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Stereospecific SuFEx reactivity of highly enantioenriched sulfondiimidoyl fluorides

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Sulfondiimidoyl fluorides are established SuFEx platforms, yet their potential in asymmetric synthesis remains largely unexplored. Herein we report stereospecific SuFEx transformations of highly enantioenriched sulfondiimidoyl fluorides to access sulfone diimines, sulfondiimidamides and sulfondiimidates with complete chirality transfer. For sulfone diimine formation, heteroleptic triorganozincates serve as mild and chemoselective carbon nucleophiles, enabling exclusive stereospecific allyl and benzyl transfer with broad functional group tolerance. The accomplished orthogonal deprotection of sulfondiimidoyl scaffolds demonstrates their additional synthetic flexibility. Collectively, this work establishes sulfondiimidoyl fluorides as robust chiral SuFEx building blocks for asymmetric synthesis.

Introduction

Development of robust transformations, which rapidly assemble complex molecular frameworks, remains a central objective of synthetic chemistry. Initially proposed by Barry Sharpless in 2013,[1] SuFEx (Sulfur Fluoride Exchange) reactions have emerged as a "click chemistry" approach that meets this challenge. The SuFEx method exploits the high chemical stability of S(VI)–F motifs, which, nonetheless, exhibit controllable and versatile reactivity toward nucleophiles. Moreover, the broad structural diversity of S(VI)–fluorides renders SuFEx a general platform with applications in organic synthesis,[2] materials science[3] and chemical biology.[4]

Among the various S(VI)–fluorides, sulfonyl fluorides have gained most attention (Fig. 1).[5] The ability to tolerate harsh reaction conditions and to unleash the desired reactivity under an appropriate reaction system has enabled their use as privileged warheads in chemical biology[6] and as valuable precursors for sulfones and sulfonamides.[5] The latter constitute a crucial functional group in drug discovery with over 70 FDA-approved drugs containing a sulfonamide.[7,8] The broad application of sulfonyl fluorides invigorated an in-depth investigation of their aza-analogues.

Mono-aza-analogues – sulfonimidoyl fluorides – retain the high stability and controlled electrophilic reactivity characteristic of S(VI)–F motifs, additionally featuring an N-vector and a stereogenic S-atom. Importantly, the SuFEx reactions with C-, N- and O-nucleophiles proceed with complete inversion of the sulfur stereocenter.[9] Notably, C- and N-substitution products – sulfoximines and sulfonimidamides – have already become well-established[10,11] bioisosteres of sulfonamides often offering improved solubility and an ADME profile with retention of potency.[12–15]

The next O- to N-atom exchange in sulfonimidoyl fluorides affords S-chiral sulfondiimidoyl fluorides introducing yet another N-vector. Despite the potential utility of these novel scaffolds, general synthetic entries toward sulfodiimidoyl fluorides have appeared only recently. While considerable progress has been achieved in the preparation of racemic derivatives,[16–23] stereoselective synthesis remains largely unexplored.[24] Herein, we aim to gain a comprehensive insight into stereochemical aspects of the respective SuFEx reactivity with C-, N- and O-nucleophiles in order to exploit the full potential of highly enantioenriched sulfondiimidoyl fluoride building blocks as a SuFEx platform.

Results and discussion

Despite the reliability of the already developed general synthetic access to racemic sulfondiimidoyl fluorides starting from S(IV) precursors,[16–23] similar preparation of the corresponding enantioenriched products was often plagued by various degrees of racemization and turned out to be a task far from trivial. Our study commenced with the synthesis of the key NH_2-sulfinamidine precursor **2** (Scheme 1). Treatment of the conveniently accessible[25] sulfinimidate **1** with LiHMDS afforded the desired building block **2** in fair yield and excellent enantiomeric purity after a single recrystallization. As

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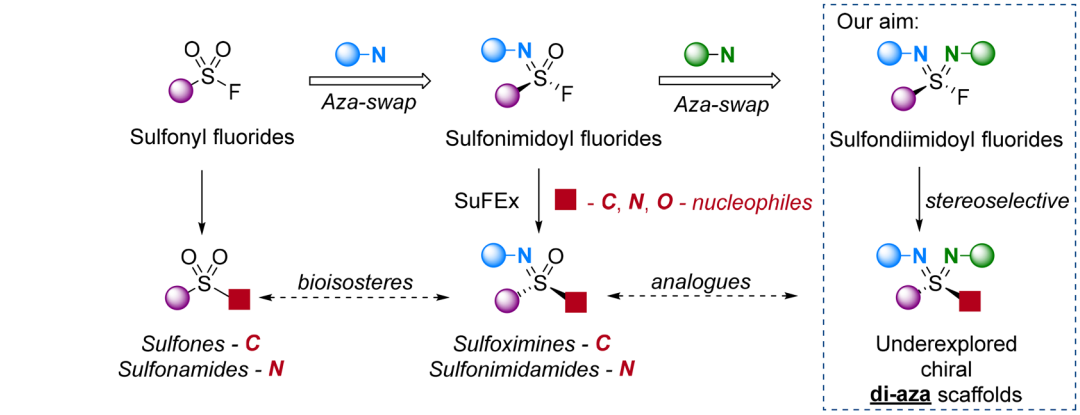
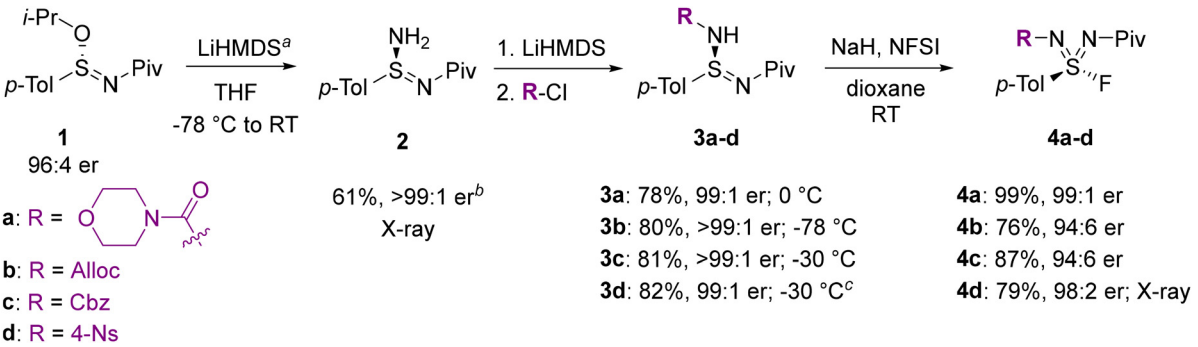


Fig. 1 Sulfonyl fluorides and their aza-analogues.



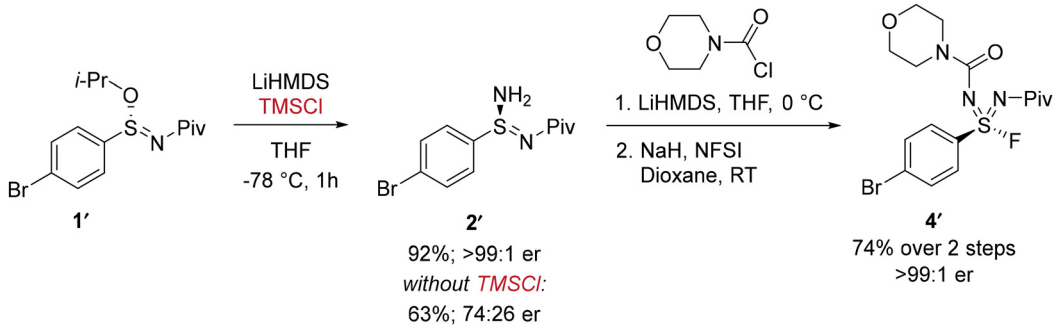
Scheme 1 Synthesis of enantioenriched sulfondiimidoyl fluorides: [a] LiHMDS serves as the amine source; [b] after single recrystallization; and [c] KHMDS instead of LiHMDS.

expected, the reaction proceeded with inversion of configuration at stereogenic sulfur as evidenced by X-ray analysis of sulfinamidine **2**. Several electron-withdrawing protecting groups were further introduced at the N-atom. The morpholine-4-carbonyl fragment could be installed in high yield without enantiopurity erosion, whereas introduction of Alloc under identical conditions led to diminished yield and partial racemization presumably due to acyl transfer. Nevertheless, lowering the reaction temperature dramatically improved the outcome, enabling the preparation of Cbz and Alloc derivatives **3b and c** in high yields and enantiopurities. Interestingly, switching the base counterion to potassium was pivotal for the successful synthesis of Ns derivative **3d**.

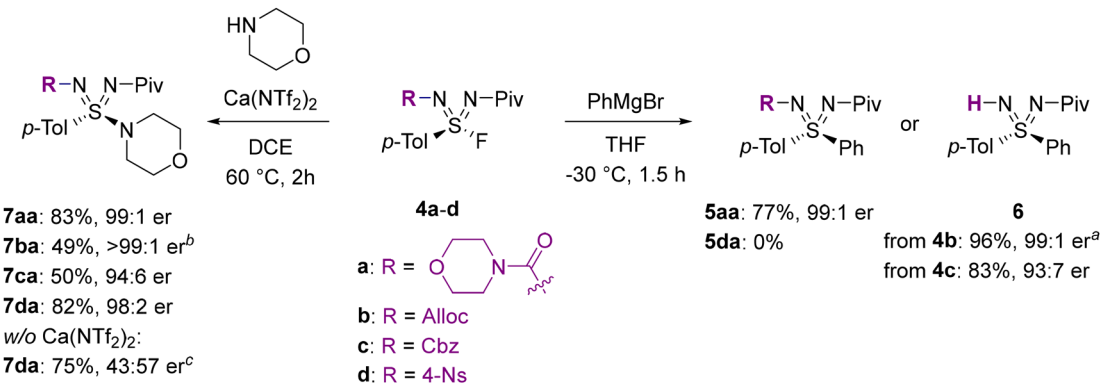
Subsequently, we found that the nature of the N-substituent strongly influenced the final *S*-fluorination. While the 4-morpholine-carbonyl derivative **4a** was obtained in quantitative yield and with a minor erosion of enantiopurity under standard conditions, noticeable racemization occurred in the case of Alloc and Cbz derivatives **4b** and **4c**, respectively. Control experiments with **4b** implicated fluoride ions present in the reaction medium as a probable cause of stereochemical erosion.[26] Addition of oxysilanes such as tetramethyldisiloxane or diethoxymethylsilane as fluoride-ion scavengers[27] improved the stereoselectivity on a small scale, but failed to resolve the problem upon attempted scale-up. In the case of less nucleophilic **3d**, a noticeable decrease in the reaction rate was observed, leading to longer reaction times. Importantly, the X-ray crystal structure of fluoride **4d** confirmed the stereoretentive character of both sulfonation and fluorination.

Relying on the stereospecific approach elaborated above, we targeted the *p*-Br-functionalized sulfondiimidoyl fluoride **4′** (Scheme 2). Unexpectedly, the reaction of sulfinimidate **1′** with LiHMDS led to significant racemization even at cryogenic temperatures. This behavior is consistent with the increased susceptibility of the *p*-Br-substituted sulfinimidate **1′** toward racemization induced by liberated lithium isopropoxide.[25] The racemization was fully suppressed upon addition of TMSCl, in line with the *in situ* silylation of the expelled isopropoxide. Downstream carbamoylation and fluorination proceeded smoothly to afford sulfondiimidoyl fluoride **4′** in 74% yield over two steps and with 99 : 1 er.

The reactivity of sulfondiimidoyl fluorides **4a–d** was initially assessed using representative C- and N-nucleophiles (Scheme 3). PhMgBr was chosen as a simple model C-nucleophile owing to the widespread use of aryl-Grignard reagents across various SuFEx transformations.[18,21,28–30] While the stable morpholine-4-carbonyl moiety was preserved, substitution reactions of Alloc- and Cbz-protected substrates **4b** and



Scheme 2 Synthesis of *p*-Br-functionalized sulfondiimidoyl fluoride.



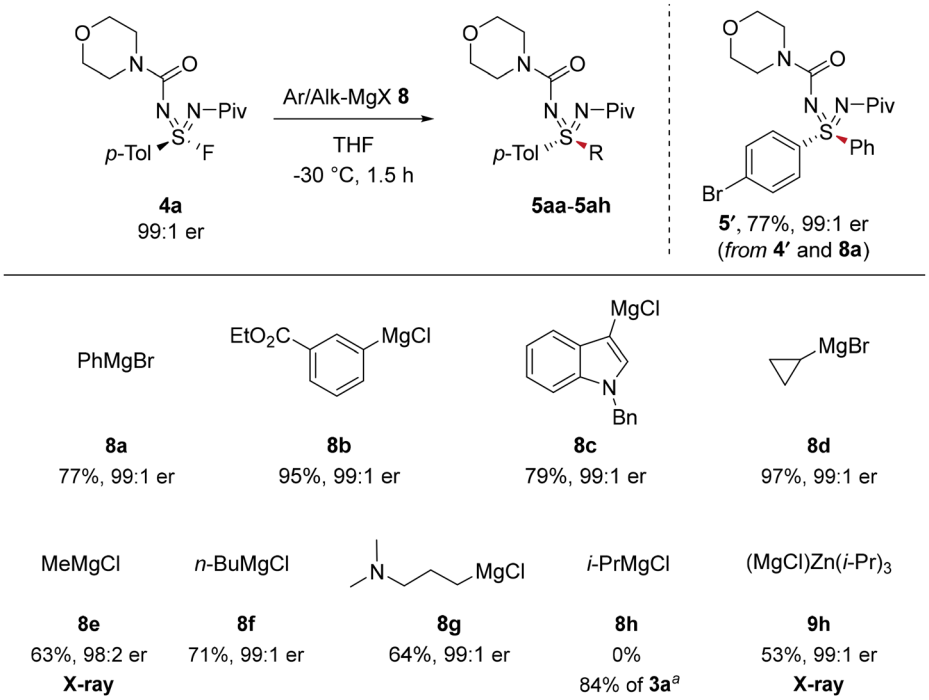
Scheme 3 SuFEx reactivity of sulfondiimidoyl fluorides toward C- and N-nucleophiles. Reaction conditions for PhMgBr: sulfondiimidoyl fluoride (1 equiv.), PhMgBr (2.5 equiv.), THF (0.1 M), −30 °C, and 1.5 h. Reaction conditions for morpholine: sulfondiimidoyl fluoride (1 equiv.), $Ca(NTf_2)_2$ (1.1 equiv.), morpholine (2.2 equiv.), DCE (0.2 M), 60 °C, and 2 h. [a] er of **4b**: 99 : 1; [b] er of **4b** > 99 : 1; and [c] 18 h at RT.

c under identical conditions led to selective removal of carbamates, affording N–H sulfone diimines **6** in high yields without racemization. Not unexpectedly, the Ns-substituted fluoride **4d** formed a complex mixture of products due to the sensitivity of the nitro group to reduction.[31]

The SuFEx reactivity toward N-nucleophiles was evaluated next. Morpholine was selected as a model nucleophile owing to its high nucleophilicity and well-documented[16–18,21,28,31] compatibility with SuFEx chemistry. While morpholine-4-carbonyl and Ns-substituted fluorides **4a** and **d** readily engaged in $Ca(NTf_2)_2$-promoted[32] substitution,[33] mixtures of products were obtained using Alloc- and Cbz-derivatives **4b** and **c**, presumably due to competitive cleavage of the respective protecting groups. Nevertheless, in all cases examined, the substitution reactions proceeded stereospecifically. The strong electron-withdrawing nature of the Ns group enabled fluoride **4d** to react with morpholine even without a promoter, albeit with nearly complete stereochemical erosion. Other fluorides did not deliver the desired substitution product in the absence of $Ca(NTf_2)_2$. On the basis of combined C- and N-nucleophile screening studies, the most versatile **4a** was selected as a platform electrophile for further investigation of the scope of nucleophiles.

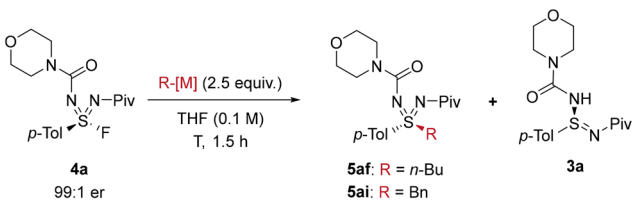
The scope of C-nucleophiles was examined first (Scheme 4). The resulting sulfone diimines represent valuable aza-analogues of medicinally relevant sulfones and sulfoximines. The phenyl group was introduced in fair yield simply using PhMgBr. More sensitive ester- and indole-containing Grignard reagents were generated by magnesium-iodine exchange and similarly readily engaged in the substitution reaction, affording sulfone diimines **5ab** and **5ac** in 95% and 79% yield, respectively. Notably, cyclopropylmagnesium bromide proved exceptionally efficient, forming the substitution product **5ad** quantitatively.

Linear alkyl derivatives **5ae**–**5ag** were obtained from the respective alkylmagnesium chlorides in fair yields and configurational inversion at the stereogenic sulfur was confirmed by X-ray analysis of *S*-methyl sulfone diimine **5ae** (Scheme 4). Unexpectedly, i-PrMgCl failed to engage in substitution, delivering the reduced sulfinamidine **3a** instead.[34,35] Nevertheless, productive substitution was achieved using the i-PrMgCl-derived zincate reagent **9h**, again proceeding with inversion of configuration as established by X-ray analysis. Prompted by this divergence in reactivity, we undertook a more detailed examination of the SuFEx reaction with various organometallic species (Table 1).



Scheme 4 Scope of alkyl and aryl C-nucleophiles. Reaction conditions: sulfondiimidoyl fluoride (1 equiv.), Ar/Alk-MgX (2.5 equiv.), THF (0.1 M), −30 °C, and 1.5 h. [a] NMR yield.

Table 1 Optimization of conditions for alkyl and benzyl nucleophiles



No.	[M]-R	From	*T*, °C	NMR yield, % 5	3a	4a	er of 5
1	*n*-BuMgCl		−30	74	4	0	99 : 1
2	*n*-BuMgBr		−30	60	23	3	N.D.
3	(MgCl)Zn(*n*-Bu)$_3$	$ZnCl_2$ + 3 *n*-BuMgCl	−30	75	5	8	99 : 1
4	*n*-BuLi		−78	15	0	0	N.D.
5	LiCu (*n*-Bu)$_2$	CuBr·LiBr + 2 *n*-BuLi	−78	7	76	0	N.D.
6	LiZn(*n*-Bu)$_3$	$ZnBu_2$ + *n*-BuLi	−78	8	0	88	N.D.
7	LiZn(*n*-Bu)$_3$	$ZnBu_2$ + *n*-BuLi	−30	84	0	0	99 : 1
8	$LiZnMe_2Bn$	BnZnCl + 2 MeLi	−30	70	4	0	N.D.
9	$LiZnMe_2Bn$	BnZnCl + 2 MeLi	−78	80	5	0	N.D.
10	$(MgBr)ZnMe_2Bn$	BnZnCl + 2 MeMgBr	−78	84	13	0	N.D.
11	**$(MgCl)ZnMe_2Bn$**	**BnZnCl + 2 MeMgCl**	**−78**	**90**	**4**	**0**	**99 : 1**

In the case of Grignard reagents, the nature of magnesium halide exerted an unexpectedly pronounced effect on the reaction outcome: switching from *n*-BuMgBr to *n*-BuMgCl suppressed the formation of sulfinamidine byproduct (Table 1, entries 2 *vs.* 1). Based on control experiments, we attribute this effect to dealkylation of the alkyl-sulfone diimine product by the respective halide ion. Generation of a triorganozincate nucleophile from *n*-BuMgCl led to no improvement over the use of the Grignard reagent itself (entry 3). While Gilman cuprate selectively reduced fluoride **4a** to sulfinamidine **3a** (entry 5), the use of highly reactive *n*-BuLi resulted in an intractable product mixture contain-

ing little of the desired substitution product (entry 4). In contrast, the use of *n*-BuLi-derived triorganozincate $LiZn(n\text{-}Bu)_3$ enabled productive substitution. Although low conversion was observed at −78 °C, the substitution proceeded smoothly at −30 °C, delivering sulfone diimine **5af** in high yield and with complete stereospecificity (entries 6 and 7).

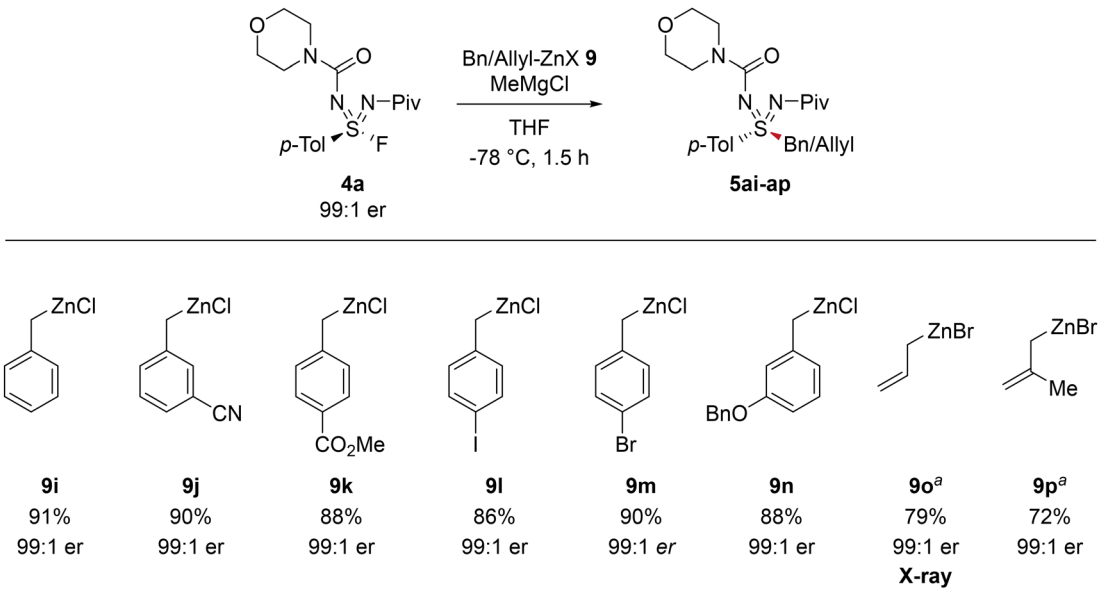
Considering the high performance of organolithium-derived trialkylzincates and our previous experience[36] in organozincate chemistry, we next evaluated easily accessible heteroleptic dimethyl benzylzincates (Table 1). Thus, $LiZnMe_2Bn$ generated *in situ* from BnZnCl and MeLi readily engaged in the substitution reaction (entries 8 and 9) and analogous MeMgBr-derived zincate exhibited comparable reactivity (entry 10). Switching the halide from bromide to chloride (entry 11) further suppressed the formation of sulfinamidine byproduct, affording the corresponding substitution product **5ai** in a very high yield without racemization. Complete selectivity of Bn *vs.* Me transfer was observed with no trace of methyl-substituted derivative **5ae** detected.

Based on these results, we decided to exploit the discovered utility of triorganozincate derivatives for the preparation of benzylic sulfone diimines (Scheme 5). Notably, the organozincate approach enabled efficient incorporation of functional groups that are typically incompatible with more reactive organometallic reagents. Accordingly, the yield of sulfone diimines **5aj–al** was unaffected by the presence of nitrile, methyl ester and aryl iodide functionalities. Aryl bromide and benzyl-protected aryl moieties were likewise introduced with high efficiency. Dimethylallylzincates generated from allylZnBr and MeLi smoothly engaged in the substitution reaction with stereochemical inversion, as confirmed by X-ray analysis of **5ao**. Analogous to benzylic zincates, complete allyl *vs.* methyl transfer selectivity was observed.

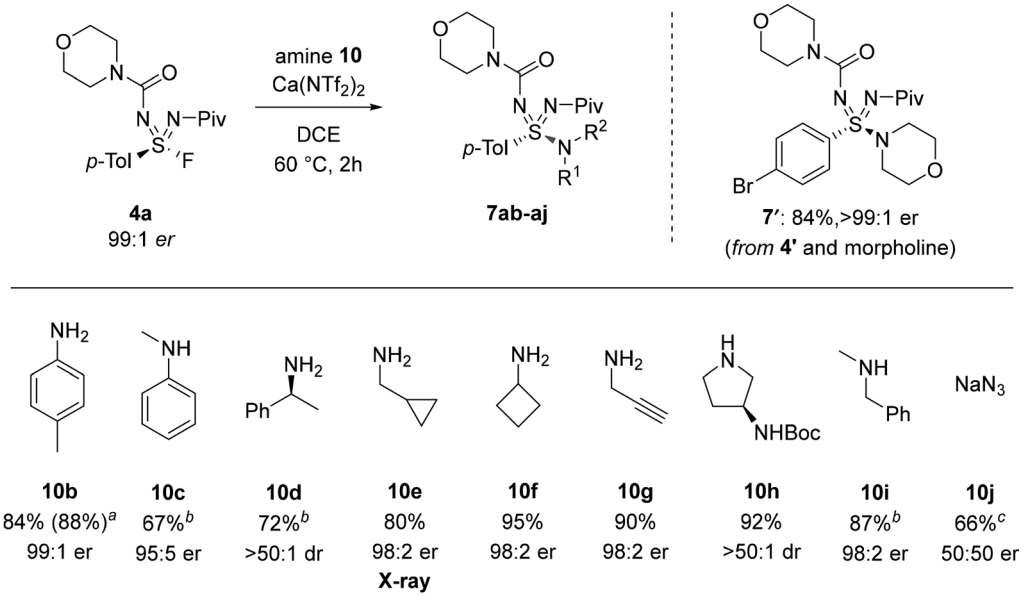
Having established stereospecific SuFEx with C-nucleophiles, we next explored the scope of N-nucleophiles to access sulfondiimidamides, di-aza analogues of sulfonamides. Under the optimized conditions,[37] fluoride **4a** was reacted with a diverse set of representative amines (Scheme 6). Anilines as well as primary and secondary amines smoothly afforded the corresponding sulfondiimidamides with high stereoselectivity. The configurational inversion at stereogenic sulfur was confirmed by X-ray analysis of the cyclopropylmethylamine derivative **7ae**. The transformation proved compatible with strained alicycles (**10e and f**), a terminal alkyne (**10g**) and a Boc-protected primary amine (**10h**). Interestingly, the substitution with NaN_3 resulted in complete racemization of the sulfur stereocenter.

To complete the exploration of SuFEx substitution reaction, we investigated the scope of O-nucleophiles using a range of phenols[38] (Scheme 7). Variation of *para*-substitution revealed broad applicability of the SuFEx reaction across a wide pK_a range. High yields and stereospecificity were observed for *p*-OMe-, *p*-Me-, *p*-CF_3- and *p*-CN-substituted phenols (**11a–d**), whereas a higher temperature was required for the strongly deactivated *p*-nitrophenol **11e**. Introduction of *ortho*-substituents (phenols **11f and g**) led to slightly prolonged reaction times, while yields and stereoselectivity remained high. Notably, SuFEx reactions with biologically relevant estrone (**11h**), the tyrosine derivative **11i** and paracetamol **11j** revealed excellent compatibility with functional groups.

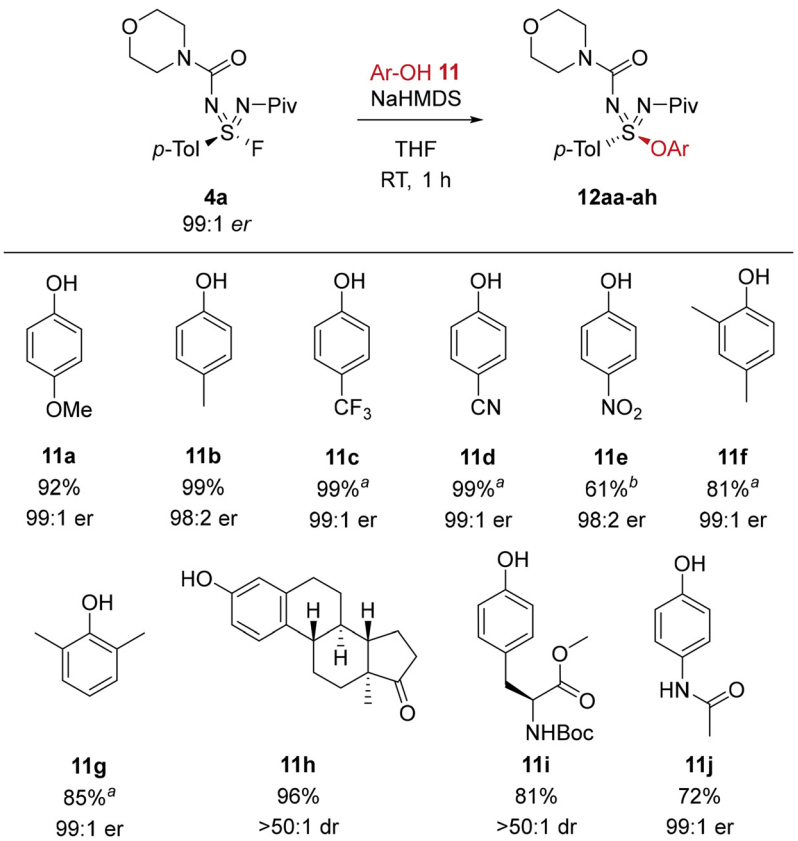
Having established the scope of SuFEx reactivity, we next turned our attention to the possibility of orthogonal deprotection of the obtained scaffolds (Scheme 8). Morpholine-4-carbonyl and Piv-protected sulfone diimine **5aa** was chosen as



Scheme 5 Scope of benzyl and allyl C-nucleophiles. Reaction conditions: sulfondiimidoyl fluoride (1 equiv.), Bn/allyl-ZnCl (2.5 equiv.), MeMgCl (5 equiv.), THF (0.1 M), −78 °C, and 1.5 h. [a] MeLi instead of MeMgBr.

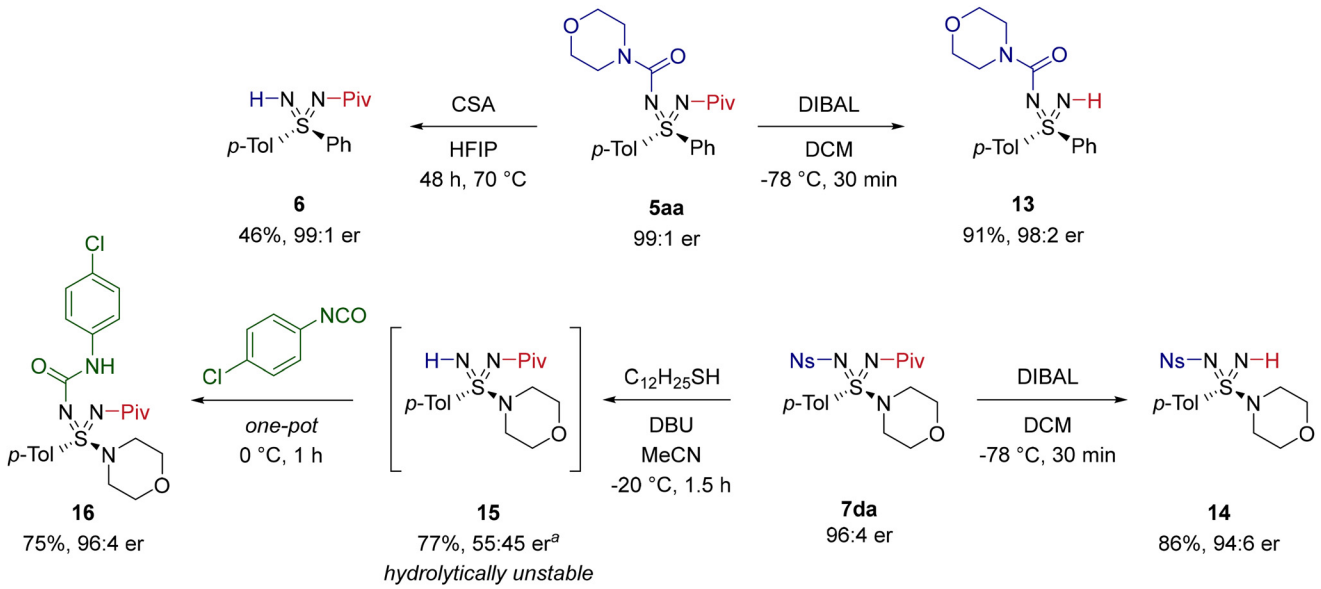


Scheme 6 Scope of N-nucleophiles. Reaction conditions: sulfondiimidoyl fluoride (1 equiv.), $Ca(NTf_2)_2$ (1.1 equiv.), amine (2.2 equiv.), DCE (0.2 M), 60 °C, and 2–18 h. [a] Yield on 1.0 mmol scale; [b] 60 °C, 18 h; and [c] at RT, 18 h, in DMF as a solvent.



Scheme 7 Scope of O-nucleophiles. Reaction conditions: sulfondiimidoyl fluoride (1 equiv.), phenol (1.2 equiv.), NaHMDS (1.2 equiv.), THF (0.05 M), RT, and 1–3 h. [a]RT, 3 h and [b]60 °C, 2 h.

a model substrate. While the selective pivaloyl deprotection was readily achieved using DIBAL, removal of the urea fragment proved more challenging. Following a preliminary screening of conditions, CSA/HFIP-promoted cleavage[30] was found to deliver the N–H sulfone diimine **6** with complete stereoselectivity, albeit in a moderate yield.



Scheme 8 Orthogonal deprotection of the obtained scaffolds. [a] enantiomer ratio measured for isolated **15**.

We then examined the orthogonal deprotection of sulfondiimidamides, promising di-aza-analogues of sulfonamides. The Ns- and Piv-protected derivative **7da** served as a model substrate. Analogous to the sulfone diimine case, the Piv group was selectively cleaved with DIBAL in high yield and with minor erosion of enantiopurity. Notably, no reduction of the sensitive nitro group was observed. In contrast, removal of the Ns group proved troublesome due to pronounced hydrolytic instability of the deprotected derivative even in mildly acidic media. While near-complete erosion of enantiopurity was observed upon isolation of N–H diimidamide **15**, *in situ* trapping with an isocyanate furnished the corresponding urea **16** in high yield and with complete stereoselectivity.[39]

Conclusions

In the present work, a stereoselective SuFEx platform was established using highly enantioenriched sulfondiimidoyl fluoride building blocks. Systematic investigation of their reactivity toward C- and N-nucleophiles revealed consistent inversion of configuration at the stereogenic sulfur atom. The configurational lability of the sulfur center encountered at various synthetic stages was investigated and resolved through rational control of reaction conditions. Heteroleptic triorganozincates were identified as mild and chemoselective C-nucleophiles, enabling exclusive stereospecific allyl or benzyl group transfer with broad functional group tolerance. Orthogonal protecting group cleavage further demonstrates synthetic versatility of the obtained scaffolds and provides a synthetic entry toward enantioenriched di-aza-analogues of sulfones and sulfonamides. Collectively the obtained results demonstrate the broad applicability of sulfondiimidoyl fluorides as chiral SuFEx hubs and provide a foundation for their application in asymmetric synthesis and medicinal chemistry.

Author contributions

Conceptualization: G. J., P. A. D., and E. S.; investigation G. J., A. J. P., J. B., and V. K.; supervision: P. A. D. and E. S.; writing – original draft: G. J. and P. A. D.; writing – review & editing: G. J., P. A. D., J. B., V. K., and E. S.; funding acquisition: E. S. All authors have given approval for the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

Supplementary information (SI): experimental details, characterization data, HPLC/CSP chromatograms, and NMR spectra. See DOI: **https://doi.org/10.1039/d6qo00230g**.

CCDC 2531871–2531876 (**2**, **4d**, **5ae**, **5ah**, **5ao**, and **7ae**) contain the supplementary crystallographic data for this paper.[40a–f]

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40 (*a*) CCDC 2531871: Experimental Crystal Structure Determination, 2026, DOI: **10.5517/ccdc.csd.cc2qzm8m**; (*b*) CCDC 2531872: Experimental Crystal Structure Determination, 2026, DOI: **10.5517/ccdc.csd.cc2qzm9n**; (*c*) CCDC 2531873: Experimental Crystal Structure Determination, 2026, DOI: **10.5517/ccdc.csd.cc2qzmbp**; (*d*) CCDC 2531874: Experimental Crystal Structure Determination, 2026, DOI: **10.5517/ccdc.csd.cc2qzmcq**; (*e*) CCDC 2531875: Experimental Crystal Structure Determination, 2026, DOI: **10.5517/ccdc.csd.cc2qzmdr**; (*f*) CCDC 2531876: Experimental Crystal Structure Determination, 2026, DOI: **10.5517/ccdc.csd.cc2qzmfs**.