Sulfur–Phenolate Exchange: SuFEx-Derived Dynamic Covalent Reactions and Degradation of SuFEx Polymers

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Abstract: The products of the SuFEx reaction between sulfonimidoyl fluorides and phenols, sulfonimidates, are shown to display dynamic covalent chemistry with other phenols. This reaction was shown to be enantiospecific, finished in minutes at room temperature in high yields, and useful for both asymmetric synthesis and sustainable polymer production. Its wide scope further extends the usefulness of SuFEx and related click chemistries.

Introduction

Click chemistry[1] has truly revolutionized materials science as an additional tool to construct structures with a high molecular diversity.[2,3] The set of click reactions that has been developed continues to grow, as exemplified via CuI-catalyzed azide-alkyne cycloadditions (CuAAC)[4] as well as metal-free click reactions such as thiol-ene,[3] oxime ligation,[5] (thio-)Michael,[6] inverse electron-demand Diels–Alder,[7] strain-promoted cycloadditions between azide-alkyne (SPAAC),[8] cyclooctyne-*o*-quinone (SPOCQ),[9] and cyclopropene-*o*-quinone reactions,[10] and more recently the sulfur(VI) fluoride exchange (SuFEx) reaction.[11] In the SuFEx reaction the S–F bond in e.g. fluorosulfates, sulfonyl fluorides or sulfonimidoyl fluorides reacts readily with silyl-protected phenols, phenolates or amines.

As a result, research into the SuFEx reaction has surged in the last 5 years.[12] To expand the range of useful SuFEx connectors, several SuFEx hubs and fluorosulfuryl transfer reagents have been developed, such as ethenesulfonyl fluoride,[13] SO_2F_2,[11a,14] SOF_4,[15] fluorosulfuryl imidazolium salt,[16] fluorosulfuryl isocyanate[17] and others.[18] Recently our group discovered that for chiral sulfonimidoyl fluorides reacting with phenolates the first intrinsically enantiospecific click reaction could be developed, as here a chiral S^{VI} center reacts exclusively with inversion of configuration.[19] Subsequently, Bull's group noted that this could be extended to amines, thus further enriching the chemistry of the sulfonimidoyl fluoride moiety.[20]

The SuFEx reaction has, among other materials, also been successfully applied to polymer science[11b,21] with the efficient formation of polymers derived from sulfonyl fluorides, fluoro-sulfates, etc. In the case of SOF_4-derived polymers this led to helical polymers[22] and the introduction of multidimensional click chemistry to the field of materials science.[23] In parallel, starting from chiral di-sulfonimidoyl fluorides the construction of the new class of polysulfonimidates was achieved via this click reaction, and the enantiospecificity thereof even allowed the efficient formation of polymers with configurational backbone chirality.[24]

In parallel, materials chemistry has been revolutionized by dynamic covalent chemistry (DCC),[25] which combines the strength of covalent bonds with the power for self-healing and responsiveness that is for example displayed in supramolecular chemistry. Unlike other click chemistries, which have also shown to allow DCC to occur (like thiol-yne and Diels–Alder reactions) this has not been shown for the SuFEx reaction. Given the high potential of this class of click reactions, this prompted us to investigate this in more detail, with a two-fold aim: 1) Demonstrate that SuFEx reactions provide another example to the rich set of DCC reactions, and perhaps with the unique advantage of this being a potentially enantiospecific reaction; 2) Construct structurally complex polymers that are also degradable, in line with the overall aim of making polymers that are stable

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enough for manifold uses, yet prevent contributing to any future "plastic soups".

This paper describes the first case of a SuFEx-derived DCC reaction via the development of Sulfur–Phenolate Exchange (SuPhenEx) reactions, which is—to the best of our knowledge—also the first case of DCC involving phenols. We characterize the reaction, describe its scope, determine the thermodynamic features of the reaction both experimentally and by theoretical (wB97XD/6-311+G(d,p) density functional theory) studies (Figure 1a), display its usefulness for asymmetric synthesis, and finally show the potential for gradual degradation of SuFEx-derived polymers under mild reaction conditions (Figure 1b).

Results and Discussion

As first part of our studies we reasoned that a significant part of the driving force of the SuFEx reaction would come from the replacement of the highly electronegative F atom by a less electron-negative O-linked moiety. Taking this idea one step further, we hypothesized that it should be energetically feasible to replace an electron-poor phenol moiety by a more electron-rich phenol. Indeed, starting from R=p-Cl in Figure 1a (50 mM in CH$_3$CN) and reacting it with 10 equiv p-OMe-phenol and 10 equiv DBU, or with 3 equiv of the corresponding sodium phenolate salt at room temperature, we observed that in both cases the reactions would go to completion (94% conversion to one product), with reaction times of 18 h and 5 min, respectively (Figure S1 and S2, Table S1 and S2, Supporting Information). In contrast, the reaction is very sluggish and does not go to completion without base, which suggested that it is the phenolate that reacts with the p-Cl compound, leading to the phenol-exchanged product. As rapid equilibration can thus be reached via the use of phenolates, the reaction outcome can be pushed towards the desired product with an excess of the more nucleophilic phenolate, and this turned out to be easily feasible even if the reaction was slightly uphill with less nucleophilic phenolates (as indicated by the σ$_p$ Hammett values[26] of the various substituents; details in Supporting Information).
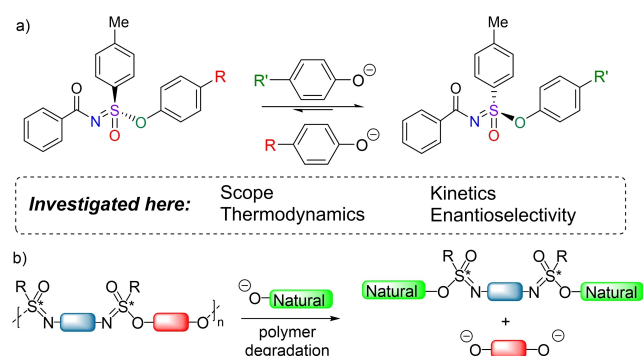
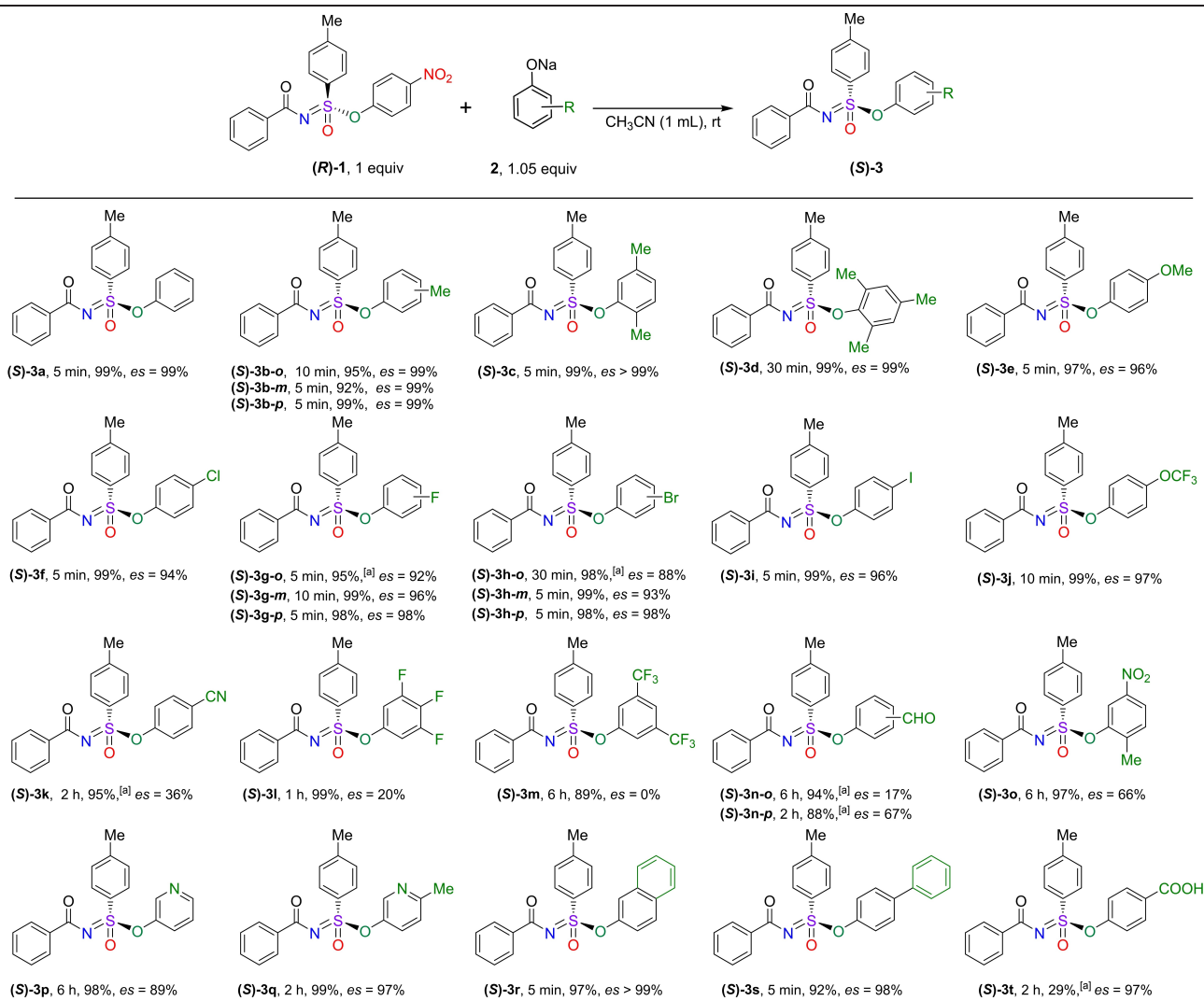Since the electro-donating power of the nucleophilic phenolate provides the driving force for this reaction, it would be favorable to start with the most electron-withdrawing, chiral phenol-derived sulfonimidate that could still be easily synthesized in high yield and provide an easy-to-handle, stable product.[19] In addition, we surmised that such and electron-withdrawing group (EWG) would strongly decrease the nucleophilicity of phenolate, leading to a higher energy barrier for identity reactions (in which nucleophile and leaving group are the same) and concomitantly suppressing background racemization of starting material.[27] p-NO$_2$ compound (**R**)-**1** turned out to be a good choice for this, as it can be isolated in good yield on a gram scale by recrystallization (typically 73%, >99% *ee*) from SuFEx reactions of the corresponding chiral sulfonimidoyl fluoride. (**R**)-**1** was then reacted in a SuPhenEx reaction with a range of phenolates, including those with EWGs or electron-donating groups (EDGs), and those with bulky substituents that would provide significant steric repulsion in the transition state and product. To our delight, such SuPhenEx reactions from (**R**)-**1** yielded for all but the most EWGs or bulky substituents a highly efficient and fast reaction: high yields of the desired sulfonimidate products (typically >95%, see Table 1 and Supporting Information) with just 1.05 equiv of phenolate in 10 min at r.t. in CH$_3$CN, without any further optimization of the reaction condition.

The reaction showed an excellent functional group tolerance, including methyl (**3b–d**), ether (**3e, j**), pyridinyl (**3p–q**), halogen (**3f–i, l, m**), aldehyde (**3n**), carboxylic acid (**3t**), cyano (**3k**), naphthyl (**3r**), and phenyl (**3s**) groups. When organized according to the σ$_p$ Hammett values of varieties of substituents, the *para*-substituents with an EDG (**3a, b-p, e, s**) or a moderate EWG (**3f, g-p, h-p, i, j**) exhibited almost quantitative yield with 95% to 99% *es* values, while for strong EWGs **3k** and **3n-p** still high yields were obtained, although with low *es*. Only the carboxylic acid derivative **3t**, which will be deprotonated under the reaction conditions, displayed moderate reactivity. For the scope of the reaction, even with multiple strong EWGs (**3l, m**), it still exhibited excellent reactivity despite the loss of enantioselectivity. Particularly interesting, the reaction can proceed well even with bulky substituents, as shown by the easy and high-yield formation of *ortho*-substituted **3b-o, 3g-o, 3h-o** and **3n-o**, while even bulky 2,4,6-trimethyl phenolate (**3d**) and 2-bromophenolate (**3h-o**) reacted efficiently at room temperature, with only relatively small extensions of the reaction time. Several phenolates (**2g-o, 2h-o, 2k, 2n-o** and **2t**) were poorly soluble in CH$_3$CN and for such phenolates 1.05 equiv of 15-crown-5 ether was used as an additive to accelerate the reaction. For less reactive phenolates, the yield could be increased—typically to >80%—upon extension of the reaction times, but this led to a gradual reduction of the *es* value of the isolated products.

Subsequently, reactant (**R**)-**1**, SuPhenEx product (**S**)-**3f** and SuFEx products (**R**)-**3f** and (**R**)-**3j**—obtained from the SuFEx reaction of preceding sulfonimidoyl fluoride (**R**)-**1b**—were subjected to X-ray crystallography.[28] This confirmed the absolute configurations of these materials (Figure 2; see

Figure 1. a) General scheme for sulfur(VI)–phenolate exchange reaction, and facets under current study. b) Degradation of polysulfonimidates.

Table 1: Sulfur–phenolate exchange reactions: Scope, reaction conditions, isolated yields and enantioselectivity.

(**R**)-**1**, 1 equiv + **2**, 1.05 equiv → (**S**)-**3**

CH₃CN (1 mL), rt

(**S**)-**3a**, 5 min, 99%, *es* = 99%

(**S**)-**3b-o**, 10 min, 95%, *es* = 99%
(**S**)-**3b-m**, 5 min, 92%, *es* = 99%
(**S**)-**3b-p**, 5 min, 99%, *es* = 99%

(**S**)-**3c**, 5 min, 99%, *es* > 99%

(**S**)-**3d**, 30 min, 99%, *es* = 99%

(**S**)-**3e**, 5 min, 97%, *es* = 96%

(**S**)-**3f**, 5 min, 99%, *es* = 94%

(**S**)-**3g-o**, 5 min, 95%,[a] *es* = 92%
(**S**)-**3g-m**, 10 min, 99%, *es* = 96%
(**S**)-**3g-p**, 5 min, 98%, *es* = 98%

(**S**)-**3h-o**, 30 min, 98%,[a] *es* = 88%
(**S**)-**3h-m**, 5 min, 99%, *es* = 93%
(**S**)-**3h-p**, 5 min, 98%, *es* = 98%

(**S**)-**3i**, 5 min, 99%, *es* = 96%

(**S**)-**3j**, 10 min, 99%, *es* = 97%

(**S**)-**3k**, 2 h, 95%,[a] *es* = 36%

(**S**)-**3l**, 1 h, 99%, *es* = 20%

(**S**)-**3m**, 6 h, 89%, *es* = 0%

(**S**)-**3n-o**, 6 h, 94%,[a] *es* = 17%
(**S**)-**3n-p**, 2 h, 88%,[a] *es* = 67%

(**S**)-**3o**, 6 h, 97%, *es* = 66%

(**S**)-**3p**, 6 h, 98%, *es* = 89%

(**S**)-**3q**, 2 h, 99%, *es* = 97%

(**S**)-**3r**, 5 min, 97%, *es* > 99%

(**S**)-**3s**, 5 min, 92%, *es* = 98%

(**S**)-**3t**, 2 h, 29%,[a] *es* = 97%

Reaction conditions: (**R**)-**1** (0.25 mmol) and phenolates **2**. [a] Adding 1.05 equiv of 15-crown-5 ether. *es* = enantiospecificity, given by %*ee*(**S**)-**3**/%*ee*(**R**)-**1** (maximum observed in chiral HPLC reaction monitoring).

(**R**)-**3f**   σ   (**S**)-**3f**

Absolute configuration by X-ray Crystallography
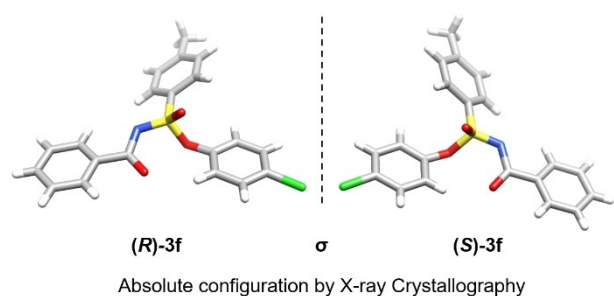
Figure 2. The X-ray crystal structures of (**R**)-**3f** (from SuFEx reaction) and (**S**)-**3f** (from SuPhenEx reaction). Color code: C, gray; O, red; S, yellow; N, blue; Cl, green; H, white.

also Supporting Information Figures S158–S162), proving that SuPhenEx reaction proceeds with inversion of absolute configuration. By virtue of this characteristic, the combina-

tion of SuFEx and SuPhenEx reactions allows the easy construction of both enantiomers of a sulfonimidate in a very facile manner (Figure S55, Supporting Information). To illustrate this, we performed SuFEx reactions using sulfoni-midoyl fluoride (**R**)-**1b** to react with 1.05 equiv sodium phenolates under ambient conditions (Table S58, Supporting Information). In line with previous findings,[19] this reaction proceeds enantiospecifically with both electron-donating or electron-withdrawing substituents on the phenolate. For phenolates, containing ether (**2e**, **2j**). halogen (**2f**, **2g-p**, **2h-p**, **2i**), or cyano (**2k**) functionalities, all showed almost quantitative yield with 97–99% *es*, leading to *R*-isomers of product. Alternatively, the SuFEx reaction with *p*-NO₂ phenolate, followed by the SuPhenEx reaction leads to opposite *S*-enantiomer. Thus, starting from one enantiomer of sulfonimidoyl fluoride (**R**)-**1b**, both enantiomeric prod-ucts can be obtained separately, which is especially conven-

ient considering the limited access to chiral precursors to (**S**)-**1b**.

To further demonstrate the scope of the SuPhenEx reaction, several natural phenolate derivatives were evaluated (Table 2). The sodium salts of *vic*-thymol, sesamol, eugenol, and tyrosol all reacted smoothly under ambient conditions with *p*-NO₂ compound (**R**)-**1** to obtain the target products ((**S**)-**4a**–**c** and (**S**)-**4e**) in quantitative yield (*es* > 99%). However, substrates containing formyl or carboxyl groups, such as vanillin, vanillic acid, and ferulic acid, although still exhibiting satisfying yields, yielded products ((**S**)-**4d** and (**S**)-**4f**) with poor stereoselectivity. Furthermore, the bisphenolate, honokiol, with bulky substituents at the *ortho* positions, also showed a good yield of a corresponding di-SuPhenEx product (**S**, **S**)-**4h** with excellent stereoselectivity (99% *es*).

We were initially puzzled by the observations for the phenolates with strong EWGs: a high yield could still be obtained, but typically with a strongly reduced *es*. Several reasons could be causing this, including racemization of the starting material under the reaction conditions (as observed by Bull for sulfonimidoyl fluorides)[20] or reaction of the product with starting phenolates both in the course of the reaction, and after complete conversion of starting material, as a slight excess of phenolate (1.05 equiv) was used.

To clarify this, we monitored the reactions of Table 1 and observed that in contrast with the corresponding SuFEx reaction,[19] hardly any racemization of the starting materials
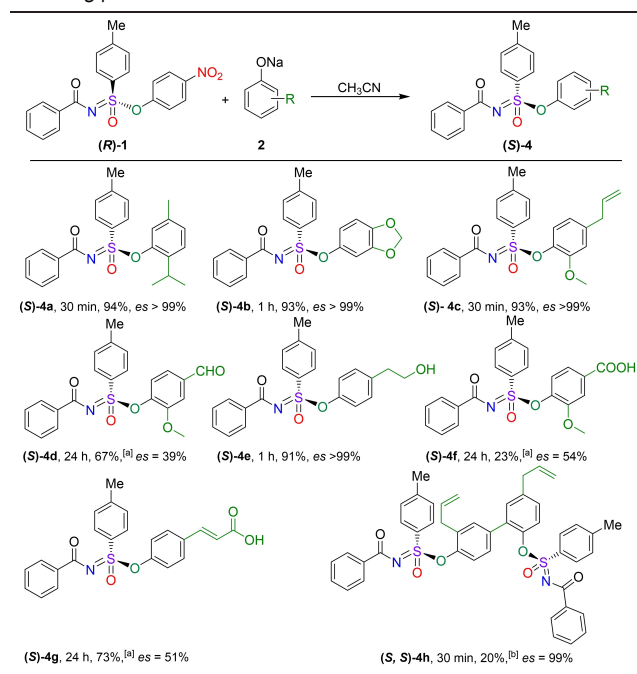
occurred. This leads to the conclusion that phenolate-induced racemization of the products seems to be the most likely explanation for this phenomenon.

In addition, we performed the reactions of Table 1 with a slightly reduced amount of phenolates (0.95 equiv). For several of tested substrates (**3a**, **3e**, **3f**) the reaction enantiospecificity increased to > 98% *es*, presumably because under this reaction condition no nucleophilic phenolate is left at the end of the reaction to induce racemization, while yields reduced only slightly (typically 5–10% less; see Table S43, Supporting Information). For substrates containing strong EWGs significantly higher *es* were observed at low reaction conversions. As two points in case, for the *o*-CHO ((**S**)-**3n,o**) and *p*-CN ((**S**)-**3k**) substituents the *es* increased from 17 to 97% and from 36 to 98%, at 12 and 14% conversion, respectively. However, at higher conversion of (**R**)-**1**, racemization of the product started to occur at rates comparable with SuPhenEx, leading to a decrease in the enantiospecificity of the reaction.

To further study several of these observations in more detail, we investigated the reaction mechanism by temperature-dependent kinetics and density functional theory calculations. First, the activation enthalpy $\Delta H^{\ddagger}$ for the reaction of (**R**)-**1** with sodium *p*-Cl phenolate was derived from a Van't Hoff plot (obtained from reaction rates obtained at six different temperatures from −30 to 0 °C) (Figure S66, Supporting Information). This yielded an experimental activation enthalpy of 14 ± 1 kcal mol⁻¹. Then we calculated the activation barrier for this reaction at the wB97XD/6-311 + G(d,p) level of theory [including SMD model to mimic acetonitrile]. If we would just use the naked anion attacking onto (**R**)-**1** this yielded an enthalpic barrier of 7.1 kcal mol⁻¹ (Figure S166, Supporting Information), i.e. clearly below the experimentally determined barrier. It is only upon inclusion of a Na⁺ cation, which stabilizes the reactant more than the TS, that the barrier increases to a nicely corresponding 13.1 kcal mol⁻¹ (see Figure 3). From these, two things can be concluded: 1) this difference of 6 kcal mol⁻¹ points to a clear role of the cation, which deserves more detailed studies, as also the studies of Ball and co-workers on the Ca²⁺ catalysis of SuFEx reactions shows.[29] 2) The calculated activation enthalpies $\Delta H^{\ddagger}$ (ranging from 9 to 19 kcal mol⁻¹; Figure 3) are in line with the observation that for all phenolates the reaction is very smooth at room temperature. In addition, the reaction enthalpies (as well as the closely matching free energies—Table S75, Supporting Information) indicate that the *p*-NO₂ substituent was a good choice for the reactant, as even for EWGs like *p*-CF₃ and *p*-CN the enthalpy is still more negative than −2.5 kcal mol⁻¹, guaranteeing the possibility for quantitative conversions. A distortion-interaction analysis[30] shows that the change in barrier is largely due to changes in the distortion energy (required to bring the reactants into the geometry of the TS) rather than in the interaction energy, which was shown to be constant to within 2 kcal mol⁻¹ for all reactions under study (Table S75, Supporting Information).

To better understand the racemization of the products, we studied a range of identity reactions (Figure S167,

Table 2: Scope of sulfur–phenolate exchange reactions with naturally occurring phenolates.

(**S**)-**4a**, 30 min, 94%, *es* > 99% (**S**)-**4b**, 1 h, 93%, *es* > 99% (**S**)-**4c**, 30 min, 93%, *es* > 99%

(**S**)-**4d**, 24 h, 67%,[a] *es* = 39% (**S**)-**4e**, 1 h, 91%, *es* > 99% (**S**)-**4f**, 24 h, 23%,[a] *es* = 54%

(**S**)-**4g**, 24 h, 73%,[a] *es* = 51% (**S**, **S**)-**4h**, 30 min, 20%,[b] *es* = 99%

Reaction conditions: (**R**)-**1** (0.25 mmol) and phenolates **2** (1.05 equiv) in CH₃CN (1 mL), rt, after specified time. Yield of isolated products. [a] Adding 1.05 equiv of 15-crown-5 ether. [b] Derived from disodium honokiol (0.49 equiv). *es* = enantiospecificity, given by %*ee*(**R**)-**3**/% *ee*(**S**)-**1** (maximum observed by chiral HPLC).
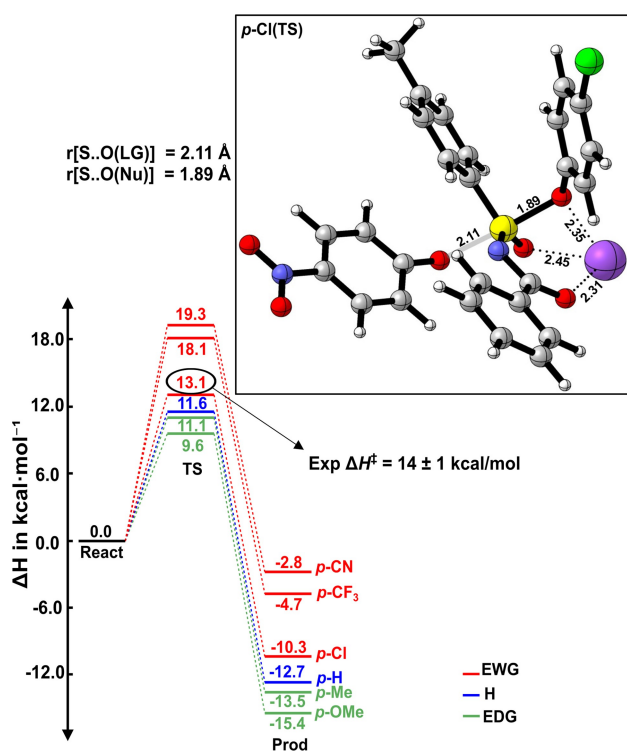
Figure 3. Reaction enthalpy diagram of the SuPhenEx reaction of p-NO$_2$ compound (**R**)-**1** with a range of phenolates. Inset: Optimized TS of the p-NO$_2$ compound with a p-Cl phenolate (in black). The optimized structures of all other p-substituted compounds are shown in the Supporting Information.

Supporting Information). The calculated activation enthalpies $\Delta H^{\ddagger}$ for these identity reactions vary in range from 19 to 22 kcal mol^{-1} for R = p-OMe to p-NO$_2$, respectively (Table S76, Supporting Information), which is significantly smaller than the span of $\Delta H^{\ddagger}$ for SuPhenEx reactions (Figure 3). Remarkably, the difference in $\Delta H^{\ddagger}$ between racemization and SuPhenEx ($\Delta\Delta H^{\ddagger}$) strongly depends on the nature of phenolate. While for EDG (p-OMe) or H the $\Delta\Delta H^{\ddagger}$ are 7.6 and 9.8 kcal mol^{-1}, respectively, for EWG (p-CN) the SuPhenEx is only slightly preferred over racemization ($\Delta\Delta H^{\ddagger} = 1.6$ kcal mol^{-1}). This is in line with reduced *es* values observed for (**S**)-**3k** and other EWG-substituted compounds.

This theoretical data thus fully explains our experimental data of the dependence of the observed *es* values on the substituent used. A) We had noted that the p-NO$_2$ compound (**R**)-**1** (rather than with e.g. the p-Cl or p-H compounds) provides higher *es* values. This is not only because the activation barriers of the reactions were lower, but also the racemization of the starting material was basically shut off as this requires a higher activation energy. B) With a reduced driving force of the reaction, the $\Delta H^{\ddagger}$ of the intended phenol-exchanging SuPhenEx reaction becomes almost isoenergetic to the (undesired) racemizing identity reaction. In other words: once the reaction for phenolates with EWGs has started to progress, an increasing amount of products can undertake a product-racemizing
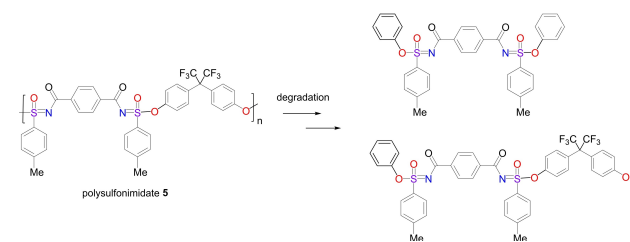
identity reaction. Especially when the reaction becomes sluggish, such racemization becomes increasingly likely, in line with the experimental observation that with more strongly EWGs the *es* values drop.

Finally, the very success of the SuPhenEx reaction prompted us to study the potential of using phenolates for the degradation of SuFEx-derived polymers. To this aim we synthesized di-sulfonimidoyl fluoride-derived polymer **5** ($M_n = 72$ kDa), and dissolved this in refluxing dry THF containing 0.13 M DBU with 0.13 M phenol or p-OMe-phenol (Figure 4). This led to the full polymer degradation (only fragments < 1.7 kDa as measured by gel permeation chromatography and LC-MS) within 48 h, showing the dynamic nature of the SuPhenEx reaction.

The observed decay is especially promising given the occurrence of many phenols in nature. In addition, polymer degradation can also be obtained, albeit much slower, when polymer **5** was dissolved in 4:1 PBS buffer/DMSO at 35 °C. This led to a gradual reduction of M_n to 43 kDa in 60 days. Combined these results point to the potential of SuFEx-based or SuPhenEx-based polymers, as these potentially combine high degrees of functionalization without long-term accumulation, i.e. "plastic soup" contribution.

Conclusion

In conclusion, we have demonstrated that the sulfur–phenolate exchange (SuPhenEx) reaction displays good to quantitative product formation within minutes at room temperature and is compatible with multiple functional groups. A combination of experiments and theoretical calculations displays that the SuPhenEx reaction is a fast, enantiospecific and concerted S$_N$2-type click reaction, thereby endowing dynamic covalent character to the products of the SuFEx click reaction. This reaction also allows the construction of both sulfonimidate enantiomers from a single sulfonimidoyl fluoride enantiomer, and can circumvent the intermediacy of sulfonimidoyl fluorides altogether, as (**R**)-**1** can also be synthesized without the involvement of fluorine chemistry and (racemizing and surface-etching) fluoride anions. Finally, SuPhenEx chemistry demonstrates that structurally complex, stable, yet also degradable polymers are within easy reach. Further mechanistic and polymer-oriented studies are currently ongoing in our labs.

Figure 4. Degradation of polysulfonimidate **5**.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Click Chemistry · Enantiospecific Suphenex · Kinetics · Reaction Mechanisms · Sulfur–Phenolate Exchange

[1] a) H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021; *Angew. Chem.* **2001**, *113*, 2056–2075; b) J. Escorihuela, A. T. M. Marcelis, H. Zuihof, *Adv. Mater. Interfaces* **2015**, *2*, 1500135; c) C. R. Becer, R. Hoogenboom, U. S. Schubert, *Angew. Chem. Int. Ed.* **2009**, *48*, 4900–4908; *Angew. Chem.* **2009**, *121*, 4998–5006.

[2] a) J. E. Moses, A. D. Moorhouse, *Chem. Soc. Rev.* **2007**, *36*, 1249–1262; b) H. C. Kolb, K. B. Sharpless, *Drug Discovery* **2003**, *8*, 1128–1137; c) B. Albada, J. F. Keijzer, H. Zuilhof, F. van Delft, *Chem. Rev.* **2021**, *121*, 7032–7058.

[3] C. E. Hoyle, C. N. Bowman, *Angew. Chem. Int. Ed.* **2010**, *49*, 1540–1573; *Angew. Chem.* **2010**, *122*, 1584–1617.

[4] a) R. Huisgen, *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 565–598; *Angew. Chem.* **1963**, *75*, 604–637; b) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599; *Angew. Chem.* **2002**, *114*, 2708–2711; c) S. Neumann, M. Biewend, S. Rana, W. H. Binder, *Macromol. Rapid Commun.* **2020**, *41*, 1900359.

[5] D. K. Kölmel, E. T. Kool, *Chem. Rev.* **2017**, *117*, 10358–10376.

[6] D. P. Nair, M. Podgórski, S. Chatani, T. Gong, W. Xi, C. R. Fenoli, C. N. Bowman, *Chem. Mater.* **2014**, *26*, 724–744.

[7] a) M. A. Tasdelen, *Polym. Chem.* **2011**, *2*, 2133–2145; b) B. L. Oliveira, Z. Guo, G. J. L. Bernardes, *Chem. Soc. Rev.* **2017**, *46*, 4895–4950.

[8] a) J. M. Baskin, J. A. Prescher, S. T. Laughlin, N. J. Agard, P. V. Chang, I. A. Miller, A. Lo, J. A. Codelli, C. R. Bertozzi, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 16793–16797; b) N. J. Agard, J. A. Prescher, C. R. Bertozzi, *J. Am. Chem. Soc.* **2004**, *126*, 15046–15047.

[9] a) A. Borrmann, O. Fatunsin, J. Dommerholt, A. M. Jonker, D. W. P. M. Lçwik, J. C. M. van Hest, F. L. van Delft, *Bioconjugate Chem.* **2015**, *26*, 257–261; b) J. J. Bruins, B. Albada, F. van Delft, *Chem. Eur. J.* **2018**, *24*, 4749–4756.

[10] D. Gahtory, R. Sen, A. R. Kuzmyn, J. Escorihuela, H. Zuilhof, *Angew. Chem. Int. Ed.* **2018**, *57*, 10118–10122; *Angew. Chem.* **2018**, *130*, 10275–10279.

[11] a) J. Dong, L. Krasnova, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2014**, *53*, 9430–9448; *Angew. Chem.* **2014**, *126*, 9584–9603; b) J. J. Dong, K. B. Sharpless, L. Kwisnek, J. S. Oakdale, V. V. Fokin, *Angew. Chem. Int. Ed.* **2014**, *53*, 9466–9470; *Angew. Chem.* **2014**, *126*, 9620–9624.

[12] a) Z. Liu, J. Li, S. Li, G. Li, K. B. Sharpless, P. Wu, *J. Am. Chem. Soc.* **2018**, *140*, 2919–2925; b) N. Wang, B. Yang, C. Fu, H. Zhu, F. Zheng, T. Kobayashi, J. Liu, S. Li, C. Ma, P. G. Wang, Q. Wang, L. Wang, *J. Am. Chem. Soc.* **2018**, *140*, 4995–4999; c) A. S. Barrow, C. J. Smedley, Q. Zheng, S. Li, J. Dong, J. E. Moses, *Chem. Soc. Rev.* **2019**, *48*, 4731–4758; d) R. W. Kulow, J. W. Wu, C. Kim, Q. Michaudel, *Chem. Sci.* **2020**, *11*, 7807–7812; e) S. Kitamura, Q. Zheng, J. L. Woehl, A. Solania, E. Chen, N. Dillon, M. V. Hull, M. Kotaniguchi, J. R. Cappiello, S. Kitamura, V. Nizet, K. B. Sharpless, D. W. Wolan, *J. Am. Chem. Soc.* **2020**, *142*, 10899–10904; f) J. Liu, L. Cao, P. C. Klauser, R. Cheng, V. Y. Berdan, W. Sun, N. Wang, F. Ghelichkhani, B. Yu, S. Rozovsky, L. Wang, *J. Am. Chem. Soc.* **2021**, *143*, 10341–10351; g) C. J. Smedley, J. A. Homer, T. L. Gialelis, A. S. Barrow, R. A. Koelln, J. E. Moses, *Angew. Chem. Int. Ed.* **2022**, *61*, e202112375; *Angew. Chem.* **2022**, *134*, e202115593; h) D. Zeng, Y. Ma, W.-P. Deng, M. Wang, X. Jiang, *Nat. Synth.* **2022**, *1*, 455–463.

[13] a) H.-L. Qin, Q. Zheng, G. A. L. Bare, P. Wu, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2016**, *55*, 14155–14158; *Angew. Chem.* **2016**, *128*, 14361–14364; b) Q. Zheng, J. Dong, K. B. Sharplesss, *J. Org. Chem.* **2016**, *81*, 11360–11362; c) R. Xu, T. Xu, M. Yang, T. Cao, S. Liao, *Nat. Commun.* **2019**, *10*, 3752–3758; d) Y.-P. Meng, S.-M. Wang, W.-Y. Fang, Z.-Z. Xie, J. Leng, H. Alsulami, H.-L. Qin, *Synthesis* **2020**, *52*, 673–687.

[14] F. C. Sousa e Silva, K. Doktor, Q. Michaudel, *Org. Lett.* **2021**, *23*, 5271–5276.

[15] a) S. Li, P. Wu, J. E. Moses, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2017**, *56*, 2903–2908; *Angew. Chem.* **2017**, *129*, 2949–2954; b) B. Gao, S. Li, P. Wu, J. E. Moses, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2018**, *57*, 1939–1943; *Angew. Chem.* **2018**, *130*, 1957–1961; c) F. Liu, H. Wang, S. Li, G. A. L. Bare, X. Chen, C. Wang, J. E. Moses, P. Wu, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2019**, *58*, 8029–8033; *Angew. Chem.* **2019**, *131*, 8113–8117.

[16] T. Guo, G. Meng, X. Zhan, Q. Yang, T. Ma, L. Xu, K. B. Sharpless, J. Dong, *Angew. Chem. Int. Ed.* **2018**, *57*, 2605–2610; *Angew. Chem.* **2018**, *130*, 2635–2640.

[17] S. Sun, B. Gao, J. Chen, K. B. Sharpless, J. Dong, *Angew. Chem. Int. Ed.* **2021**, *60*, 21195–21199; *Angew. Chem.* **2021**, *133*, 21365–21369.

[18] a) A. L. Tribby, I. Rodríguez, S. Shariffudin, N. D. Ball, *J. Org. Chem.* **2017**, *82*, 2294–2299; b) C. Veryser, J. Demaerel, V. Bieliunas, P. Gilles, W. M. De Borggraeve, *Org. Lett.* **2017**, *19*, 5244–5247; c) H. Zhou, P. Mukherjee, R. Liu, E. Evrard, D. Wang, J. M. Humphrey, T. W. Butler, L. R. Hoth, J. B. Sperry, S. K. Sakata, C. J. Helal, C. W. am Ende, *Org. Lett.* **2018**, *20*, 812–815; d) G. Laudadio, A. d A Bartolomeu, L. M. H. M. Verwijlen, Y. Cao, K. T. de Oliveira, T. Noël, *J. Am. Chem. Soc.* **2019**, *141*, 11832–11836.

[19] D.-D. Liang, D. E. Streefkerk, D. Jordaan, J. Wagemakers, J. Baggerman, H. Zuilhof, *Angew. Chem. Int. Ed.* **2020**, *59*, 7494–7500; *Angew. Chem.* **2020**, *132*, 7564–7570.

[20] a) S. Greed, E. L. Briggs, F. I. M. Idiris, A. J. P. White, U. Lücking, J. A. Bull, *Chem. Eur. J.* **2020**, *26*, 12533–12538.

[21] a) H. Wang, F. Zhou, G. Ren, Q. Zheng, H. Chen, B. Gao, L. Klivansky, Y. Liu, B. Wu, Q. Xu, J. Lu, K. B. Sharpless, P. Wu, *Angew. Chem. Int. Ed.* **2017**, *56*, 11203–11208; *Angew. Chem.* **2017**, *129*, 11355–11360; b) M. Wang, H.-S. Jin, X.-M. Chen, B.-

P. Lin, H. Yang, *Polym. Chem.* **2019**, *10*, 3657–3664; c) B. Cao, L. Zhang, Q. Zheng, F. Zhou, L. M. Klivansky, J. Lu, Y. Liu, J. Dong, P. Wu, K. B. Sharpless, *Nat. Chem.* **2017**, *9*, 1083–1088; d) X. Xiao, F. Zhou, J. Jiang, H. Chen, L. Wang, D. Chen, Q. Xu, J. Lu, *Polym. Chem.* **2018**, *9*, 1040–1044; e) C. Lu, Q. Liu, P. Gu, D. Chen, F. Zhou, H. Li, Q. Xu, J. Lu, *Polym. Chem.* **2014**, *5*, 2602–2610; f) C. Yang, J. P. Flynn, J. Niu, *Angew. Chem. Int. Ed.* **2018**, *57*, 16194–16199; *Angew. Chem.* **2018**, *130*, 16426–16431.

[22] S. Li, G. Li, B. Gao, S. P. Pujari, X. Chen, H. Kim, F. Zhou, L. M. Klivansky, Y. Liu, H. Driss, D.-D. Liang, J. Lu, P. Wu, H. Zuilhof, J. Moses, K. B. Sharpless, *Nat. Chem.* **2021**, *13*, 858–867.

[23] a) S. Park, H. Song, N. Ko, C. Kim, K. Kim, E. Lee, *ACS Appl. Mater. Interfaces* **2018**, *10*, 33785–33789; b) D. Gahtory, R. Sen, S. Pujari, S. Li, Q. Zheng, J. E. Moses, K. B. Sharpless, H. Zuilhof, *Chem. Eur. J.* **2018**, *24*, 10550–10556; c) J. Yatvin, K. Brooks, J. Locklin, *Angew. Chem. Int. Ed.* **2015**, *54*, 13370–13373; *Angew. Chem.* **2015**, *127*, 13568–13571.

[24] D.-D. Liang, S. P. Pujari, M. Subramaniam, M. Besten, H. Zuilhof, *Angew. Chem. Int. Ed.* **2022**, *61*, e202116158; *Angew. Chem.* **2022**, *134*, e202115158.

[25] a) Y. Jin, C. Yu, R. J. Denman, W. Zhang, *Chem. Soc. Rev.* **2013**, *42*, 6634–6654; b) P. Chakma, D. Konkolewicz, *Angew. Chem. Int. Ed.* **2019**, *58*, 9682–9695; *Angew. Chem.* **2019**, *131*, 9784–9797; c) N. Zheng, Y. Xu, Q. Zhao, T. Xie, *Chem. Rev.* **2021**, *121*, 1716–1745; d) *Dynamic Covalent Chemistry: principles, reactions, and applications* (Eds.: W. Zhang, Y. Jin), Wiley, Hoboken, **2017**; e) *Dynamic Combinatorial Chemistry* (Eds.: J. N. H. Reek, S. Otto), Wiley-VCH, Weinheim, **2010**; f) R. L. E. Furlan, S. Otto, J. K. M. Sanders, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 4801–4804; g) A. G. Orrillo, R. L. E. Furlan, *Angew. Chem. Int. Ed.* **2022**, *61*, e202201168; *Angew. Chem.* **2022**, *134*, e202201168.

[26] C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165–195.

[27] T. H. Lowry, K. S. Richardson, *Mechanism and Theory in Organic Chemistry*, 3rd ed., Harper Collins, New York, **1987**.

[28] Deposition Numbers 2159137 (for (**R**)-**1b**), 2159138 (for (**R**)-**3f**), 2159140 (for (**R**)-**3j**), 2159141 (for (**R**)-**1**) and 2159142 (for (**S**)-**3f**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

[29] a) S. Mahapatra, C. P. Woroch, T. W. Butler, S. N. Carneiro, S. C. Kwan, S. R. Khasnavis, J. Gu, J. K. Dutra, B. C. Vetelino, J. Bellenger, C. W. am Ende, N. D. Ball, *Org. Lett.* **2020**, *22*, 4389–4394; b) P. Mukherjee, C. P. Woroch, L. Cleary, M. Rusznak, R. W. Franzese, M. R. Reese, J. W. Tucker, J. M. Humphrey, S. M. Etuk, S. C. Kwan, C. W. am Ende, N. D. Ball, *Org. Lett.* **2018**, *20*, 3943–3947.

[30] F. M. Bickelhaupt, K. N. Houk, *Angew. Chem. Int. Ed.* **2017**, *56*, 10070–10086; *Angew. Chem.* **2017**, *129*, 10204–10221.