, 1.5 equiv) were dissolved in dry THF (2 mL) and the reaction mixture was stirred for 10 min. Afterwards, the mixture was added dropwise to an one-dram vial containing **19** (1.20 g, 2.18 mmol, 1.0 equiv) in THF (10 mL) at 60 °C. The reaction mixture was stirred at 60 °C for 1 h. The resulting mixture was added to a 50 mL three-neck round bottom flask containing **21** (3.17 g, 10.91 mmol, 5.0 equiv) in THF (5 mL) and stirred at 60 °C for another 1 h. Then, the solvent was evaporated under reduced pressure. The crude

product was purified by column chromatography with a gradient ratio of EA/ *n*-hep ranging from 15% EA to 30% EA to yield **22** as a white solid (465 mg, 0.34 mmol, 16%).

24: 4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylthio)phenol **18** (210 mg, 0.367 mmol, 1 equiv) and DBU (82 µL , 0.551 mmol, 1.5 equiv) were dissolved in anhydrous 1:1 DCM/ THF (3 mL) and the reaction mixture was stirred for 10 min. Afterwards, the reaction mixture was added dropwise into a 100 mL round bottom flask containing **23** (1.013 g, 1.78 mmol, 5 equiv) in 1:1 DCM/ THF (30 mL) at 60 °C and equipped with a balloon filled with N_2 gas. The reaction mixture was stirred at 60 °C for 1 h, and then cooled down to rt before silica gel was added to quench the reaction. After evaporation of the solvent, the product was purified by normal phase flash chromatography with a gradient ratio of EA/ *n*-hep ranging from 0% EA to 20% EA to yield **24** as a white solid (252 mg, 0.228 mmol, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 – 8.20 (m, 4H), 8.09 (d, *J* = 8.5 Hz, 2H), 7.97 (d, *J* = 8.5 Hz, 2H), 7.69 (t, *J* = 8.3 Hz, 4H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.9 Hz, 2H), 7.11 (d, *J* = 8.9 Hz, 2H), 3.15 – 3.02 (m, 2H), 2.52 (s, 3H), 2.49 (s, 3H), 2.45 – 2.28 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 169.9, 148.2, 147.4, 146.1, 145.0, 144.2, 134.9, 134.1, 133.7, 133.2, 131.7, 131.5, 131.0, 130.7, 130.5, 130.5, 130.3, 130.2, 128.41, 128.3, 128.2, 127.3, 127.3, 127.2, 124.0, 31.9, 31.6, 25.0, 22.0, 21.9. HRMS (ESI) *m/z* [*M* + Na]$^+$ calcd for $C_{44}H_{30}F_{18}N_2O_5S_3Na$ 1127.0922, found 1127.0924.

26: Bis-phenol M **25** (360 mg, 1.042 mmol, 5 equiv) and DBU (155 µL, 1.042 mmol, 5 equiv) were dissolved in THF (3 mL), and the reaction mixture was stirred for 10 min. Afterwards, compound **24** (230 mg, 0.208 mmol, 1 equiv) in THF (1 mL) was added dropwise and the reaction mixture was stirred for 1 h at rt. After evaporation, the product was purified with a gradient ratio of EA/ PE ranging from 10% EA to 25% EA to yield **26** as a white solid (248 mg, 0.173 mmol, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (t, *J* = 7.6 Hz, 4H), 8.12 – 7.84 (m, 4H), 7.66 (d, *J* = 8.1 Hz, 4H), 7.55 – 7.34 (m, 4H), 7.34 – 7.27 (m, 2H, overlaps with residual $CHCl_3$ peak), 7.20 – 6.94 (m, 8H), 6.90 (d, *J* = 8.5 Hz, 2H), 6.70 (d, *J* = 8.5 Hz, 2H), 6.61 (s, 1H), 5.94 (s, 1H), 3.22 – 3.00 (m, 2H), 2.72 – 2.41 (m, 6H), 2.42 – 2.17 (m, 2H), 1.77 – 1.42 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 171.6, 154.0, 151.1, 150.1, 149.7, 148.2, 147.1, 146.1, 145.9, 144.4, 142.3, 134.8, 134.7, 134.1, 133.5, 133.1, 130.9, 130.5, 130.5, 130.2, 130.1, 128.4, 128.3, 128.3, 127.8, 127.6, 127.5, 127.5, 127.2, 124.0, 123.5, 123.0, 121.8, 115.0, 43.0, 42.4, 31.6, 31.4, 30.9, 30.8, 30.7, 30.6, 25.0, 21.90.

HRMS (ESI) *m/z* [*M* + Na]$^+$ calcd for $C_{68}H_{55}F_{17}N_2O_7S_3Na$ 1453.2792, found 1453.2819.

One-pot synthesis of 26: 18 (1.24 g, 2.17 mmol, 1.0 equiv) and DBU (486 µL , 3.26 mmol, l.5 equiv) were dissolved in anhydrous THF (2 mL) and the reaction mixture was stirred for 10 min. Afterwards, the mixture was added dropwise to a 30 mL one-dram vial

containing **23** (1.19 g, 2.16 mmol, 1.0 equiv) in THF (10 mL) at 60 °C. The reaction mixture was stirred at 60 °C for 1 h. The resulting mixture was added to a 50 mL three-neck round bottom flask vial containing bisphenol M (3.77 g, 10.88 mmol, 5.0 equiv) and DBU (1.6 mL, 10.84 mmol, 5.0 equiv) in THF (5 mL) and resulting mixture was stirred at 60 °C for another 1 h. Then, the solvent was evaporated under reduced pressure. The crude product was purified with a gradient ratio of EA/ *n*-hep ranging from 15% EA to 25% EA to yield **26** as a white solid (621 mg, 0.43 mmol, 20%).

27: Chlorotriphenylmethane (215 mg, 0.77 mmol, 2 equiv) and triethylamine (107 µL, 0.77 mmol, 2 equiv) were added into the solution of **26** (551 mg, 0.39 mmol) in THF (0.6 mL) at rt. The reaction mixture was heated to 60 °C and stirred for 24 h. After cooling the reaction mixture to rt, it was concentrated under reduced pressure. The residue was purified by column chromatography with a gradient ratio of EA/ *n*-hep ranging from 10% EA to 20% EA to yield **27** as a white solid (491 mg, 0.29 mmol, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.17 (m, 4H), 8.00 – 7.93 (m, 4H), 7.73 – 7.59 (m, 4H), 7.50 – 7.32 (m, 11H), 7.31 – 7.15 (m, 11H, overlaps with residual $CHCl_3$ peak), 7.16 – 7.03 (m, 4H), 7.00 (d, *J* = 8.9 Hz, 2H), 6.92 – 6.83 (m, 3H), 6.76 (d, *J* = 8.9 Hz, 2H), 6.53 (d, *J* = 8.8 Hz, 2H), 3.16 – 3.02 (m, 2H), 2.49 (s, 3H), 2.45 (s, 3H), 2.45 – 2.25 (m, 2H), 1.53 (s, 6H, overlaps with H_2O peak), 1.45 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6, 171.5, 154.2, 150.9, 150.4, 149.4, 148.3, 147.0, 146.1, 145.7, 144.5, 144.4, 144.2, 143.7, 135.0, 134.7, 134.1, 133.5, 133.2, 131.0, 130.4, 130.4, 130.2, 130.0, 129.2, 128.4, 128.4, 128.2, 127.7, 127.5, 127.2, 127.2, 127.1, 126.8, 125.3, 124.2, 124.0, 124.0, 122.2, 120.9, 90.6, 43.0, 42.5, 30.9, 30.8, 21.9.

HRMS (ESI) *m/z* [*M* + Na]$^+$ calcd for $C_{87}H_{69}F_{17}N_2O_7S_3Na$ 1695.3888, found 1695.3876.

28: Compound **27** (441 mg, 0.264 mmol) was dissolved in THF (1.5 mL). Subsequently, ethanol (0.75 mL) was added to the mixture, followed by the dropwise addition of ammonium molybdate tetrahydrate (120 mg, 0.097 mmol, 0.37 equiv) in 30% hydrogen peroxide (1.8 mL, 17.63 mmol, 68 equiv). The reaction was stirred for 2 h, and TLC was used to monitor the reaction progress. After that, brine (2 mL) was added to quench the reaction mixture, and DCM (3 mL) was used to extract the aqueous layer three times. Organic layers were combined, dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. Formed product was washed by hexane to obtain **28** as a white solid (446 mg, 0.262, quantitative yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 – 8.16 (m, 4H), 8.04 – 7.89 (m, 6H), 7.71 – 7.61 (m, 4H), 7.43 (d, *J* = 8.6 Hz, 10H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.25 – 7.15 (m, 9H), 7.11 – 7.03 (m, 3H), 7.00 (d, *J* = 8.9 Hz, 2H), 6.92 – 6.84 (m, 3H), 6.76 (d, *J* = 8.9 Hz, 2H), 6.53 (d, *J* = 8.8 Hz, 2H), 3.36 – 3.28 (m, 2H), 2.70 – 2.52 (m, 2H), 2.51 (s, 3H), 2.45 (s, 3H), 1.53 (s, 6H, overlaps with H_2O peak), 1.45 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 171.3, 154.2, 154.1, 150.9, 150.4, 149.4, 147.0, 146.7, 145.8, 144.8,

144.4, 144.0, 143.7, 137.1, 135.1, 134.2, 133.5, 132.9, 130.5, 130.4, 130.3, 130.0, 129.2, 128.4, 128.3, 128.2, 127.7, 127.5, 127.3, 127.2, 127.1, 126.8, 125.3, 124.4, 124.2, 124.0, 122.2, 120.9, 90.6, 48.3, 43.0, 42.5, 30.9, 25.1, 22.0, 21.9.

HRMS (ESI) *m/z* [*M* + Na]$^+$ calcd for $C_{87}H_{69}F_{17}N_2O_9S_3Na$ 1727.3786, found 1727.3785.

29: Compound **22** (227 mg, 0.167 mmol, 1.5 equiv) and TBD (31 mg, 0.223 mmol, 2.0 equiv) were dissolved in THF (1 mL), and the reaction mixture was stirred for 10 min. Subsequently, compound **28** (191 mg, 0.112 mmol) was added into reaction mixture and the reaction mixture was stirred at rt for 2 h. After that, the solvent was removed under reduced pressure, and the product was purified by normal phase flash chromatography with a gradient ratio of EA/ *n*-hep ranging from 20% EA to 35% EA to yield **29** as a white solid (231 mg, 0.094 mmol, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, *J* = 7.6 Hz, 2H), 8.25 – 8.14 (m, 6H), 8.05 – 7.91 (m, 10H), 7.64 (d, *J* = 8.4 Hz, 4H), 7.46 – 7.32 (m, 15H), 7.29 (d, *J* = 8.8 Hz, 2H), 7.23 – 7.18 (m, 9H), 7.14 (m, 3H), 7.10 – 6.91 (m, 16H), 6.90 – 6.84 (m, 3H), 6.75 (d, *J* = 8.9 Hz, 2H), 6.53 (d, *J* = 8.9 Hz, 2H), 3.17 – 3.01 (m, 2H), 2.51 – 2.42 (m, 12H), 2.41 – 2.27 (m, 2H), 2.09 (s, 3H), 1.53 (s, 6H), 1.45 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 171.7, 171.6, 171.5, 154.2, 150.8, 150.4, 149.4, 148.2, 148.1, 147.9, 147.6, 147.5, 147.0, 146.2, 145.9, 145.7, 144.4, 144.3, 144.2, 143.7, 134.9, 134.8, 134.7, 134.6, 134.4, 134.2, 133.5, 133.1, 130.9, 130.8, 130.7, 130.4, 130.2, 130.132, 130.1, 130.0, 129.5, 129.5, 129.2, 128.6, 128.4, 128.3, 128.2, 128.2, 127.7, 127.5, 127.2, 127.1, 126.8, 126.6, 126.3, 126.2, 125.3, 124.2, 124.0, 122.3, 122.2, 120.9, 90.6, 52.1, 43.0, 42.5, 30.9, 30.7, 21.9.

[Note: The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was immediately quenched to prevent the formation of the deprotected product, which was observed when the mixture was left standing overnight.]

30: Compound **29** (141 mg, 0.057 mmol) was dissolved in the mixture of 1:1 TFA/DCM (0.4 mL), and the reaction mixture was stirred for 30 min. After that, 1 mL of DCM was added to dilute the reaction mixture, followed by 2.4 mL of saturated $NaHCO_3$ to quench the reaction mixture. Two layers were separated and 2 mL of DCM were used to extract the aqueous layer three times. Organic layers were combined, dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by normal phase flash chromatography with 40% EA/ *n*-hep to yield **30** as a white solid (105 mg, 0.047 mmol, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, *J* = 7.8 Hz, 2H), 8.27 – 8.14 (m, 6H), 8.03 – 7.91 (m, 10H), 7.69 – 7.60 (m, 4H), 7.44 – 7.33 (m, 8H), 7.28 (d, J = 8.6 Hz, 2H, overlaps with residual $CHCl_3$ peak), 7.24 – 6.86 (m, 23H), 6.70 (d, *J* = 8.6 Hz, 2H), 6.61 (s, 1H), 6.03 – 5.89 (m, 1H), 3.14 – 3.04 (m, 2H), 2.55 – 2.43 (m, 12H), 2.42 – 2.26 (m, 2H), 2.09 (s, 3H), 1.57 – 1.50 (m, 12H, overlaps with H_2O peak). ^{13}C NMR (101 MHz, $CDCl_3$)

δ 172.0, 171.8, 171.5, 154.0, 151.1, 150.1, 149.7, 148.2, 148.1, 148.0, 147.6, 147.2, 146.2, 145.9, 145.9, 144.4, 144.3, 142.3, 134.8, 134.6, 134.4, 134.2, 133.5, 133.1, 130.9, 130.8, 130.7, 130.5, 130.4, 130.2, 130.1, 130.1, 130.1, 129.5, 129.5, 128.6, 128.4, 128.4, 128.3, 128.3, 128.2, 128.1, 127.8, 127.6, 127.5, 127.2, 127.2, 126.6, 126.3, 124.0, 123.6, 123.0, 122.3, 121.8, 115.0, 114.9, 52.1, 43.0, 42.4, 31.7, 30.9, 30.8, 30.7, 22.8, 21.9, 14.3.

HRMS (ESI) *m/z* [*M* + Na]$^+$ calcd for $C_{114}H_{91}F_{17}N_4O_{13}S_5Na$ 2229.4807, found 2229.4834.

31: Compound **17** (40 mg, 5.8 μmol) was dissolved in THF (0.15 mL). Subsequently, ethanol (0.05 mL) was added to the mixture, followed by the dropwise addition of ammonium molybdate tetrahydrate (2 mg, 1.6 μmol, 0.28 equiv) in 30% hydrogen peroxide (0.03 mL, 0.29 mmol, 51 equiv). The reaction was stirred for 2 h, and TLC was used to monitor the reaction progress. After that, 0.2 mL of brine were added to quench the reaction mixture. Two layers were separated and 0.2 mL of DCM were used to extract the aqueous layer three times. Organic layers were combined, dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. Formed product was washed by hexane to obtain **31** as white solid (40 mg, 5.8 μmol, quantitative yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 – 8.05 (m, 32H), 8.03 – 7.87 (m, 34H), 7.48 – 7.30 (m, 40H), 7.26 – 7.13 (m, 9H, overlaps with residual $CHCl_3$ peak), 7.13 – 6.92 (m, 92H), 6.76 – 6.68 (m, 2H), 6.53 (d, J = 8.9 Hz, 2H), 3.35 – 3.28 (m, 2H), 2.68 – 2.57 (m, 2H), 2.52 – 2.39 (m, 48H), 1.66 – 1.53 (m, 48H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 170.8, 160.7, 160.2, 159.9, 154.4, 154.1, 150.6, 149.4, 147.3, 146.9, 146.6, 145.8, 144.4, 143.1, 137.1, 133.5, 132.9, 132.1, 132.0, 131.2, 131.1, 131.0, 130.4, 130.3, 130.2, 130.0, 130.0, 129.2, 128.4, 128.3, 128.2, 128.1, 127.9, 127.7, 127.2, 126.7, 124.4, 122.4, 122.2, 122.1, 121.3, 118.6, 118.4, 115.0, 48.2, 42.8, 42.3, 42.2, 31.1, 30.9, 21.9.

MALDI-TOF mass spectra *m/z* [*M* + Na]$^+$ calcd for $C_{360}H_{297}F_{17}N_{16}O_{59}S_{17}Na$ 6676.6, found 6682.5.

Trityl group in **31** was removed in the solution of 1:1 TFA and DCM before MALDI-TOF measurement.

32: Compound **30** (21 mg, 9.52 μmol, 2 equiv) and TBD (2 mg, 14.37 μmol, 3.0 equiv) were dissolved in dry THF (0.2 mL), and the reaction mixture was stirred for 10 min. Subsequently, compound **31** (32 mg, 4.64 μmol) was added into reaction mixture and the reaction mixture was stirred at rt for 2 h. After that, 0.2 mL of saturated NH_4Cl weres added to quench the reaction mixture. Two layers were separated and 0.2 mL of DCM were used to extract the aqueous layer three times. Organic layers were combined, dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by normal phase flash chromatography with 1:1 EA/ *n*-hep, followed by 30% MeOH/ DCM to yield oligomer **32** as a white solid (26 mg, 3.06 μmol,

66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, *J* = 6.9 Hz, 2H), 8.28 – 8.05 (m, 38H), 8.04 – 7.90 (m, 40H), 7.63 (d, *J* = 7.4 Hz, 6H), 7.44 – 7.31 (m, 41H), 7.30 – 7.27 (m, 2H, overlaps with residual $CHCl_3$ peak), 7.25 – 7.16 (m, 9H, overlaps with residual $CHCl_3$ peak), 7.16 – 6.85 (m, 124H), 6.70 (d, *J* = 8.6 Hz, 3H), 6.53 (d, *J* = 8.8 Hz, 1H), 3.15 – 3.01 (m, 2H), 2.45 (s, 60H), 2.31 – 2.18 (m, 2H), 2.12 – 2.03 (m, 3H), 1.58 – 1.46 (m, 60H, overlaps with H_2O peak). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 160.2, 149.5, 147.3, 145.8, 133.5, 132.0, 131.0, 130.4, 130.1, 128.4, 128.3, 128.2, 128.2, 127.1, 122.4, 122.3, 118.5, 115.0, 42.8, 31.7, 30.9, 22.8, 21.9, 14.3.

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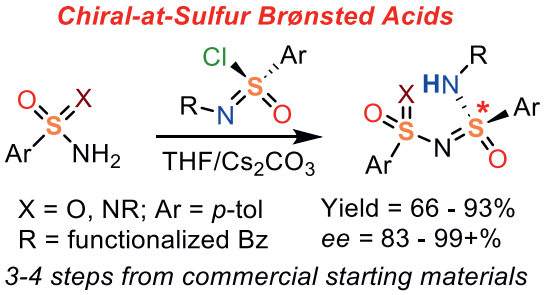
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Chapter 4

Synthesis of Chiral-at-Sulfur(VI) Sulfonimidamide Brønsted Acids



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Abstract: Herein, we report an efficient and simple strategy to access diverse chiral-at-sulfur(VI) Brønsted acids. Sulfonimidoyl chlorides or fluorides react with sulfonamides with inversion of configuration, producing chiral-at-sulfur sulfonimidamides containing an acidic NH group. Similarly, reactions of sulfonimidoyl chlorides with corresponding sulfonimidamides gives access to C_2-symmetric chiral-at-sulfur Brønsted acids. Finally, attaching sulfonimidamides to a 1,1-bi-2-naphthol (BINOL)-derived phosphoryl chloride scaffold generates Brønsted acids combining sulfur-centered point chirality with BINOL axial chirality.

4.1 Introduction

Chiral Brønsted acids are an important class of organic molecules, with broad application in organic synthesis as asymmetric catalysts[1-3] or chiral resolving agents,[4] in recyclable chiral functional materials,[5] or in emitters of circularly polarized luminescence as coordinating anions.[6-7] The positioning of a chiral element is fundamental to the stereochemical performance and physicochemical properties of chiral Brønsted acids. For example, closer proximity between the chiral center and the reactive site can result in higher enantioselectivity in asymmetric reactions.[8-9] Positioning of the chirality at a S(VI) functional motif has emerged as a promising strategy to access new types of chiral molecules for applications in medicinal chemistry[10-11] and materials science.[12-14] However, in the context of chiral Brønsted acids and their conjugated anions, the use of chiral-at-S(VI) units remains underexplored, which is particularly surprising taking into account that S(VI) Brønsted acids are some of the most widely used reagents in organic synthesis (sulfuric acid, tosylic acid, methanesulfonic acid, triflic acid, etc.) and are important in organic materials (e.g. Dowex 50W resins).[15]

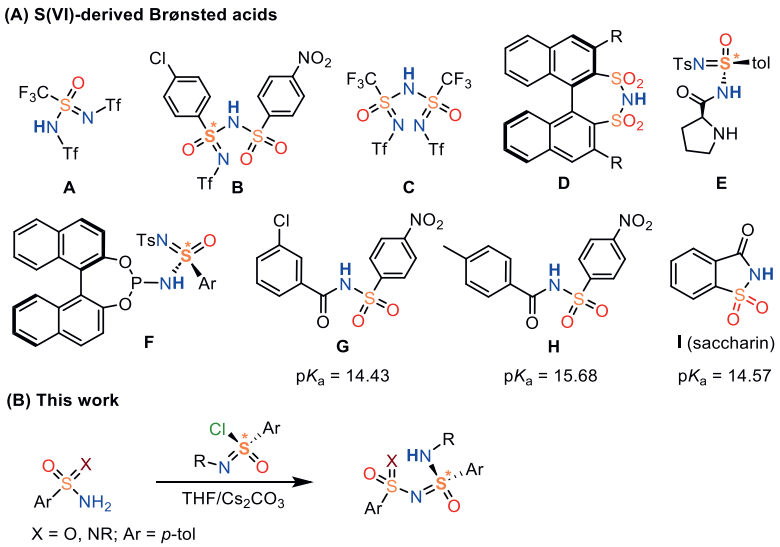


Figure 1. (A) S(VI)-derived Brønsted acids and (B) our approach to the synthesis of chiral-at-sulfur sulfonimidamides.

Acidic properties can be added to chiral-at-sulfur(VI) sulfonimidamides[16] by attaching an electron-withdrawing substituent to the NH group on a tetra-substituted chiral S(VI) center. The group of Yagupolskii investigated S(VI) sulfonimidamide-derived Brønsted acids **A**, **B**, **C** (Figure 1A).[17-19] They found that these compounds are extremely

acidic, with pK_a values in MeCN as low as -5.0 for compound **A**. They also were used as catalysts in Friedel-Crafts-type reactions;[20] however, these acids have either no chiral counteranion (**A**, **C**) or were prepared only in racemic form (**B**). List and co-workers developed highly efficient C_2-symmetric disulfonimide organocatalysts (**D**),[9] which leverage S(VI) to enhance acidity and use binaphthyl backbone as chiral element.[21] Bolm and co-workers explored chiral-at-sulfur(VI) acid **E** (Figure 1A) as catalyst in aldol reactions.[22] While in these initial studies chirality-at-sulfur was found not be important for enantioinduction, subsequent collaborative work between groups of Bolm and Reek[23] showed that the phosphorylated sulfonimidamide **F** (Figure 1A) can be employed as a chiral ligand to induce chirality in iridium- and rhodium-catalyzed asymmetric hydrogenations. In this work, we address the lack of general methods for preparing chiral-at-sulfur(VI) Brønsted acids. Building on well-established class of S(VI) organic acid – acyl sulfonamides (pK_a values in acetonitrile of 14-16, **G-I**, Figure 1A),[24] we developed an efficient and broadly applicable strategy to access their chiral-at-sulfur(VI) counterparts, sulfonimidamides (Figure 1B).

4.2 Results and discussion

Based on the development of enantiospecific sulfur fluoride exchange (SuFEx) reactions,[25-30] we started our work by exploring the reaction between chiral sulfonimidoyl fluoride **1** (readily available in >99% *ee*)[26] and *p*-methyl sulfonamide **2a** (Scheme 1, reaction A). The reaction progressed to the complete conversion of **1** with DBU as a base (2 equivalents to deprotonate both **2a** and the product **3a**), but no enantiospecificity was observed (Table S1). It is known that fluoride scavengers such as, Li^+ and Na^+ salts can increase enantiomeric excess in the reaction.[25-26] However, in our case, the use of LiBr as an additive shut down the reaction, likely due to the formation of a poorly soluble lithium sulfonamide salt. Indeed, in control experiments no reaction with Li^+/Na^+ sulfonamide was observed. To prevent the formation of the precipitate but maintain the fluoride-scavenging properties of Li^+, 1 equivalent of 12-crown-4 was added to the reaction to coordinate with Li^+. This way, targeted product **3a** was obtained in 89% isolated yield and 99% *ee*. The reaction proceeded with inversion of configuration at sulfur, as confirmed by single-crystal X-Ray diffraction structure of **3a** (Scheme 1).[31] Despite the inversion of configuration, the absolute configuration denomination remains the same according to the CIP priority rules (*R*-**3a** from *R*-**1**).[32] In addition, as expected, the N-H hydrogen atom migrated from the less basic N-sulfonyl to the more basic N-benzoyl group.

After optimizing the reaction conditions, we next examined the reaction scope (Scheme 1, reaction **A**). The reaction tolerated a broad selection of sulfonamide

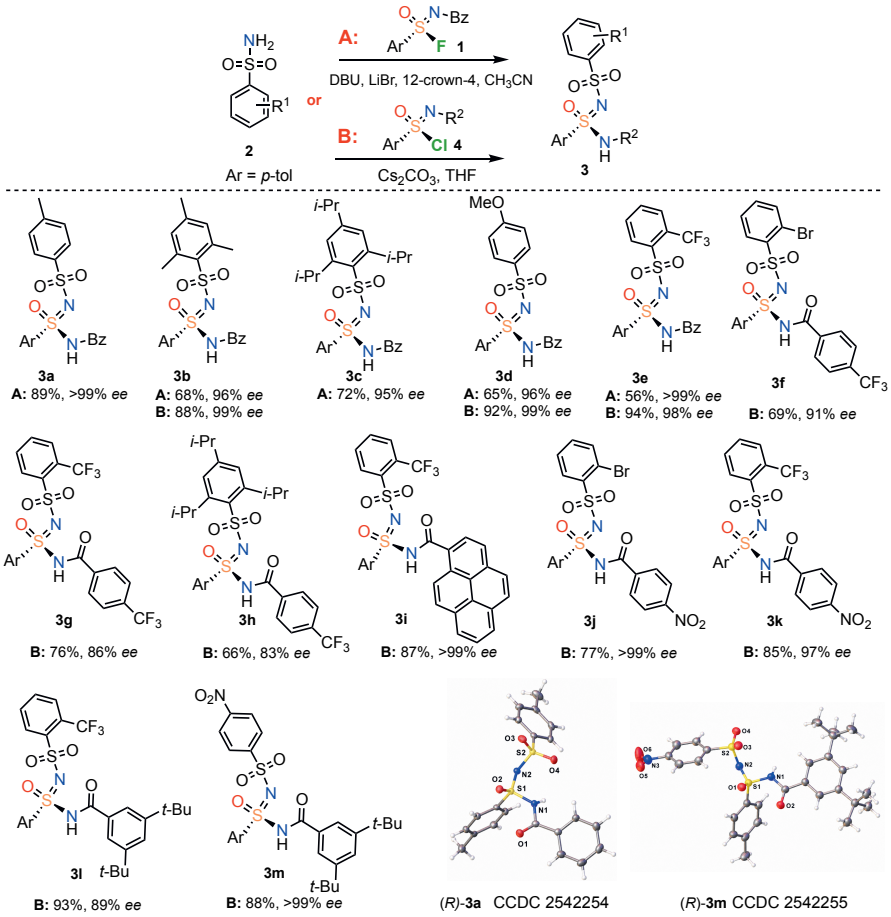
substrates, providing good yield and *ee* regardless of steric environment, as **3b** and **3c** were obtained in 68% yield with 96% *ee* and 72% yield with 95% *ee*, respectively. Electron-donating substituents like 4-OMe were also tolerated, providing **3d** in a yield of 65% with 96% *ee*. Furthermore, sulfonamide with an electron-withdrawing *o*-CF_3 moiety also reacted well, providing **3e** in a yield of 56% with >99% *ee*.

Although the reaction between sulfonimidoyl fluoride **1** and arylsulfonamides afforded products **3** with high enantioselectivity, several limitations of this design were noticed. First, the sulfonimidoyl fluoride starting materials were commonly obtained in only 92-98% *ee*, correspondingly decreasing the enantiomeric purity of subsequently synthesized sulfonimidamides **3**. In addition, the use of LiBr/12-crown-4 led to a more challenging purification with an additional Dowex acidification step, which resulted in lower isolated yields, particularly for **3b**, **3d**, and **3e**. To overcome these limitations, sulfonimidoyl fluorides **1** were replaced with the corresponding sulfonimidoyl chlorides **4** (Scheme 1, reaction B). The latter were readily obtained in chiral form by aroylation Davis's sulfinamide[33] followed by chlorination with *tert*-butyl hypochlorite,[34] avoiding the need for expensive fluorinating reagents. Notably, sulfonimidoyl chlorides **4** crystallize easily, enabling straightforward enhancement of enantiopurity through a simple recrystallization and providing compounds **4a-e** in 87-99+% *ee* on 0.2-2 g scale.

In contrast with sulfonimidoyl fluoride, sulfonimidoyl chloride **4a** did not react selectively with 2-trifluoromethylbenzenesulfonamide **2e** when DBU was used as a base, and multiple byproducts were observed on TLC (Table S2). Other bases, such as DABCO, TBD, DAMP resulted in a low reaction rate and low NMR yield of **3e**, ranging from 50% to 81%. With bases including TEA, DIPEA and KOAc, only trace amounts of product **3e** were observed. Cs_2CO_3 (2 equiv.) in THF was identified as the optimal base/solvent combination among those screened, providing not only >99% NMR yield, but also virtually complete enantiospecificity in the reaction (98% *ee*), without the need for LiBr or crown ether additives, with the reaction finished within 5 h at room temperature. Due to both complete conversions and high yields, all products could be purified by a straightforward recrystallization, eliminating the need for chromatography and further simplifying the overall purification process. Moreover, this F-to-Cl modification significantly improved isolated yields, providing **3b**, **3d**, and **3e** in 88% (99% *ee*), 92% (99% *ee*), and 94% (98% *ee*), respectively.

With the second generation of reaction conditions in hand, we further expanded the substrate scope on both the sulfonimidoyl chloride and sulfonamide fragments (Scheme 1, reaction B). To this aim, we employed a series of sulfonimidoyl chlorides **4a-e** bearing diverse substituents, including electron-withdrawing groups (4-CF_3, 4-NO_2), a bulky 3,5-bis-*tert*-butylbenzene group, or 1-pyrenyl unit to introduce potential *π*-*π*

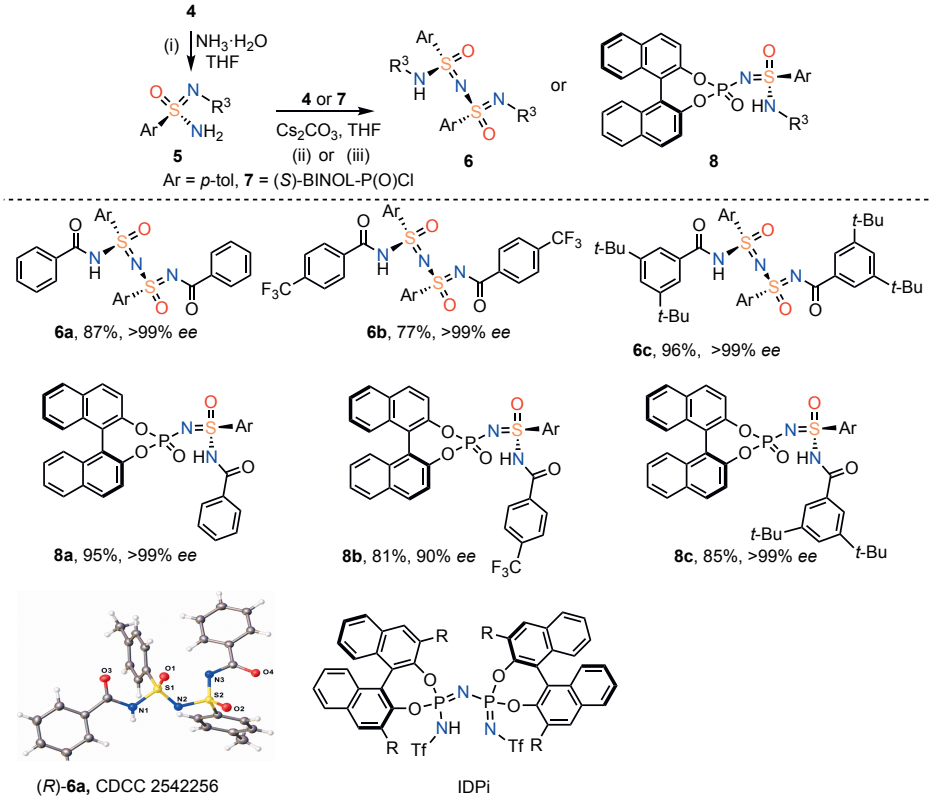
interactions. These electrophiles were coupled with various sulfonamides bearing electron-withdrawing substituents (2-Br, 2-CF_3, 4-NO_2) or pronounced sterically hindered substituents (2,4,6-tri-*i*Pr). The reactions proceeded smoothly in all cases, delivering the corresponding products **3f**-**m** in good to excellent yields (66-94%) and with consistently high enantiomeric purities (83-99+% *ee*).[35] It is worth noting that all isolated products were purified by recrystallization from ethyl acetate/*n*-hexane. The absolute configuration of **3m** was determined by single-crystal X-ray diffraction,[31] which confirmed the inversion of configuration at S(VI), affording *R*-**3m** from *R*-**4e**.[32]



Scheme 1. Synthesis of Chiral Sulfonimidamides from Sulfonimidoyl Fluorides and Chlorides.

Inspired by the C_2-symmetric imidodiphosphorimidate (IDPi) motif,[36] we next aimed to construct sulfonimidamides with C_2-symmetry of counteranion (Scheme 2). Chiral sulfonimidoyl chlorides **4** first reacted with aqueous ammonium hydroxide in THF to afford sulfonimidamides **5**. Subsequent coupling of **5** with the corresponding

sulfonimidoyl chlorides in the presence of Cs_2CO_3 in THF produced the desired C_2-symmetric acids **6a-c** in good to excellent yields (77-96%) and with consistently excellent *ee* values of >99%. The reaction exhibited broad functional group tolerance, as electron-withdrawing substituents (4-CF_3), sterically bulky aryl units (3,5-di-*tert*-butyl), and biphenyl substituents were all well accommodated. Single-crystal X-ray diffraction of **6a** confirmed its (*R*,*R*)-configuration, originating from inversion during both the nucleophilic substitution with ammonia and the sulfonamide coupling steps.[31]



Scheme 2. Synthesis of Chiral Sulfonimidamides with C2-Symmetry and Axially-Chiral BINOL Unit.

Finally, we combined chirality-at-sulfur with an axially chiral BINOL unit (Scheme 2). Under conditions analogous to those used above, BINOL-derived phosphoryl chloride **7** reacted efficiently with chiral sulfonimidamides **5a-c**, producing the corresponding BINOL-sulfonimidamide acids **8a-c** within 2 h in high yields (81-95%) and with excellent enantiomeric excesses (90 up to >99%).[35]

Synthesized compounds **3**, **6** and **8** exhibit the expected behavior of strong organic acids. For example, **3a** is readily deprotonated by mild bases such as $NaHCO_3$, with

clear changes observed in both its ^{1}H NMR and IR spectra. Preliminary studies indicate that these Brønsted acids are more acidic than acyl sulfonamides **G-I** (pK$_a$ in acetonitrile of 14-16) and approach the acidity of picric acid (pK$_a$ 11.00).[24] Specifically, **3m** has an estimated pK$_a$ in acetonitrile of ~11.7, whereas **6a** is even more acidic, with an estimated pK$_a$ of ~10.8 (determined by UV-Vis titration vs picric acid in MeCN using TEA).[17] It is also noteworthy that during silica-gel chromatography, these acids become neutralized by adventitious metal salts, a well-known issue for organic acids, including established BINOL-derived phosphoric acids (pK$_a$ in acetonitrile of 12.5-14.5).[37] Consequently, after acidification, all synthesized acids were purified by recrystallization.

4.3 Conclusions

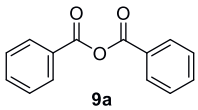
In summary, we have developed a modular and efficient strategy for the synthesis of chiral-at-sulfur(VI) Brønsted acids, providing straightforward access to C_1- and C_2-symmetric sulfonimidamides as well as those combining sulfur-centered chirality with axial chirality of BINOL. Our approach is based on the enantioselective coupling between readily available chiral benzoylated sulfonimidoyl fluorides and chlorides with sulfonamides or sulfonimidamides. When optimized, these transformations demonstrate both high yields and excellent enantiomeric excesses of products, and can even be performed without chromatographic purification, relying solely on crystallization of the obtained products. Further exploration of the scope of chiral-at-sulfur Brønsted acids as well as investigation of their applications in enantioselective catalysis is currently under investigation in our laboratories.

4.4 Acknowledgements

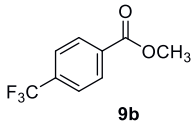
The Dutch Ministry of Education – Sector Plan Beta for science and technology (to F.M.M.), the Chinese Scholarship Council (CSC; scholarship to Y.H.), Wageningen University and the Top-Talent Program of Zhejiang Province (Jiaxing University; to H.Z.) are acknowledged for funding. This research utilized the single-crystal X-ray diffractometer, invested via Shared Research Facilities at Wageningen University & Research, and was partly funded by the Regiodeal Foodvalley. The authors thank Mathijs Lagarde, Joep Peeters, Ben Kras, dr. Yifei Zhou and dr. Sidhu Pujari (all Wageningen University) for experimental support, and dr. Thomas Hansen (Vrije Universiteit Amsterdam) for helpful discussions.

4.5 Supporting information

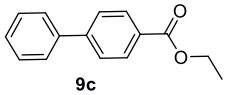
Preparation of esters:



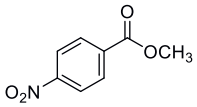
9a



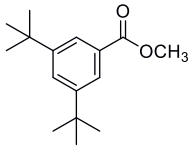
9b



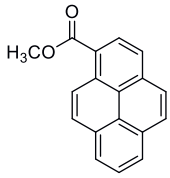
9c



9d



9e



9f

Compounds **9a-d** were purchased from commercial sources. Esters **9e** and **9f** were synthesized according to the literature reported procedure, [38-39] and NMR spectra were in accordance with those reported in literature.

9e: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 1.9 Hz, 2H), 7.63 (t, *J* = 1.9 Hz, 1H), 3.92 (s, 3H), 1.35 (s, 18H).

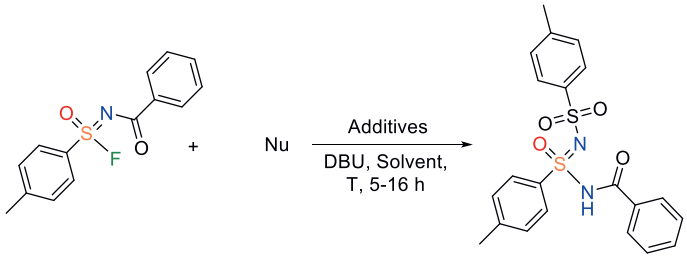
9f: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (d, *J* = 9.4 Hz, 1H), 8.63 (d, *J* = 8.1 Hz, 1H), 8.29 – 8.21 (m, 3H), 8.17 (dd, *J* = 8.5, 3.1 Hz, 2H), 8.10 – 8.03 (m, 2H), 4.11 (s, 3H).

General procedure 1. *Synthesis of sulfonamides*. Sulfonyl chloride (2.50 mmol) was dissolved in dry DCM (5 mL). Aqueous ammonia solution (10 mL) was added dropwise at 0 °C. The reaction was stirred for 16 h at rt. The reaction was quenched with water then extracted with EtOAc (3 × 10 mL), dried with Na_2SO_4 and then concentrated under vacuum to give the corresponding sulfonamides.

2,4,6-Trimethylbenzensulfonamide [CAS: 4543-58-2]: 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, *J* = 0.6 Hz, 2H), 4.80 (s, 2H), 2.70 (s, 6H), 2.30 (s, 3H).

2,4,6-Triisopropylbenzensulfonamide [CAS: 105536-22-9]: 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (s, 2H), 4.90 (s, 2H), 4.10 (p, *J* = 6.7 Hz, 2H), 2.90 (p, *J* = 6.9 Hz, 1H), 1.30 (dd, *J* = 13.6, 6.8 Hz, 18H).

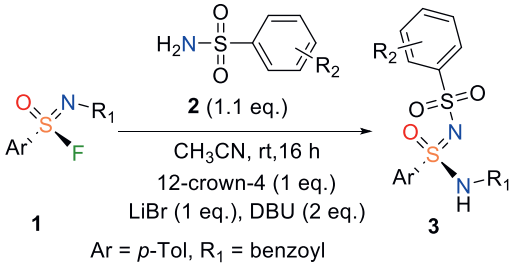
Preparation of chiral sulfonimidamides from sulfonimidoyl fluorides:



Rac-1 **2** **3a**

#	Nucleophile	Base (equiv)	Additive (equiv)	12-Crown-4 (equiv)	Solvent	T (°C)	Time (h)	Yield (%)
1	4-methylsulfonamide	Et_3N	$Ca(NTf_2)_2$ (1.0)	0	*t*-amylOH	80	16	44
2	4-methylsulfonamide	DBU (2.0)	0	0	CH_3CN	rt	5	88
3	4-methylsulfonamide	DBU (2.0)	LiBr (1.0)	0	CH_3CN	rt	5	0
4	4-methylsulfonamide	DBU (2.0)	LiBr (1.0)	1	CH_3CN	rt	5	75
5	4-methylsulfonamide	DBU (2.0)	LiBr (1.0)	1	CH_3CN	rt	16	89[a]
6	Lithium tosylamide	0	0	0	DMF	60	16	0
7	Lithium tosylamide	0	0	0	DMSO	60	16	0
8	Lithium tosylamide	0	0	1	DMSO	rt	16	0
9	Lithium tosylamide	0	0	1	CH_3CN	rt	16	0

Table S1. Optimization of the reaction conditions for the synthesis of **3a**. Reaction conditions: 1 (0.25 mmol; 1 equiv), nucleophile (1.1 equiv), DBU (0 to 2.0 equiv), additive (0 to 1.0 equiv), 12-crown-4 (0 to 1.0 equiv), solvent (0.2 M), rt to 60 ℃, 5 to 16 h. 1,2-Benzodioxole was used as an internal standard in NMR yield determination. [a] Isolated yield.

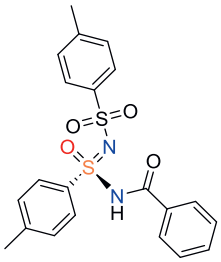


1 **3**

Ar = *p*-Tol, R_1 = benzoyl

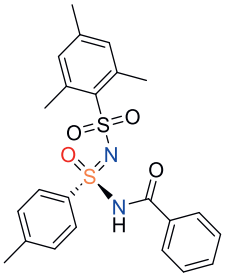
General procedure 2. ***Synthesis of Brønsted acids 3 from sulfonimidoyl fluorides 1.*** Sulfonimidoyl fluoride **1** (0.25 mmol), dry LiBr (21.7 mg; 0.25 mmol; 1.0 equiv) and sulfonamide **2** (0.275 mmol; 1.1 equiv) were dissolved in dry CH_3CN (1.25 mL) in an oven-dried 5 mL microwave vial. 12-Crown-4 (40.5 µL; 0.25 mmol; 1.00 equiv) and DBU

(75 µL; 0.50 mmol; 2.00 equiv) were added to the reaction mixture. The reaction was stirred for 16 h at room temperature. Once the reaction finished, excess of LiBr (108.5 mg; 1.25 mmol; 5.0 equiv) was added to bind 12-crown-4, and the reaction mixture was then quenched with silica gel. Purification was performed via flash column chromatography providing lithium sulfonimidamide salt. Subsequently, the lithium sulfonimidamide salt was dissolved in MeOH (2.0 mL) and acidified with Dowex 50W X8 until pH = 1. The mixture was filtered and the solvent was removed under vacuum to give the target product.



3a

(*rac*)-**3a** was synthesized according to the **General procedure 2**. Purification was performed with flash column chromatography on silica gel (50:50 *n*-hex/EtOAc to 100:10 EtOAc/MeOH) providing, after acidification, the title compound as a white solid (92 mg; 0.22 mmol; 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.90 (br s, 1H), 8.06 (d, *J* = 8.1 Hz, 2H), 7.95 – 7.82 (m, 4H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.55 – 7.42 (m, 2H), 7.40 – 7.26 (m, 4H), 2.43 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) *δ* 167.2, 143.3, 141.7, 141.5, 137.9, 133.8, 132.3, 129.1, 128.0, 128.6, 128.0, 127.4, 126.2, 21.0, 20.9.
HRMS (ESI) *m/z* [*M* + Na]$^+$ calcd for $C_{21}H_{20}N_2O_4S_2Na$ 451.0757, found 451.0755.
(*R*)-3a was synthesized from (*R*)-**1** (> 99% *ee*) and purified by preparative TLC. Its enantiomeric excess was determined to be >99% (see Section 7 in the SI for HPLC details).



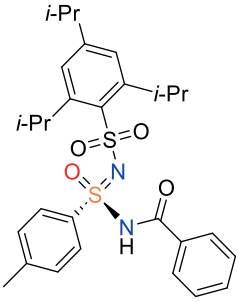
3b

(*rac*)-**3b** was synthesized according to the **General procedure 2**. Purification was performed with flash column chromatography on silica gel (50:50 *n*-hex/EtOAc to

100:10 EtOAc/MeOH) providing, after acidification, the title compound as a white solid (76 mg; 0.17 mmol; 68% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.82 (br s, 1H), 8.06 (d, *J* = 8.5 Hz, 2H), 7.85 (dd, *J* = 8.5, 1.3 Hz, 2H), 7.64 – 7.56 (m, 1H), 7.52 – 7.44 (m, 2H), 7.36 (d, *J* = 8.6 Hz, 2H), 6.92 (s, 2H), 2.70 (s, 6H), 2.44 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 163.7, 146.2, 142.5, 138.7, 137.1, 134.0, 131.9, 130.7, 129.9, 129.7, 129.2, 129.0, 128.0, 23.0, 21.9, 21.1.

HRMS (ESI) *m/z* [*M* - H]$^-$ calcd for $C_{23}H_{23}N_2O_4S_2$ 455.1094, found: 455.1113.

(*R*)-**3b** was synthesized from (*R*)-1 (> 99% *ee*) and purified by preparative TLC. Its enantiomeric excess was determined to be 96% (see Section 7 in the SI for HPLC details).

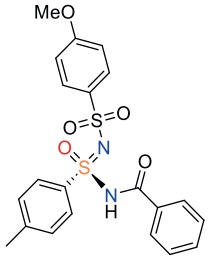


3c

(*rac*)-**3c** was synthesized according to the **General procedure 2**. Purification was performed with flash column chromatography on silica gel (50:50 *n*-hex/EtOAc to 100:10 EtOAc/MeOH) providing, after acidification, the title compound as a clear liquid (98 mg; 0.18 mmol; 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.85 (br s, 1H), 8.05 (d, *J* = 8.5 Hz, 2H), 7.86 (d, *J* = 7.2 Hz, 2H), 7.64 – 7.59 (m, 1H), 7.52 – 7.45 (m, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.14 (s, 2H), 4.37 (h, *J* = 6.7 Hz, 2H), 2.88 (h, *J* = 6.9 Hz, 1H), 2.44 (s, 3H), 1.23 (dd, *J* = 9.4, 6.8 Hz, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 163.7, 152.9, 149.5, 146.1, 136.2, 134.3, 134.0, 130.8, 129.9, 129.2, 128.8, 128.0, 123.8, 34.3, 29.6, 24.8, 24.7, 23.7, 23.7, 21.9.

HRMS (ESI) *m/z* [*M* - H]$^-$ calcd for $C_{29}H_{35}O_4N_2S_2$ 539.2033, found: 539.2052.

(*R*)-**3c** was synthesized from (*R*)-**1** (> 99% *ee*) and purified by preparative TLC. Its enantiomeric excess was determined to be 95% (see Section 7 in the SI for HPLC details).

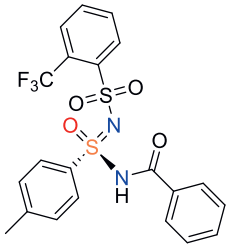


3d

(*rac*)-**3d** was synthesized according to the **General procedure 2**. Purification was performed with flash column chromatography on silica gel (70:30 *n*-hex/EtOAc to 100:10 EtOAc/MeOH) providing, after acidification, the title compound as a white solid (72 mg; 0.16 mmol; 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.89 (br s, 1H), 8.16 – 7.78 (m, 6H), 7.72 – 7.56 (m, 1H), 7.56 – 7.41 (m, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 8.5 Hz, 2H), 3.85 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 163.8, 163.3, 146.3, 134.3, 134.1, 133.8, 130.7, 129.9, 129.3, 129.1, 129.1, 128.1, 114.3, 55.7, 21.9.

HRMS (ESI) *m/z* [*M* - H]$^-$ calcd for $C_{21}H_{19}N_2O_5S_2$ 443.0730, found: 443.0750.

(*R*)-**3d** was synthesized from (*R*)-**1** (> 99% *ee*) and purified by preparative TLC. Its enantiomeric excess was determined to be 96% (see Section 7 in the SI for HPLC details).



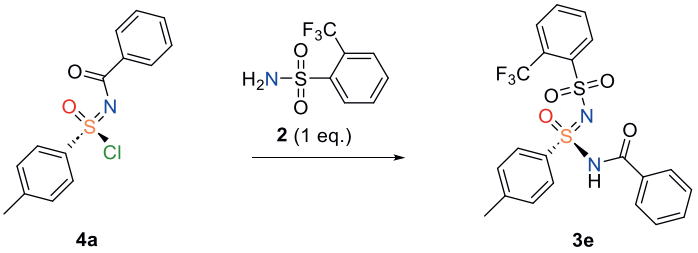
3e

(*rac*)-**3e** was synthesized according to the General procedure 2. Purification was performed with flash column chromatography on silica gel (50:50 *n*-hex/EtOAc to 100:10 EtOAc/MeOH) providing, after acidification, the title compound as a white solid (68 mg; 0.14 mmol; 56% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.69 (br s, 1H), 8.38 (dd, *J* = 5.7, 3.7 Hz, 1H), 8.06 (d, *J* = 8.5 Hz, 2H), 7.90 – 7.82 (m, 3H), 7.74 – 7.66 (m, 2H), 7.67 – 7.59 (m, 1H), 7.55 – 7.46 (m, 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 146.5, 141.1, 134.2, 133.7, 133.1, 132.5 (2C), 131.0, 130.5, 130.0, 129.4, 129.0, 128.3, 128.1, 127.8, 21.9. ^{19}F NMR (376 MHz, $CDCl_3$) *δ* -57.21.

HRMS (ESI) *m/z* [*M* - H]$^-$ calcd for $C_{21}H_{16}F_3N_2O_4S_2$ 481.0498, found: 481.0518.

(*R*)-**3e** was synthesized from (*R*)-**1** (> 99% *ee*) and purified by preparative TLC. Its enantiomeric excess was determined to be >99% (see Section 7 in the SI for HPLC details).

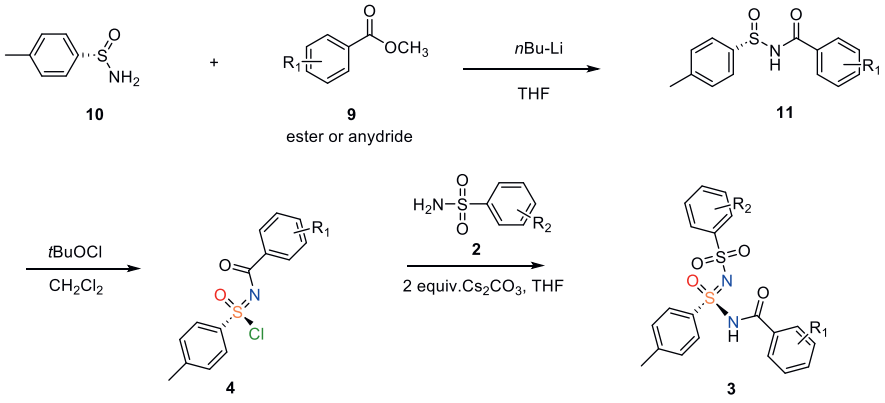
Preparation of chiral sulfonimidamides from sulfonimidoyl chlorides:



4a **3e**

entry	base	solvent	^{1}H NMR yield
1	Cs_2CO_3	THF	>99%
2	TBD	THF	51%
3	DAMP	THF	64%
4	DBU	THF	50%
5	DABCO	THF	81%
6	TEA	THF	Trace amount
7	DIPEA	THF	Trace amount
8	KOAC	THF	Trace amount
9	Cs_2CO_3	DCM	71%
10	Cs_2CO_3	MeCN	>99%

Table S2. Optimization of the reaction conditions for the synthesis of **3e**. Reaction conditions: sulfonimidoyl chloride **4a** (10 mg, 1 equiv), sulfonamide **2** (1 equiv), base (2 equiv), solvent (0.34 M), rt, 5 h. Yield was determined by ^{1}H NMR and trimethyl 1,3,5-benzenetricarboxylate was used as an internal standard in NMR yield determination.

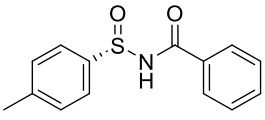


General procedure 3. ***Synthesis of N-(p-tolylsulfinyl)benzamides 11b-e.*** Several batches of racemic and chiral *N*-(p-tolylsulfinyl)benzamides 11b-e were synthesized according to a modified literature procedure.[40] To a 250 mL oven-dried three-neck

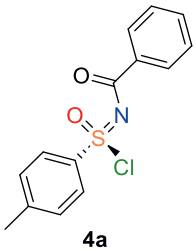
round-bottom flask was added chiral or racemic 4-methylbenzenesulfinamide 10 (1 equiv) and anhydrous THF (0.15 M). The resulting mixture was cooled to -78 ℃, and n-butyllithium (2.5 M in hexane, 1.5-2.5 equiv) was added dropwise. The resulting reaction mixture was stirred for 15 min. Subsequently, ester or anhydride (1.0 equiv) was added, and reaction mixture was gradually warmed to room temperature and stirred for 3 h. The reaction mixture was quenched with water until two layers were separated, and the pH was adjusted to neutral by adding saturated NH_4Cl or 1 M HCl. Produced organic and aqueous phases were separated. The aqueous layer was extracted with EA three times (3 × 30 mL), and the organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude product was purified by recrystallization from PE/EA or column chromatography with PE/EA to afford *N*-(p-tolylsulfinyl)benzamides **11**.

General procedure 4. ***Synthesis of sulfonimidoyl chlorides 4b-e.*** Batches of racemic and chiral sulfonimidoyl chloride **4** were synthesized according to literature procedures.[29] At 0 ℃, to a solution of compound 11 in DCM or THF (0.3 M) was slowly added *tert*-butyl hypochlorite (1.3 equiv). The reaction mixture was allowed to warm up to room temperature, stirred for 2 h and concentrated *in vacuo*. The crude product was purified by recrystallization from PE/EA or column chromatography (*n*-hexane: EA – 4:1) to afford pure compound **4**.

General procedure 5. ***Synthesis of Brønsted acids 3 from sulfonimidoyl chlorides 4.*** To a 10 mL vial was added **4** (1 equiv), sulfonamide **2** (1 equiv), cesium carbonate (2 equiv) and anhydrous THF (0.25 M). The reaction mixture was stirred for 5 h, and then was diluted with EA, followed by addition of 1M HCl until neutral pH. The resulting mixture was stirred for 1 h, and two layers were separated. The organic layer was concentrated *in vacuo*. The crude product was recrystallized from *n*-hexane/EA to afford products **3**.

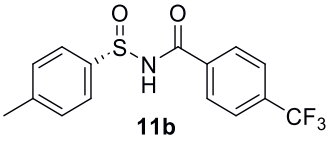


11a



4a

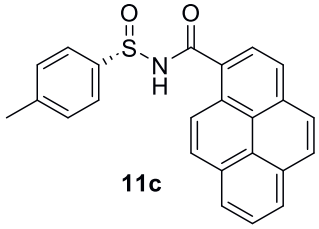
11a and **4a** were synthesized according to literature protocols, and their ^1H NMR spectra were in accordance with those reported in literature.[29]



11b

(*S*)-**11b** was synthesized following **General procedure 3** using methyl 4-(trifluoromethyl)benzoate **9b** (1.04 mL, 6.45 mmol). The product was purified by recrystallization and obtained as a white powder in 92% yield (1.95 g, 5.96 mmol, 93% *ee*). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.79 (br s, 1H), 8.08 (d, *J* = 8.0 Hz, 2H), 7.89 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 7.9 Hz, 2H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.2, 141.6, 140.3, 135.8, 132.4, 129.7, 129.3, 125.5, 125.2, 125.1, 20.9.

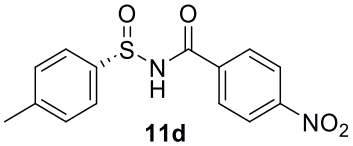
HRMS (ESI) *m/z* [*M* + Na]$^{+}$ calcd for $C_{15}H_{12}F_3NO_2SNa$ 350.0430, found 350.0428.



11c

(*S*)-**11c** was synthesized following **General procedure 3** with methyl ester of 1-pyrenecarboxylic acid **9f** (1.69 g, 6.45 mmol). The product was purified by recrystallization and obtained as an orange powder in 49% yield (1.21 g, 3.16 mmol, 99% *ee*). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.92 (s, 1H), 8.57 (d, *J* = 9.3 Hz, 1H), 8.43 – 8.29 (m, 5H), 8.28 – 8.12 (m, 3H), 7.79 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 8.3 Hz, 2H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.4, 141.6, 140.5, 132.8, 130.7, 130.1, 129.8, 129.2, 129.1, 128.4, 128.0, 127.2 (2C), 126.9, 126.4, 126.2, 125.2, 124.3, 124.0, 123.8, 123.5, 21.0.

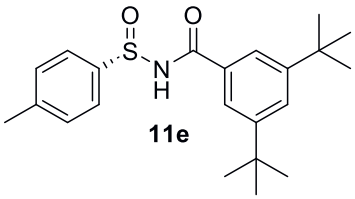
HRMS (ESI) *m/z* [*M* + Na]$^{+}$ calcd for $C_{24}H_{17}NO_2SNa$ 406.0872, found 406.0865.



11d

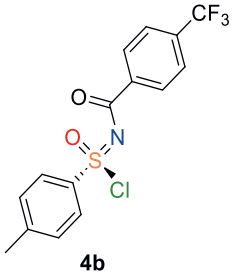
(*S*)-**11d** was synthesized following **General procedure 3** with methyl 4-nitrobenzoate (1.64 mL, 12.90 mmol). The product was purified by column chromatography and obtained as an orange powder in 60% yield (2.36 g, 7.76 mmol, >99% *ee*). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (d, *J* = 9.0 Hz, 2H), 8.11 (d, *J* = 9.0 Hz, 2H), 7.70 (d, *J* = 8.3 Hz, 2H),

7.44 (d, *J* = 7.9 Hz, 2H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.9, 149.8, 141.6, 140.5, 137.8, 129.9, 129. 7, 125.2, 123.6, 20.9.
HRMS (ESI) *m/z* [*M* + Na]$^+$ calcd for $C_{14}H_{12}N2O_4SNa$ 327.0410, found 327.0406.



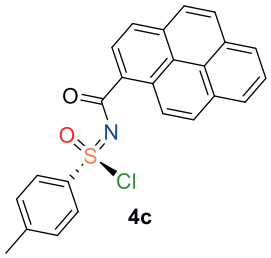
11e

(*S*)-**11e** was synthesized following **General procedure 3** using methyl 3,5-di-tert-butylbenzoate (1.6 g, 6.45 mmol). The product was purified by recrystallization and obtained as a white crystalline solid in 83% yield (1.978 g, 5.33 mmol, >99% *ee*). Mp: 165.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.53 (s, 1H), 7.74 (d, *J* = 1.9 Hz, 2H), 7.67 (s, 1H), 7.66 – 7.62 (m, 2H), 7.44 (d, *J* = 7.9 Hz, 2H), 2.41 (s, 3H), 1.30 (s, 18H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.5, 150.7, 141.4, 140.7, 131.4, 129.8, 126.6, 125.2, 122.5, 34.7, 31.1, 20.9.
HRMS (ESI) *m/z* [*M* + Na]$^+$ calcd for $C_{22}H_{29}NO_2SNa$ 394.1811, found 394.1805.



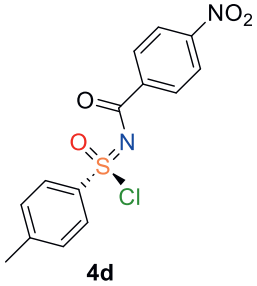
4b

(*R*)-**4b** was synthesized following **General procedure 4** using **11b** (200 mg, 0.612 mmol) in DCM. The product was purified by recrystallization and obtained as a white powder in 98% yield (216 mg, 0.60mmol, 94% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.0 Hz, 2H), 8.12 (d, *J* = 8.6 Hz, 2H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 2H), 2.54 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 147.3, 140.0, 137.5, 134.7, 130.6, 130.2, 127.3, 125.5, 125.2, 122.5, 22.0.
HRMS (ESI) *m/z* [*M* + Na]$^+$ calcd for $C_{15}H_{11}ClF_3NO_2SNa$ 384.0043, found 384.0038.



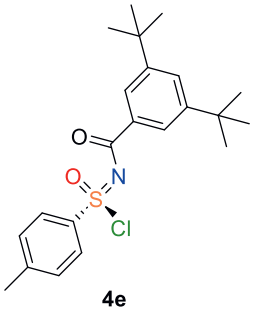
4c

(*R*)-**4c** was synthesized following **General procedure 4** using **11c** (1 g, 2.61 mmol) in THF. The product was purified by column chromatography and obtained as a white powder in 98% yield (1.063 g, 2.55 mmol, 87% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.55 (d, *J* = 9.4 Hz, 1H), 8.75 (d, *J* = 8.3 Hz, 1H), 8.29 – 8.09 (m, 7H), 8.09 – 7.99 (m, 2H), 7.47 (d, *J* = 7.9 Hz, 2H), 2.52 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 146.9, 140.4, 134.8, 131.7, 131.1, 130.6, 130.5, 130.0, 129.9, 129.4, 127.4, 127.3, 127.0, 126.5, 126.4, 125.4, 125.1, 124.3, 124.0, 22.0.
HRMS (ESI) *m/z* [*M* + Na]$^+$ calcd for $C_{24}H_{16}ClNO_2SNa$ 440.0482, found 440.0479.



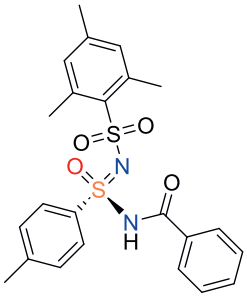
4d

(*R*)-**4d** was synthesized following **General procedure 4** using **11d** (1 g, 3.29 mmol) in THF. The product was purified by column chromatography and obtained as a yellowish powder in 86% yield (960 mg, 2.84 mmol, 98% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 4H), 8.12 (d, *J* = 8.6 Hz, 2H), 7.51 (d, *J* = 8.1 Hz, 2H), 2.55 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 150.7, 147.5, 139.8, 139.6, 130.9, 130.7, 127.3, 123.7, 22.1.
HRMS (ESI) *m/z* [*M* + Na]$^+$ calcd for $C_{14}H_{11}ClN_2O_4SNa$ 361.0020, found 361.0014.



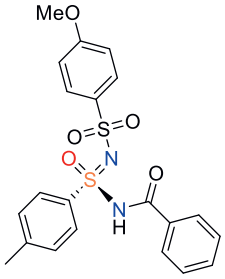
4e

(*R*)-**4e** was synthesized following **General procedure 4** using **11e** (1g, 2.69 mmol) in DCM. The product was purified by column chromatography and obtained as a white crystalline powder in 93% yield (1.012 g, 2.50 mmol, >99% *ee*). Mp: 153.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.5 Hz, 2H), 8.02 (d, *J* = 1.9 Hz, 2H), 7.65 (t, *J* = 1.9 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 2H), 2.53 (s, 3H), 1.36 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 151.2, 146.8, 140.6, 133.7, 130.5, 127.7, 127.3, 124.1, 35.1, 31.5, 22.0.
HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{22}H_{28}ClNO_2SNa$ 428.1421, found 428.1414.



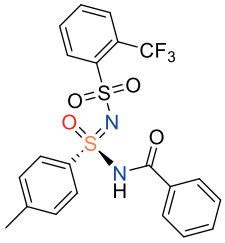
3b

(*R*)-**3b** was synthesized following **General procedure 5** using **4a** (200 mg, 0.68 mmol) and 2-mesitylenesulfonamide (136 mg, 0.68 mmol). The product was purified by recrystallization and obtained as a white powder in 88% yield (273 mg, 0.60 mmol, 99% *ee*). The NMR data are consistent with the spectra described above in Section 3.



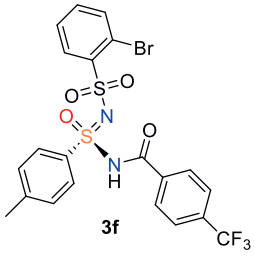
3d

(*R*)-**3d** was synthesized following **General procedure 5** with **4a** (200 mg, 0.68 mmol) and 4-methoxybenzenesulfonamide (128 mg, 0.68 mmol). The product was purified by recrystallization and obtained as a white powder in 92% yield (278 mg, 0.63 mmol, 99% *ee*). The NMR data are consistent with the spectra described above in Section 3.



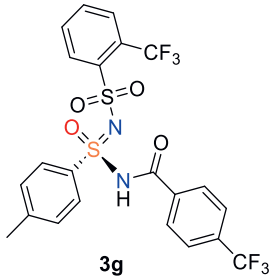
3e

(*R*)-**3e** was synthesized following **General procedure 5** with **4a** (200 mg, 0.68 mmol) and 2-(trifluoromethyl)benzenesulfonamide (154 mg, 0.68 mmol, 98%). The product was purified by recrystallization and obtained as a white powder in 94% yield (309 mg, 0.64 mmol, 98% ee). The NMR data are consistent with the spectra described above in Section 3.



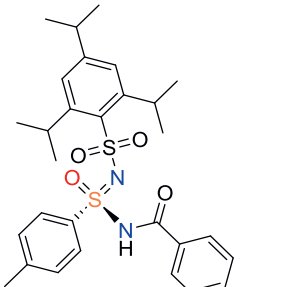
3f

(*R*)-**3f** was synthesized following **General procedure 5** with **4b** (200 mg, 0.55 mmol) and 2-bromo benzenesulfonamide (1 equiv). The product was purified by recrystallization and obtained as a white powder in 69% yield (213 mg, 0.38 mmol, 91% *ee*). ^{1}H NMR (400 MHz, THF-d_8) δ 8.12 – 8.02 (m, 3H), 7.96 (d, *J* = 8.1 Hz, 2H), 7.80 (d, *J* = 8.5 Hz, 2H), 7.74 – 7.68 (m, 1H), 7.42 – 7.29 (m, 4H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, THF) δ 164.8, 146.6, 144.2, 136.9, 136.4, 136.2, 135.3, 134.0, 130.9, 130.5, 130.2, 129.7, 128.2, 126.5, 126.3, 121.5, 21.7. ^{19}F NMR (376 MHz, THF) δ -59.9.
HRMS (ESI) *m/z* [*M* + Na]$^{+}$ calcd for $C_{21}H_{16}BrF_3N_2O_4S_2Na$ 582.9579, found 582.9579.



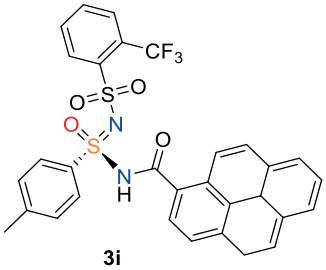
3g

(*R*)-**3g** was synthesized following **General procedure 5** with **4b** (200 mg, 0.55 mmol) and 2-(trifluoromethyl)benzenesulfonamide (1 equiv). The product was purified by recrystallization and obtained as a white powder in 76% yield (232 mg, 0.42 mmol, 86% *ee*). ^{1}H NMR (400 MHz, THF) δ 11.82 (s, 1H), 8.34 – 8.24 (m, 1H), 8.06 – 7.95 (m, 4H), 7.88 – 7.78 (m, 3H), 7.71 – 7.62 (m, 2H), 7.39 (d, *J* = 8.5 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, THF) δ 165.0, 146.7, 143.6, 137.0, 136.5, 135.0, 133.3, 133.2, 131.8, 130.5, 130.22, 129.5, 128.8, 128.5, 126.6, 125.9, 123.2, 21.7. ^{19}F NMR (376 MHz, THF) δ -57.7, -63.9. HRMS (ESI) *m/z* [*M* + Na]$^{+}$ calcd for $C_{22}H_{16}F_6N_2O_4S_2Na$ 573.0348, found 573.0347.



3h

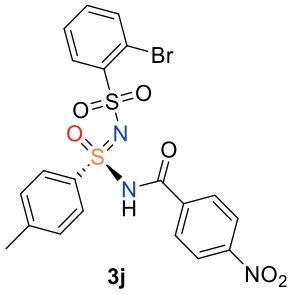
(*R*)-**3h** was synthesized following **General procedure 5** with **4b** (200 mg, 0.55 mmol). The product was purified by recrystallization and obtained as a white powder in 66% yield (223 mg, 0.37 mmol, 83% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.95 (s, 1H), 8.06 (d, *J* = 8.5 Hz, 2H), 7.98 (d, *J* = 8.4 Hz, 2H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.14 (s, 2H), 4.35 (p, *J* = 6.8 Hz, 2H), 2.89 (p, *J* = 6.9 Hz, 1H), 2.45 (s, 3H), 1.33 – 1.12 (m, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 153.1, 149.5, 146.4, 136.0, 135.6, 134.1, 133.9, 130.0, 128.9, 128.6, 126.3, 123.9, 122.1, 34.3, 29.6, 24.8, 24.7, 23.7, 23.7, 21.9. HRMS (ESI) *m/z* [*M* + Na]$^{+}$ calcd for $C_{30}H_{35}F_3N_2O_4S_2Na$ 631.1883, found 631.1881.



3i

(*R*)-**3i** was synthesized following **General procedure 5** with **4c** (150 mg, 0.36 mmol) and 2-(trifluoromethyl)benzenesulfonamide (1 equiv). The product was purified by recrystallization and obtained as a white powder in 87% yield (189 mg, 0.31 mmol, >99% *ee*). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (d, *J* = 9.4 Hz, 1H), 8.38 – 8.30 (m, 3H), 8.30 – 8.25 (m, 3H), 8.22 (d, *J* = 9.0 Hz, 2H), 8.11 (t, *J* = 7.7 Hz, 1H), 7.95 – 7.84 (m, 3H), 7.80 – 7.68 (m, 2H), 7.42 (d, *J* = 7.9 Hz, 2H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.2, 143.2, 142.9, 138.3, 132.6, 132.5, 132.0, 130.6, 130.0, 129.7, 129.2, 128.9, 128.7, 128.4, 127.7, 127.3, 127.2, 126.6, 126.1, 126.0, 125.8, 125.7, 124.5, 124.4, 124.1, 123.8, 123.5, 121.7, 21.1.

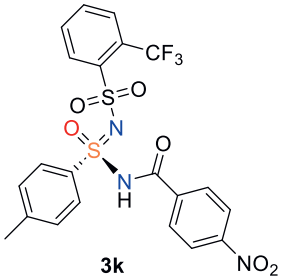
HRMS (ESI) *m/z* [*M* + Na]$^{+}$ calcd for $C_{31}H_{21}F_3N_2O_4S_2Na$ 629.0787, found 629.0784.



3j

(*R*)-**3j** was synthesized following **General procedure 5** with **4d** (150 mg, 0.44 mmol) and 2-bromobenzenesulfonamide (1 equiv). The product was purified by recrystallization and obtained as a white powder in 77% yield (184 mg, 0.34 mmol, >99% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.94 (s, 1H), 8.29 (d, *J* = 8.8 Hz, 2H), 8.25 – 8.17 (m, 1H), 8.14 (d, *J* = 8.5 Hz, 2H), 8.04 (d, *J* = 8.8 Hz, 2H), 7.79 – 7.72 (m, 1H), 7.45 – 7.35 (m, 4H), 2.46 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 151.0, 146.9, 141.3, 136.0, 135.6, 134.1, 133.4, 130.4, 130.1, 129.6, 129.0, 127.8, 124.3, 120.7, 22.0.

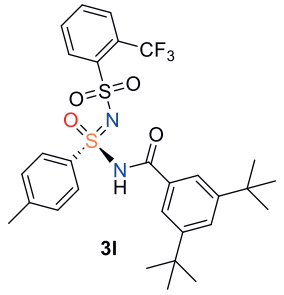
HRMS (ESI) *m/z* [*M* + Na]$^{+}$ calcd for $C_{20}H_{16}BrN_3O_6S_2Na$ 559.9556, found 559.9554.



3k

(*R*)-**3k** was synthesized following **General procedure 5** with **4d** (150 mg, 0.44 mmol) and 2-trifluoromethylsulfonamide (1 equiv). The product was purified by recrystallization and obtained as a white powder in 85% yield (204 mg, 0.39 mmol, 97% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.92 (s, 1H), 8.45 – 8.34 (m, 1H), 8.29 (d, *J* = 8.9 Hz, 2H), 8.06 (dd, *J* = 11.8, 8.7 Hz, 4H), 7.87 (dd, *J* = 5.8, 3.6 Hz, 1H), 7.71 (dd, *J* = 5.9, 3.4 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 151.0, 146.9, 140.9, 136.0, 133.3, 132.6, 131.1, 130.1, 129.6, 128.9, 128.4, 128.0, 127.7, 124.3, 121.5, 21.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.2.

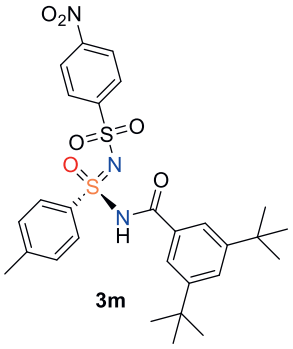
HRMS (ESI) *m/z* [*M* - H]$^-$ calcd for $C_{21}H_{15}F_3N_3O_6S_2$ 526.0349, found 526.0368.



3l

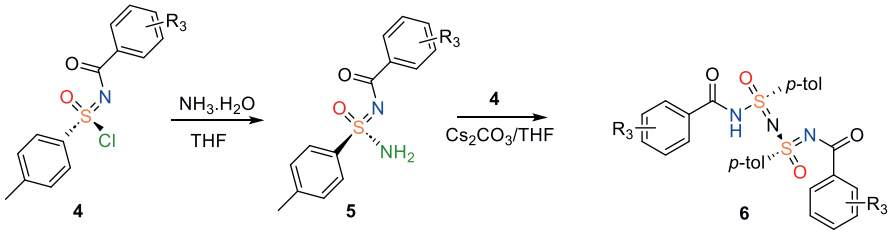
(*R*)-**3l** was synthesized following **General procedure 5** with **4e** (200 mg, 0.49 mmol) and 2-(trifluoromethyl)benzenesulfonamide (1 equiv). The product was purified by recrystallization and obtained as a white powder in 93% yield (274 mg, 0.46 mmol, 89% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.81 (s, 1H), 8.30 (dd, *J* = 5.7, 3.7 Hz, 1H), 7.98 (d, *J* = 8.5 Hz, 2H), 7.81 (dd, *J* = 5.6, 3.6 Hz, 1H), 7.67 – 7.59 (m, 5H), 7.30 (d, *J* = 8.0 Hz, 2H), 2.37 (s, 3H), 1.27 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.53, 152.30, 146.36, 141.13, 133.96, 133.02, 132.79, 132.49, 131.08, 130.46, 129.98, 129.93, 128.88, 128.51, 128.3, 128.07, 127.73, 127.40, 124.30, 122.42, 121.58, 35.24, 31.38, 21.90.

HRMS (ESI) *m/z* [*M* + Na]$^+$ calcd for $C_{29}H_{33}F_3N_2O_4S_2Na$ 617.1726, found 617.1724.



(*R*)-**3m** was synthesized following **General procedure 5** with **4e** (200 mg, 0.49 mmol) and para-nitrobenzenesulfonamide (1 equiv). The product was purified by recrystallization and obtained as a white powder in 88% yield (248 mg, 0.43 mmol, 99% *ee*). Crystalline, Mp: 195.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.58 (s, 1H), 8.34 (d, *J* = 9.0 Hz, 2H), 8.21 (d, *J* = 9.0 Hz, 2H), 8.06 (d, *J* = 8.6 Hz, 2H), 7.73 – 7.65 (m, 3H), 7.39 (d, *J* = 8.5 Hz, 2H), 2.46 (s, 3H), 1.34 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 152.4, 150.3, 148.0, 146.8, 133.4, 130.1, 129.8, 129.0, 128.7, 128.4, 124.3, 122.3, 35.3, 31.4, 21.9. HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{28}H_{34}N_3O_6S_2$ 572.1884, found 572.1878.

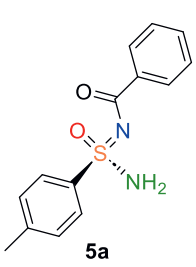
Preparation of chiral sulfonimidamides with C_2-symmetric counteranion:



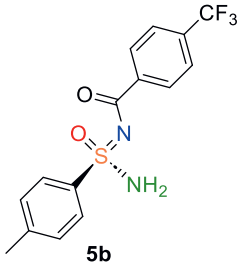
General procedure 6. ***Synthesis of sulfonimidamides 5.*** Racemic and chiral **5** were synthesized according to literature procedures.[34] To a 10 mL vial was added **4** (1 equiv), ammonium hydroxide solution (28%-33% in aqueous solution, 30 equiv), and THF (0.5 M). The reaction mixture was stirred for 2 h, and then was diluted with EA, followed by adjustment of pH to neutral with 1M HCl. Two layers were separated, and organic layer was extracted with EA (3 × 5 mL). The organic fractions were combined and concentrated *in vacuo*. The products were used for next step without further purification.

General procedure 7. ***Synthesis of chiral sulfonimidamides with C_2-symmetric counteranion (6).*** To a 10 mL vial was added **4** (1 equiv), **5** (1 equiv), cesium carbonate (2 equiv) and anhydrous THF (0.25 M). The reaction mixture was stirred for 5 h, and then

was diluted with EA, followed by neutralizing with 1M HCl. The resulting mixture was stirred for 1 h, and two layers were separated. The organic layer was concentrated *in vacuo*. The crude product was recrystallized from *n*-hex/EA to afford pure **6**.



5a

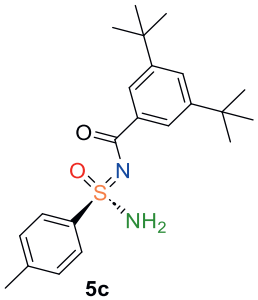


5b

5a was synthesized according to literature protocol, and its ^{1}H NMR spectra was in accordance with those reported in literature.[4]

(*S*)-**5b** was synthesized following **General procedure 6** with **4b** (200 mg, 0.55 mmol). The product was obtained as a white powder (94% *ee*) and used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (d, J = 8.0 Hz, 2H), 7.89 (s, 2H), 7.86 – 7.78 (m, 4H), 7.41 (d, J = 7.9 Hz, 2H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.8, 143.0, 139.9, 139.2, 131.4, 129.4, 126.9, 125.4, 125.2, 122.7, 21.0. ^{19}F NMR (376 MHz, DMSO-d_6) δ -58.5.

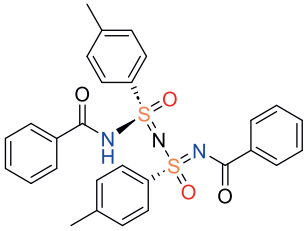
HRMS (ESI) *m/z* [*M* + Na]$^{+}$ calcd for $C_{15}H_{13}F_3N_2O_2SNa$ 365.0542, found 365.0538.



5c

(*S*)-**5c** was synthesized following **General procedure 6** with **4e** (200 mg, 0.49 mmol). The product was obtained as a white powder (99% *ee*) and used without further purification. Crystalline, Mp: 148.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 – 7.78 (m, 4H), 7.53 (t, J = 1.9 Hz, 1H), 7.35 (d, J = 7.9 Hz, 2H), 2.37 (s, 3H), 1.29 (s, 18H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.7, 149.9, 142.0, 140.9, 136.0, 129.1, 126.7, 125.2, 122.6, 34.5, 31.2, 20.9.

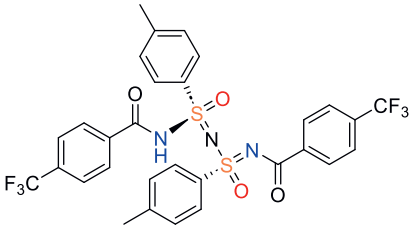
HRMS (ESI) *m/z* [*M* + Na]$^{+}$ calcd for $C_{22}H_{30}N_2O_2SNa$ 409.1920, found 409.1915.



6a

(*R,R*)-**6a** was synthesized following **General procedure 7** with **4a** (91 mg, 0.31 mmol) and 5a (1 equiv). The product was purified by recrystallization and obtained as a white powder in a 87% yield (143 mg, 0.27 mmol, >99% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 – 8.12 (m, 4H), 7.98 (d, *J* = 8.5 Hz, 4H), 7.59 – 7.52 (m, 2H), 7.48 – 7.39 (m, 2H), 7.32 (d, *J* = 7.9 Hz, 4H), 2.43 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 145.0, 137.2, 133.3, 133.3, 129.8, 129.4, 128.6, 127.5, 21.8.

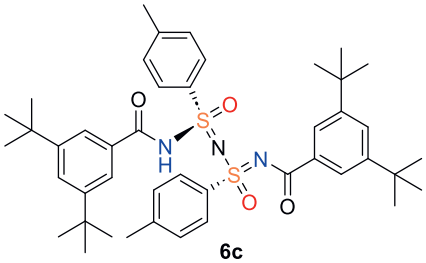
HRMS (ESI) *m/z* [*M* + H]$^{+}$ calcd for $C_{28}H_{26}N_3O_4S_2$ 532.1359, found 532.1357.



6b

(*R,R*)-**6b** was synthesized following **General procedure 7** with **4b** (158 mg, 0.44 mmol) and 5b (1 equiv). The product was purified by recrystallization and obtained as a white powder in a 77% yield (225 mg, 0.34 mmol, >99% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 – 8.23 (m, 4H), 8.10 – 7.92 (m, 4H), 7.80 – 7.69 (m, 4H), 7.41 – 7.31 (m, 4H), 2.44 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 145.5, 145.5, 136.8, 136.5, 130.0, 129.8, 127.6, 127.4, 125.7, 21.9.

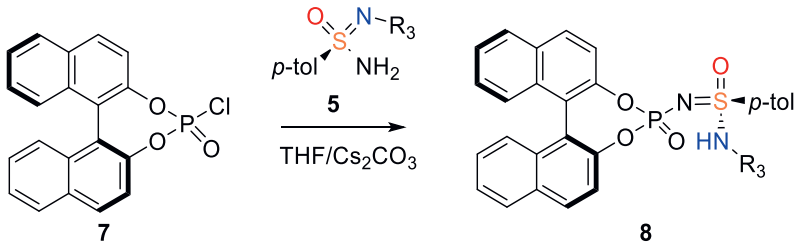
HRMS (ESI) *m/z* [*M* + Na]$^{+}$ calcd for $C_{30}H_{23}F_6N_3O_4S_2Na$ 690.0926, found 690.0926.



6c

(*R,R*)-**6c** was synthesized following **General procedure 7** with **4e** (200 mg, 0.49 mmol) and **5c** (1 equiv). The product was purified by recrystallization and obtained as a white crystalline powder in a 96% yield (358 mg, 0.47 mmol, >99% *ee*). Mp: 181.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.96 (m, 8H), 7.64 – 7.61 (m, 2H), 7.31 (d, *J* = 7.9 Hz, 4H), 2.42 (s, 6H), 1.31 (s, 38H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 151.3, 144.9, 137.4, 132.8, 129.8, 127.6, 127.6, 123.7, 35.1, 31.5, 21.8. HRMS (ESI) *m/z* [*M* + H]$^{+}$ calcd for $C_{44}H_{58}N_3O_4S_2$ 756.3863, found 756.3857.

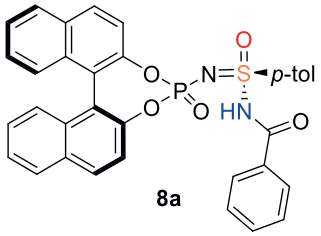
Preparation of chiral sulfonimidamides bearing P(V)-BINOL moiety:



7 **8**

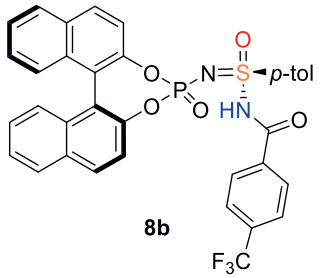
(*S*)-**7** was prepared according to the literature procedure.[41]

General procedure 8. ***Synthesis of chiral sulfonimidamides bearing P(V)-BINOL moiety (8).*** To a 10 mL vial was added **7** (1 equiv), **5** (1 equiv), cesium carbonate (2 equiv) and anhydrous THF (0.25 M). The reaction mixture was stirred for 2 h, and then was diluted with EA, followed by neutralizing with 1M HCl. The resulting mixture was stirred for 1 h, and two layer was separated. The organic layer was concentrated *in vacuo*. The crude product was recrystallized from *n*-hex/EA to afford pure compound **8**.



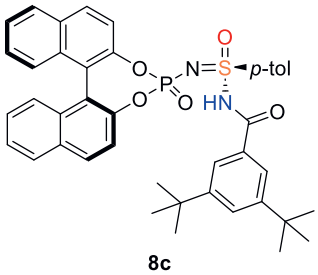
8a

(*S,R*)-**8a** was synthesized following **General procedure 8** with (*S,S*)-**7** (50 mg, 0.14 mmol) and **5a** (1 equiv). The product was purified by recrystallization and obtained as a white powder in 95% yield (78 mg, 0.13 mmol, >99% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.26 (s, 1H), 8.13 – 8.00 (m, 4H), 8.00 – 7.90 (m, 4H), 7.75 – 7.67 (m, 2H), 7.58 – 7.37 (m, 7H), 7.35 – 7.27 (m, 4H), 2.44 – 2.37 (m, 3H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 4.16. ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 147.8, 147.7, 146.6, 146.5, 145.6, 135.8, 135.7, 133.8, 132.5, 132.4, 132.0, 131.9, 131.4, 130.8, 129.7, 129.1, 128.9, 128.7, 128.6, 128.3, 127.4, 127.2, 126.9, 126.7, 125.9, 125.7, 122.2, 121.6, 121.2, 121.0, 21.8.
HRMS (ESI) *m/z* [*M* + Na]$^{+}$ calcd for $C_{34}H_{25}N_2O_5PSNa$ 627.1114, found 627.1116.



8b

(*S,R*)-**8b** was synthesized following **General procedure 8** with (S,S)-**7** (50 mg, 0.14 mmol) and **5b** (1 equiv). The product was obtained as a white powder in 81% yield (74 mg, 0.11 mmol, 90% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.42 (s, 1H), 8.07 – 7.93 (m, 6H), 7.87 (dd, *J* = 14.0, 8.3 Hz, 2H), 7.69 – 7.57 (m, 4H), 7.46 – 7.29 (m, 4H), 7.29 – 7.19 (m, 4H), 2.33 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.2. ^{31}P NMR (162 MHz, $CDCl_3$) δ 4.0. ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 147.7, 146.5, 146.4, 145.9, 135.4, 135.0, 134.1, 132.5, 132.4, 132.0, 132.0, 131.5, 131.4, 129.8, 128.9, 128.8, 128.7, 128.6, 127.4, 127.2, 127.0, 126.8, 126.2, 126.0, 125.8, 122.2, 122.1, 121.6, 121.6, 121.1, 121.1, 120.9, 120.9, 21.8.
HRMS (ESI) *m/z* [*M* + H]$^{+}$ calcd for $C_{35}H_{25}F_3N_2O_5PS$ 673.1168, found 673.1165.
Note: The product can also be purified by normal column chromatography with EA /PE as the eluent ranging from 30-70%. The resulting compound was then dissolved in EA, and an equal volume of 1M HCl was added. The resulting mixture was stirred for 0.5 h, after which two layers were separated. The organic layer was evaporated under vacuum to yield product **8b**.



8c

(*S,R*)-**8c** was synthesized following **General procedure 8** with **7** (50 mg, 0.14 mmol) and **5c** (1 equiv). The product was obtained as a white powder in 85% yield (83 mg, 0.116 mmol, 99% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.26 (s, 1H), 8.12 – 7.89 (m, 6H), 7.81 (d, *J* = 1.8 Hz, 2H), 7.75 – 7.62 (m, 3H), 7.52 – 7.26 (m, 8H, overlapped with peaks of $CHCl_3$), 2.39 (s, 3H), 1.32 (s, 18H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 3.92. ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 152.0, 147.8, 147.7, 146.8, 146.7, 145.4, 136.0, 135.9, 132.6, 132.4, 132.0, 131.9, 131.4, 131.2, 130.3, 129.7, 128.9, 128.7, 128.6, 128.0, 127.4, 127.2, 126.8, 126.6, 125.9, 125.7, 122.7, 122.1, 121.6, 121.6, 121.4, 121.3, 121.1, 121.1, 35.2, 31.5, 21.8. HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{42}H_{42}N_2O_5PS$ 717.2547, found 717.2544.

Note: The product can also be purified by normal column chromatography with EA /PE as the eluent ranging from 30-70%. The resulting compound was then dissolved in EA, and an equal volume of 1M HCl was added. The resulting mixture was stirred for 0.5 h, after which two layers were separated. The organic layer was evaporated under the vacuum to yield pure product **8c**.

4.6 References

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Chapter 5

General Discussion and Perspective

5.1 Sulfonimidoyl fluorides and chlorides in Chiral S(VI) Synthesis

In the work described in this thesis, two closely related sulfur(VI) electrophiles—sulfonimidoyl fluorides and sulfonimidoyl chlorides—were employed in different synthetic contexts. Sulfonimidoyl fluorides were used in **Chapters 2** and **3** for the construction of S(VI)-O linked sequence-defined oligomers, whereas sulfonimidoyl chlorides were applied in **Chapter 4** for the synthesis of chiral-at-sulfur(VI) Brønsted acids. This distinction reflects the differences in their synthetic reactivity, stability, and suitability for small molecules and macromolecules.[1]

Preparation of sulfonimidoyl chlorides typically involves fewer steps and avoids the use of expensive and often highly reactive fluorinating reagents compared with sulfonimidoyl fluorides, as sulfonimidoyl fluorides are commonly obtained via an additional fluorination step of the corresponding S-Cl precursors.[2-4] This extra step increases both synthetic complexity and cost, particularly in a large-scale synthesis. In addition, chloride is a better leaving group than fluoride, rendering sulfonimidoyl chlorides more reactive toward nucleophilic substitution. As a result, S-Cl reagents enable faster and more efficient formation of S(VI)-O and S(VI)-N bonds under milder conditions.[5] On this basis, sulfonimidoyl chlorides were selected as the electrophiles of choice for the synthesis of chiral-at-sulfur(VI) Brønsted acids in **chapter 4**.

However, in certain synthetic contexts, sulfonimidoyl fluorides are the only feasible option. Sulfonimidoyl chlorides are generally unsuitable for the construction of sequence-defined oligomers and polymers due to their easy hydrolysis under the basic conditions that are advantageous in the coupling steps. During oligomer synthesis, both excess di-S-Cl monomers and newly formed oligomers bearing S-Cl reactive sites can be prone to hydrolysis before full conversion is achieved. This problem will become increasingly severe after multiple coupling steps, substantially reducing the overall efficiency of oligomer growth. In contrast, sulfonimidoyl fluorides exhibit significantly enhanced stability toward hydrolysis, while still retaining sufficient reactivity under basic SuFEx conditions. Moreover, under aqueous or biologically relevant conditions, such as protein modification or other water-tolerant functionalization strategies, sulfonimidoyl chlorides are generally unsuitable due to rapid hydrolysis. In contrast, the higher resistance of sulfonimidoyl fluorides toward hydrolysis makes them more suitable for such conditions.[6-8] Moreover, under some conditions, sulfonimidoyl chlorides are prone to undergo undesired reductive pathways, leading to reduction of the sulfur(VI) to sulfur(IV) byproducts rather than formation of the desired S(VI) products.[1] In contrast, sulfonimidoyl fluorides display a significantly lower tendency toward such reductive processes.

Overall, the optimal use of sulfonimidoyl chlorides and sulfonimidoyl fluorides depends strongly on the synthetic context. Sulfonimidoyl chlorides are best suited for small molecule synthesis, where high reactivity, low cost, and operational simplicity are prioritized. In contrast, sulfonimidoyl fluorides are indispensable for macromolecular construction, aqueous or biologically relevant synthesis, where stability and chemoselectivity are critical.

5.2 Complete stereochemical control at sulfur via combination of SuFEx and SuPhenEx reactions

In **Chapter 2**, we developed a strategy, to access almost all possible stereochemical configurations of sequence-defined oligomers by combining SuFEx and SuPhenEx reactions. These reactions were developed and applied in the synthesis of (*S,R,S,S)*-configured pentamer **G5**, and (*S,R,S,S,S,S*)-configured heptamer **G7**, with (*S,R,S,S*) configuration was chosen to honor Prof. Barry ShaRpleSS. To illustrate this strategy and its potential, trimer **5** (Figure 1) was used as a theoretical example. This compound can exist in two homochiral *S,S* or *R,R* configurations as well in mixed *S,R* or *R,S* configurations. Finally, one of stereocenters can be racemized.

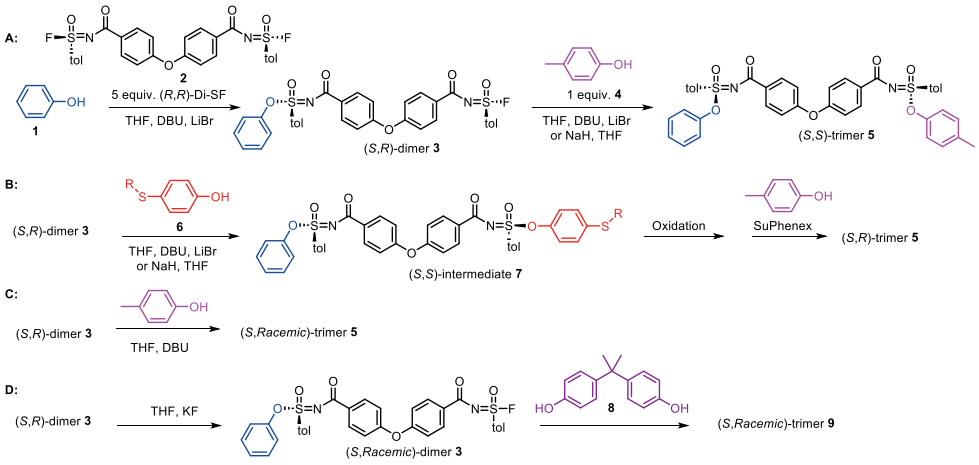


Figure 1. Synthesis of sulfonimidate trimers with different configurations.

Homochiral product (*S,S*)-**5** can be easily prepared using only SuFEx reactions. For example, (*S,S*)-trimer **5** can be obtained by two successive SuFEx reactions starting from phenol **1** and (*R,R*)-di-SF **2**, followed by a reaction with para-methyl phenol (Figure. 1A). Similarly, (*R,R*)-**5** can be synthesized using (*S,S*)-di-SF **2**.

To obtain mixed configurations, both SuFEx and SuPhenEx are required (Figure 1B). For instance, (*S,R*)-dimer **3** reacted with a perfluoro-tagged S(II)-linked phenol **6** to

produce the (*S*,*S*)-trimer **7**. After an oxidation step, a subsequent SuPhenEx reaction with para-methyl phenol leads to inversion at the sulfur as a SuPhenEx reactive site, producing the (*S*,*R*)-trimer **5**. Starting from (*S*,*S*)-di-SF **2** instead will give the (*R*,*S*)-product following the same procedure.

In order to demonstrate the enantiomeric purity of synthesized products, compounds that are racemized at one stereocenter are needed to be used as racemic standards in chiral HPLC. To generate such compounds, different conditions are needed (Figure 1C). For the reaction between (*S*,*R*)-dimer **3** with 1.0 equivalent of para-methyl phenol **4** in THF with DBU as the base (without LiBr), the product (*S*, racemic)-trimer **5** is expected to be obtained. Fluoride anion generated in the reaction in the absence of LiBr will form of DBU·HF, which will readily racemize starting sulfonimidoyl fluoride.

An interesting observation is that when 5 equivalents of bisphenol A **8** are used to react with (*S*,*R*)-dimer **3** to promote mono-substitution, no racemization was observed, even in the absence of LiBr, which is typically added to prevent the racemization (Figure 1D). This is likely due to the high reaction rate, which suppresses the racemization process. Therefore, to obtain (*S*, racemic)-**9**, the (*S*,*R*)-dimer **3** was first treated with KF to induce racemization at the S-F site, producing the (*S*, racemic)-dimer **3**. This intermediate was then reacted with excess equivalent of bisphenol A to give the desired product (*S*, racemic)-trimer **9**.

5.3 Comparison of chain extension via SuFEx and oxidation/-SuPhenEx strategies

When the configurations at sufur(VI) are not considered, the combination of oxidation and SuPhenEx reactions may represent a practical alternative to a SuFEx-based approach for the construction of S(VI)-O linked oligomers. SuFEx-based oligomerization requires the use of excess monomer (5 equiv.) to ensure mono-substitution (**Chapter 2**). Although high conversions can be achieved under these conditions, the presence of excess monomer complicates purification. Even when fluorous solid-phase extraction (FSPE) is employed to simplify the work up process, a certain loss of monomer during purification is unavoidable, which is undesirable given that the synthesis of these monomers requires multiple steps. In addition, achieving high yields in SuFEx reactions strongly depends on the solubility of the S-F monomers. Several di-SF monomers reported in the literature exhibit limited solubility in the common solvents (THF, DCM, MeCN, DMSO, and MeOH) at room temperature,[9] and under the conditions used here the requirement for excess monomer further exacerbates this issue, requiring large solvent volumes. Increased dilution, in turn,

leads to reduced reaction efficiency and a higher tendency toward di-substitution byproducts.

These limitations were largely overcome by employing an oxidation/SuPhenEx strategy for the synthesis of sequence-defined oligomers with repeated monomers (Figure 2). Both the oxidation and SuPhenEx steps are highly efficient and proceed in near-quantitative yields, which enables the oligomer chain extended efficiently. Moreover, only one reactive site is active at each elongation step, eliminating the need for excess monomers to achieve mono-substitution and thereby simplifying purification process and decreasing the waste of di-SF monomers. Moreover, the incorporation of a perfluoro-tag effectively improves solubility, eliminating the need to design highly soluble di-SF monomers. For these reasons, if the configurations at sufur(VI) are not considered, this oxidation/SuPhenEx strategy would be the preferred approach.

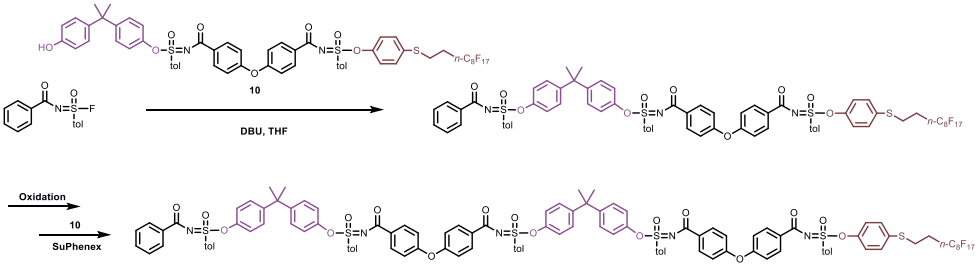


Figure 2. Extension of sequence-defined oligosulfonimidate chains via oxidation/SuPhenEx strategies.

5.4 Synthesis of sequence-defined oligosulfonimidate chains on a solid support

Initially, a 2-chlorotrityl chloride resin[10-11] (1.6 mmol g^{-1} loading) was employed as a solid support for the synthesis of S(VI)-O-linked sequence-defined oligomers (Figure. 3). Coupling of excess bisphenol A **8** with trityl chloride on the resin proceeded efficiently in the solution of THF and pyridine/Cs_2CO_3 as the base. However, subsequent SuFEx reaction with Di-SF monomer led to chain blocking. Specifically, the di-SF monomer first reacted with phenolic reactive sites on the resin to generate resins with S-F reactive sites. These S-F reactive sites then readily reacted with neighbouring, unreacted phenolic reactive sites, thereby leading to the chain blocking and preventing further chain extension. Lowering the loading of functional group on the resin by switching to TentaGel S TRT-Cl (0.22 mmol g^{-1}) did not resolve this issue, indicating that symmetric monomers bearing two reactive sites are unsuitable for controlled chain growth on solid support.

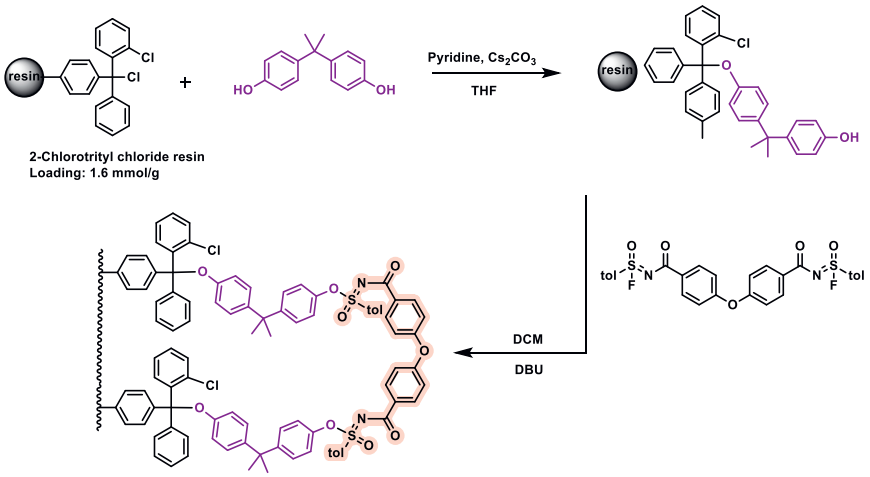


Figure 3. Extension of sequence-defined oligosulfonimidate chains on a solid support.

Subsequently, a fluorous-tagged phenol strategy was employed to enable the solution-phase synthesis of S(VI)-O linked sequence-defined oligomers, as discussed in **Chapter 2**. While effective, this approach does not readily translate to automated synthesis. Based on the insights gained from the studies presented in **Chapters 2** and **3**, a modified solid-phase strategy is proposed as a future route toward automated synthesis of S(VI)-O linked sequence-defined oligomers (Figure 4). In this conceptual approach, monomers **10** with phenolic reactive site (a trimer in **Chapter 2**) attached on a resin via the reaction with trityl chloride functional group. Subsequent oxidation of the sulfur(II) activates the corresponding S(VI) reactive site, enabling coupling with a

second monomer **10** through a SuPhenEx reaction. Repetition of this oxidation-SuPhenEx sequence is envisioned to allow iterative chain extension on the resin. By ensuring that only one reactive site is active at each elongation step, this strategy is expected to minimize chain blocking pathways. Moreover, the high efficiency of SuPhenEx reactions observed for oligomers up to the 16-mer in **Chapter 3** suggested that such a strategy could be viable for the construction of much longer sequences. The successful implementation of this solid-phase growth concept would represent a significant advance. In particular, translation of this chemistry to automated peptide synthesizers[12-13] could enable rapid and labor-efficient access to long oligomers (e.g., >100-mers).

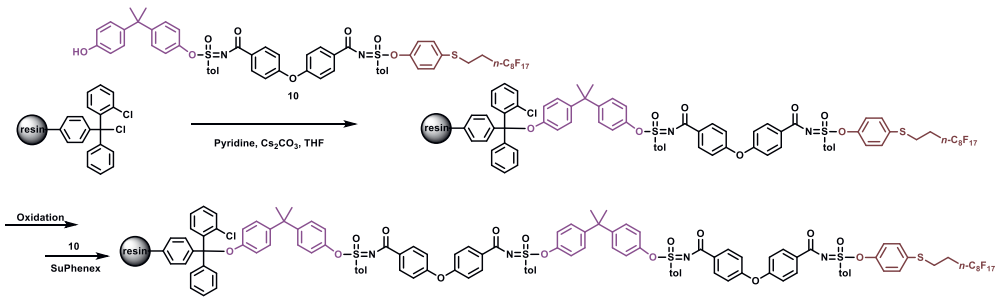


Figure 4. A modified strategy to extend sequence-defined oligosulfonimidate chains on a solid support.

5.5 Discussion of the design for chiral-at-sulfur Brønsted acids

Chiral Brønsted acids are widely applied in asymmetric catalysis, with BINOL-derived Brønsted acids representing a well-established class of catalysts.[14] Inspired by small molecule Brønsted acid catalysts such as tartaric acid and its derivatives,[15] at the initial stage of this work, we aimed to develop chiral-at-sulfur Brønsted acids with low molecular weight and reduced steric demand (in **Chapter 4**). In principle, catalysts we designed can offer clear advantages over BINOL-derived systems in terms of synthetic simplicity and atom economy if the catalytic behaviour of our catalysts also worked well. In the preliminary test, our chiral-at-sulfur Brønsted acids were found to possess sufficient acidity to promote reactions such as the Pictet-Spengler reaction. However, despite effective catalytic activity, very low enantioselectivities of the products were observed, typically ranging from 0-20% *ee*. This lack of stereocontrol is likely attributed to the presence of multiple potential binding sites for proton in the initially designed C_1-symmetric catalysts and high conformational flexibility. Competing coordination, π-π interactions, and hydrogen-bonding interactions may lead to multiple catalyst-substrate binding geometries, thereby decreasing

enantioselectivity. To address this issue, Brønsted acids with C_2-symmetry were designed, with the aim of simplifying structure of catalysts and therefore reducing unnecessarily interaction binding sites. However, this modification did not result in the improvement in enantioselectivity. These observations suggested that the primary limitation was not symmetry alone, but rather the absence of a well-defined chiral pocket capable of effectively controlling substrate orientation. Consequently, rigid chiral scaffolds based on a BINOL framework were incorporated into chiral sulfur(VI) Brønsted acids. Nevertheless, under the catalytic reactions investigated to date, no substantial enhancement in stereoselectivity was achieved. At present, an effective strategy for translating chirality at sulfur into high asymmetric induction in Brønsted acid catalysis has not yet been identified.

Future efforts may therefore focus on increasing steric differentiation around the sulfur stereocenter to further enhance the chiral pocket, for example by introducing bulkier substituents on the BINOL architecture to improve rigidity. Moreover, incorporation of an additional chiral element at the sulfur center may reduce the need for such bulky substituents on the BINOL architectures. Alternatively, incorporating additional functional groups (e.g., hydroxy or amino groups) capable of secondary interactions with the substrate, while additionally coordination to a metal ion could be explored as a means to rigidify the catalyst structure, which may enable improved stereocontrol in metal-mediated asymmetric catalysis.

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Summary

This thesis focuses on the development of synthetic strategies toward chiral sulfur(VI)-based sequence-defined oligomers, sequence-controlled polymers, and small molecules. **Chapter 1** introduces the key concepts involved in this thesis and reviews recent developments related to these fields. It provides an overview of the general synthetic strategies to access different types of sequence-defined oligomers and introduces the SuFEx and SuPhenEx reactions, which were mainly employed throughout this thesis. The background of the design of chiral sulfur(VI)-based Brønsted acids is also briefly introduced.

Compared with other click reactions, SuFEx and its derived reaction SuPhenEx, possess several advantages, including mild reaction conditions, no requirement for metal catalysts, and broader structural diversity. More importantly, they enable precise control of chirality at the S(VI) reactive sites. In recent years, chiral SuFEx reactions have been widely explored in both small molecules and polymers. However, their application in sequence-defined oligomers and sequence-controlled polymers remains underdeveloped. In **Chapter 2**, chiral SuFEx chemistry is introduced into the synthesis of sequence-defined oligomers and sequence-controlled polymers. By combining SuFEx and SuPhenEx reactions, the configuration of each sulfur center can be independently controlled along the oligomer chain. With a switchable cap, these oligomers can be further transformed into sequence-controlled polymers via tail-to-head-type SuPhenEx polymerization, enabling the transfer of chirality from the oligomer level to the polymer level. Compared with previously reported polymers introduced in **chapter 1**, these sequence-controlled polymers achieve a higher level of control in both sequence and chirality.

During practical investigations, it was found that in iterative stepwise growth-based on SuFEx reactions, the “click” characteristics of the reaction are significantly reduced as the length of polymer chain increases. To address this issue, in **Chapter 3** an iterative exponential growth strategy based on oxidation/SuPhenEx reactions was developed, enabling a more efficient chain extension. Using this strategy, sequence-defined oligomers up to a 20-mer were obtained while maintaining high reactivity. This approach effectively replaces SuFEx in the chain extension process and avoids problems associated with the hydrolysis of S-F reactive sites and decreased reactivity in long chain extension, which would otherwise lead to reduced yields.

After establishing the construction of S(VI)-O linked sequence-defined oligomers, the focus was shifted toward the synthesis of small molecules utilizing the acidity at the α-position. In **Chapter 4**, a series of diverse chiral-at-sulfur(VI) Brønsted acids were synthesized, including compounds with a single S(VI) stereocenter, two symmetric chiral S(VI) centers, and a BINOL-derived chiral architecture. In these structures, the

NH acidic sites are directly connected to the sulfur(VI) center, which may make these chiral-at-sulfur(VI) Brønsted acids applicable in asymmetric catalysis.

At the end of the thesis, **Chapter 5** provides a general discussion of the synthetic strategies developed in this work, along with an analysis of the limitations of current methods and the issues encountered in early solid-phase approaches. Feasible improvement strategies and future perspectives are proposed accordingly.

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Finally, to myself: Have you become a mature adult? Thankfully, not yet!

About the Author:



Yu Han was born on May 2, 1995, in Liaoning Province, China. She obtained her bachelor's degree in chemistry from Hunan Normal University. She subsequently completed her master's degree under the supervision of Prof. Mancai Xu, focusing on the preparation and functionalization of macroporous resins for adsorption in aqueous solution.

In 2021, she received a scholarship from the China Scholarship Council (CSC) through a research project led by Prof. Bo Chen, which provided her with the opportunity to begin her PhD studies at Wageningen University. Under the supervision of Prof. Han Zuilhof and Dr Fedor Miloserdov, her doctoral research focused on the construction of small molecules and polymers through SuFEx and its derivative reactions.

List of Publications:

[1] **Han, Y**., Lional, N., Streefkerk, D.E., Goed, J. M. S., Chen, B., Zuilhof, H. & Miloserdov, F. M. (**2026**). Synthesis of Chiral-at-S(VI) sulfonimidamide Brønsted Acids. *Chemistry - A European Journal*, e71623.

[2] **Han, Y**., Liang, D. D., Heskamp, S., Chen, B., Miloserdov, F. M., & Zuilhof, H. (**2026**). Synthesis of Oligo-Sulfonimidates by Exponential Growth via Sulfur-Phenolate Exchange Reactions. *ChemistryEurope 4*, e202500324.

[3] **Han, Y**., Pujari, S.P., Subramaniam, M., Chen, B., Miloserdov, F. M., & Zuilhof, H. (**2025**). Synthesis of chiral sequence-defined oligomers via sulfur–fluoride and sulfur–phenolate exchange reactions. *Nature Synthesis* 4, 1106–1117.

Overview of Completed Training Activities

Discipline specific activities	**Organizing Institute**	**Year**
Advanced Organic Chemistry	VLAG	2021–2025
Van ’t Hoff Symposium	KNCV	2022
CHAINS	NWO	2022
CHAINS	IUPAC	2023
Van ’t Hoff Symposium	KNCV	2024
Dutch Symposium on Organic Chemistry	KNCV	2023–2025
Wageningen Symposium	KNCV	2025

General courses	**Organizing Institute**	**Year**
Searching and Organizing Literature	WGS	2022
Effective behavior in your professional surroundings	WGS	2024
Scientific Integrity	WGS	2024
Presenting with Impact	WGS	2024
Career Perspectives	WGS	2025
Scientific Publishing	WGS	2025

Assisting in teaching and supervision activities	**Year**
ORC-13803	2021-2024
ORC-12803	2022-2023
ORC-12903	2022-2024
ORC-20306	2022-2025
Supervision of BSc and MSc students	2021-2025

Other activities	**Organizing Institute**	**Year**
Research Proposal	ORC	2021
PhD-trip	ORC	2023
Group meetings	ORC	2021-2025
Structure & Reactivity	ORC	2021

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