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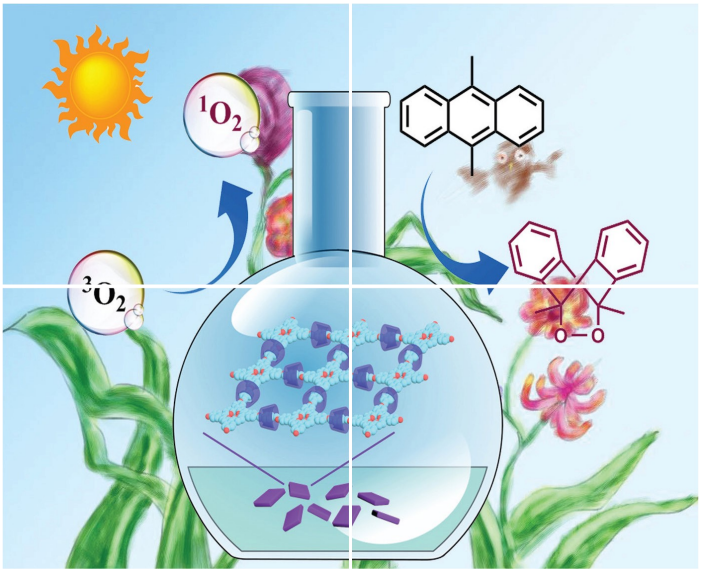

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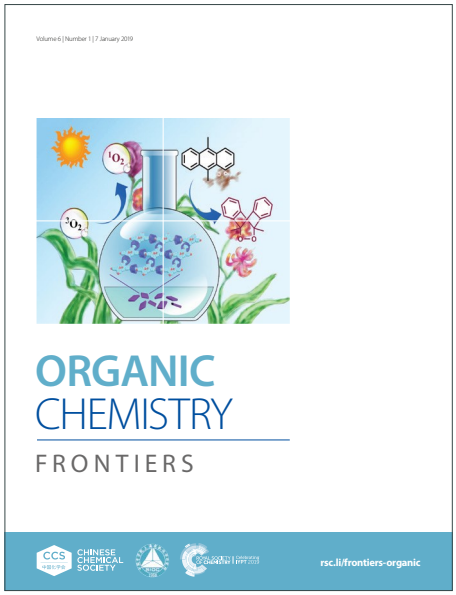

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Stereospecific SuFEx Reactivity of Highly Enantioenriched Sulfondiimidoyl Fluorides

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Abstract. 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.

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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 motif, which, nonetheless, displays 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 various *S*(VI)-fluorides sulfonyl fluorides have gained most attention (Figure 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 for *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 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 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 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.

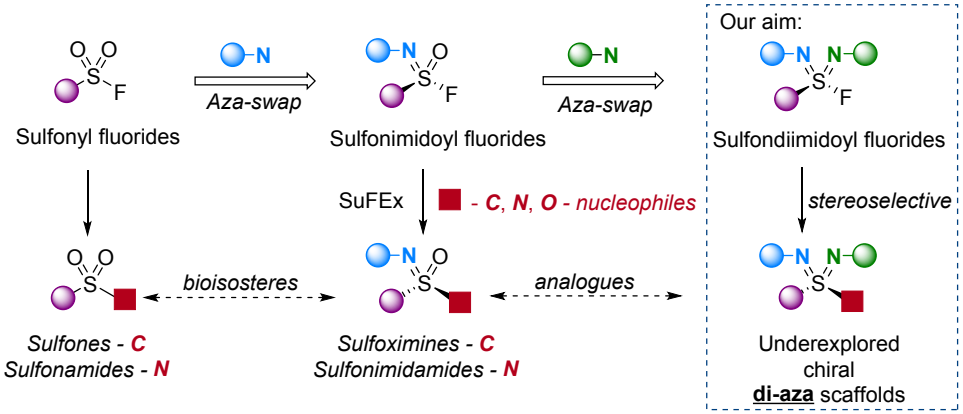

Figure 1. Sulfonyl fluorides and their aza-analogues

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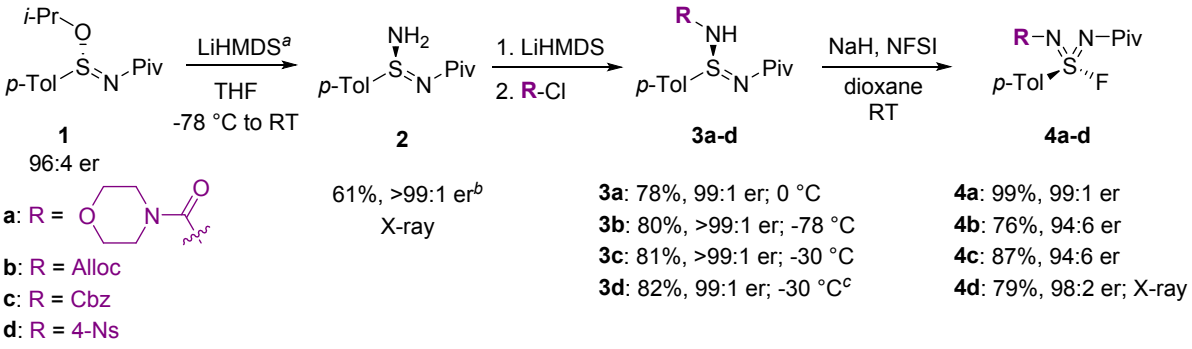
Results and discussion

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 degree of racemization and turned out to be a task far from trivial. Our study commenced with the synthesis of 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. Expectedly, 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. 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 preparation of Cbz and Alloc derivatives **3b**,**c** in high yields and enantiopurities. Interestingly, switching the base counterion to potassium was pivotal for the successful synthesis of Ns-derivative **3d**.

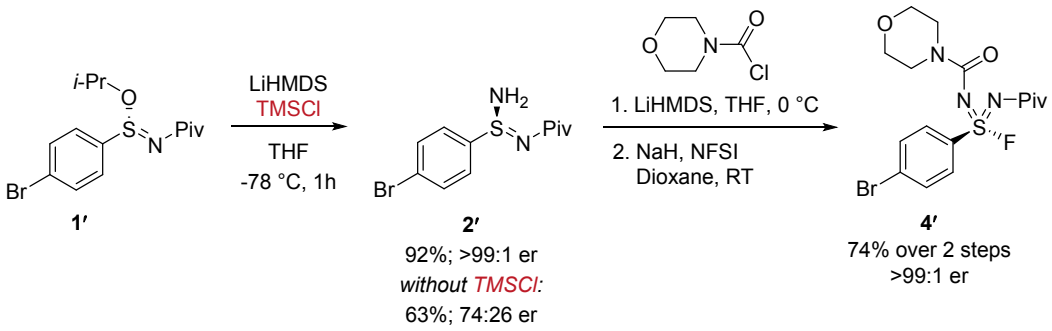


Scheme 1. Synthesis of enantioenriched sulfondiimidoyl fluorides; (a) LiHMDS serves as the amine source; (b) after single recrystallization; (c) KHMDS instead of LiHMDS

Subsequently, we found that the nature of the *N*-substituent strongly influenced the final *S*-fluorination. While 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 small scale, but failed to resolve the problem upon attempted scale-up. In the case of less nucleophilic **3d** noticeable decrease of reaction rate was observed leading to longer reaction times. Importantly, X-ray crystal structure of fluoride **4d** confirmed the stereoretentive character of both sulfonation and fluorination.

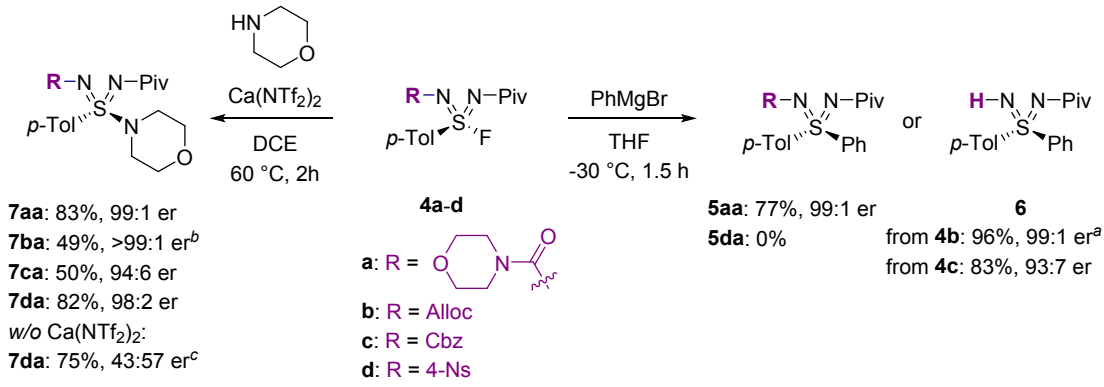
Relying on the stereospecific approach elaborated above, we targeted the *p*-Br-functionalized sulfondiimidoyl fluoride **4'** (Scheme 2). Unexpectedly, the reaction of sulfinimidate **1'** with LiHMDS led to significant racemization even at cryogenic temperatures. This behavior is consistent with increased 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 *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.



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

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



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, 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, 2 h. (a) er of **4b** 99:1 (b) er of **4b** >99:1 (c) 18 h at RT

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. Whereas morpholine-4-carbonyl and Ns-substituted fluorides **4a**,**d** readily engaged in $Ca(NTf_2)_2$-promoted[32] substitution,[33] mixtures of products were obtained using Alloc- and Cbz-derivatives **4b**,**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

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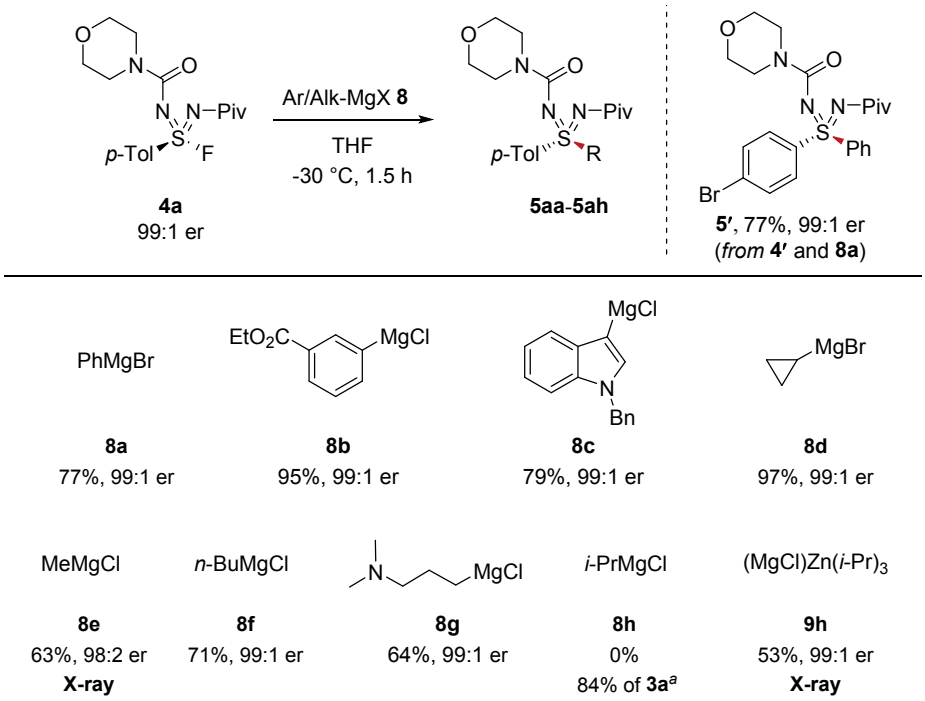
fluoride **4d** to react with morpholine even without a promoter, albeit with nearly complete stereochemical erosion. Other fluorides did not deliver the desired substitution product in the absence of $Ca(NTf_2)_2$. On the basis of combined *C*- and *N*-nucleophile screening studies, the most versatile **4a** was selected as a platform electrophile for further investigation of nucleophile scope.

The scope of *C*-nucleophiles was examined first (Scheme 4). The resulting sulfone diimines represent valuable aza-analogues of medicinally-relevant sulfones and sulfoximines. 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.



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, 1.5 h. (a) NMR yield

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 *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).

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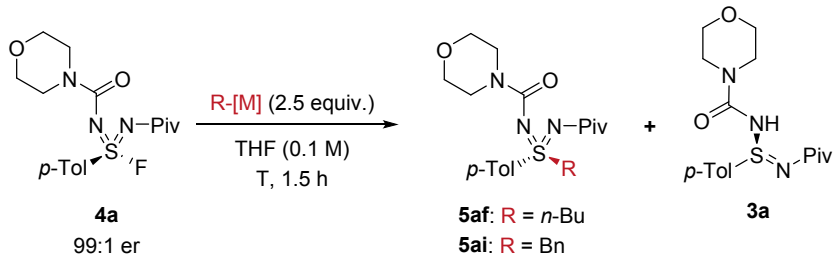
Table 1. Optimization of conditions for alkyl and benzyl nucleophiles.



4a
99:1 er

5af: R = *n*-Bu
5ai: R = Bn

3a

No	[M]-R	From	T, °C	NMR yield, %			er of 5
				5	3a	4a	
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, entry 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 triorganozincate nucleophile from *n*-BuMgCl gave no improvement over the use of the Grignard reagent itself (entry 3). Whereas Gilman cuprate selectively reduced fluoride **4a** to sulfinamidine **3a** (entry 5), the use of highly reactive *n*-BuLi resulted in an intractable product mixture containing little of the desired substitution (entry 4). In contrast, the use of *n*-BuLi-derived triorganozincate LiZn(*n*-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 6,7).

Considering the high performance of organolithium-derived trialkylzincates and our previuos experience[36] in organozincate chemistry, we next evaluated easily accessible

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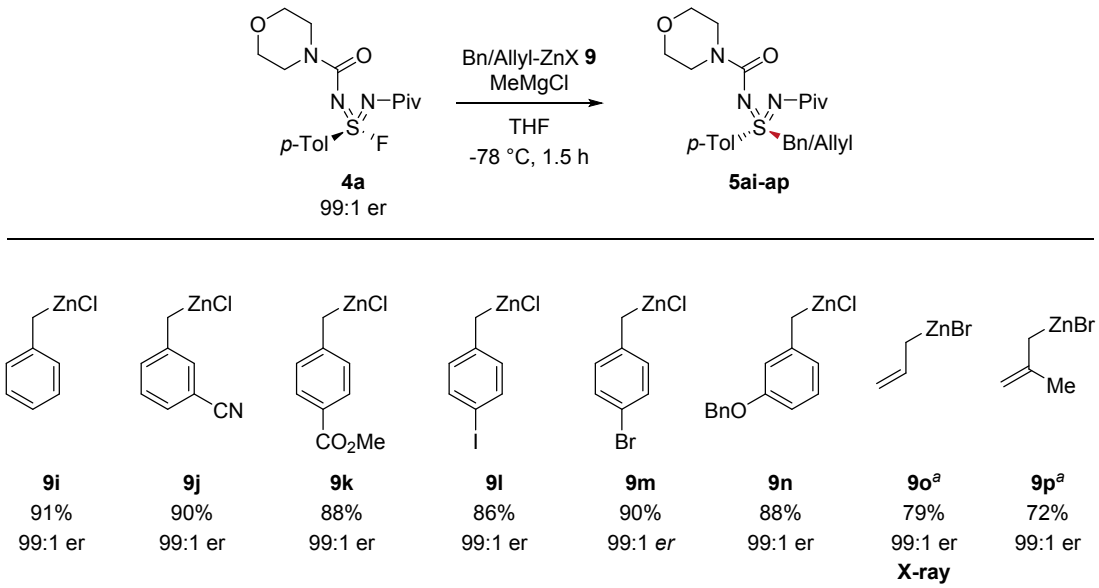
heteroleptic dimethyl benzylzincates (Table 1). Thus, $LiZnMe_2Bn$ generated in situ from BnZnCl and MeLi readily engaged in the substitution reaction (entries 8,9) and analogous MeMgBr-derived zincate displayed comparable reactivity (entry 10). Switching the halide from bromide to chloride (entry 11) 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 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 confirmed by X-ray analysis of **5ao**. Analogously to benzylic zincates, complete allyl vs. methyl transfer selectivity was observed.



9i	**9j**	**9k**	**9l**	**9m**	**9n**	**9o**[a]	**9p**[a]
91%	90%	88%	86%	90%	88%	79%	72%
99:1 er	99:1 er	99:1 er	99:1 er	99:1 *er*	99:1 er	99:1 er	99:1 er
						X-ray	

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, 1.5 h. (a) MeLi instead of MeMgBr

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 cyclopropylmethylamine derivative **7ae**. The transformation proved compatible with strained alicycles (**10e,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.

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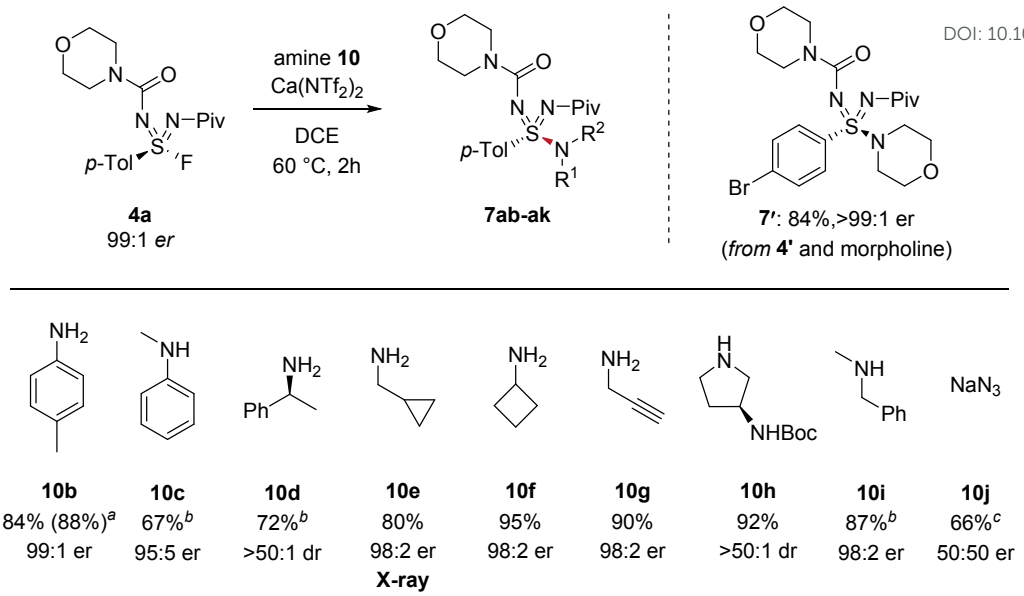

Scheme 6. Scope of *N*-nucleophiles. Reaction conditions: sulfondiimidoyl fluoride (1 equiv.), $Ca(NTf_2)_2$ (1.1 equiv.), amine (2.2 equiv.), DCE (0.2 M), 60 °C, 2–18 h. (a) yield on 1.0 mmol scale (b) 60 °C, 18 h; (c) at RT, 18 h, in DMF as solvent.

To complete the exploration of SuFEx substitution manifold, 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**,**g**) led to slightly prolonged reaction times, while yields and stereoselectivity remained high. Notably, SuFEx reactions with biologically relevant estrone (**11h**), tyrosine derivative **11i** and paracetamol **11j** revealed excellent compatibility with functional groups.

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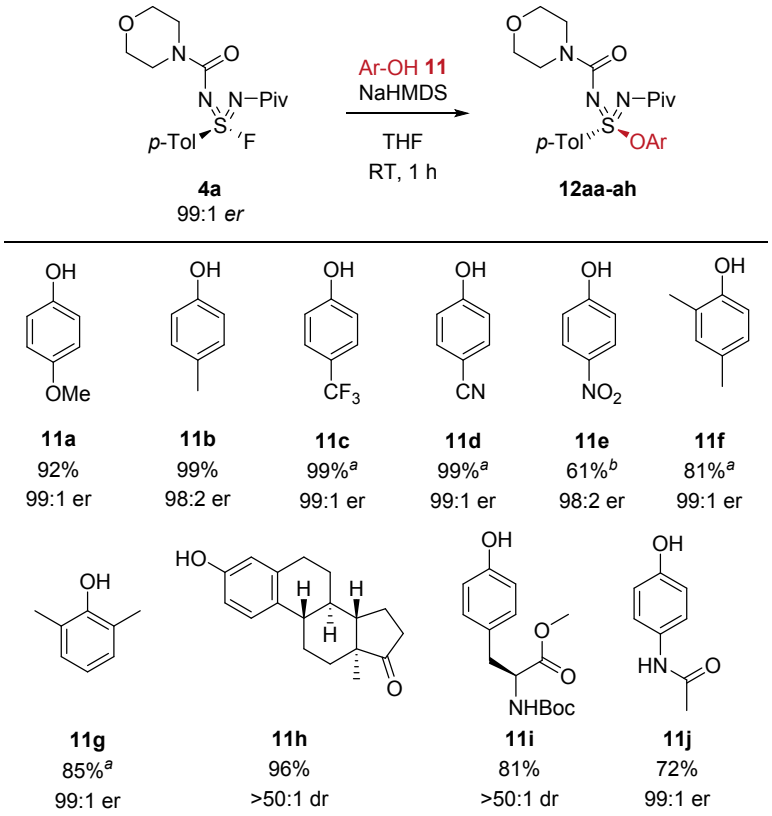

Scheme 7. Scope of *O*-nucleophiles. Reaction conditions: sulfondiimidoyl fluoride (1 equiv.), phenol (1.2 equiv.), NaHMDS (1.2 equiv.), THF (0.05 M), RT, 1–3 h. (a) RT, 3 h; (b) 60 ˚C, 2 h.

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 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.

We then examined the orthogonal deprotection of sulfondiimidamides, promising di-aza-analogues of sulfonamides. Ns- and Piv-protected derivative **7da** served as a model substrate. Analogously to the sulfone diimine case, 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 Ns-group proved troublesome due to pronounced hydrolytic instability of the deprotected derivative even in mildly acidic media. Whereas near-complete erosion of enantiopurity was observed upon isolation of the *N*-H diimidamide **15**, *in situ* trapping with an isocyanate furnished the corresponding urea **16** in high yield and with complete stereoselectivity.[39]

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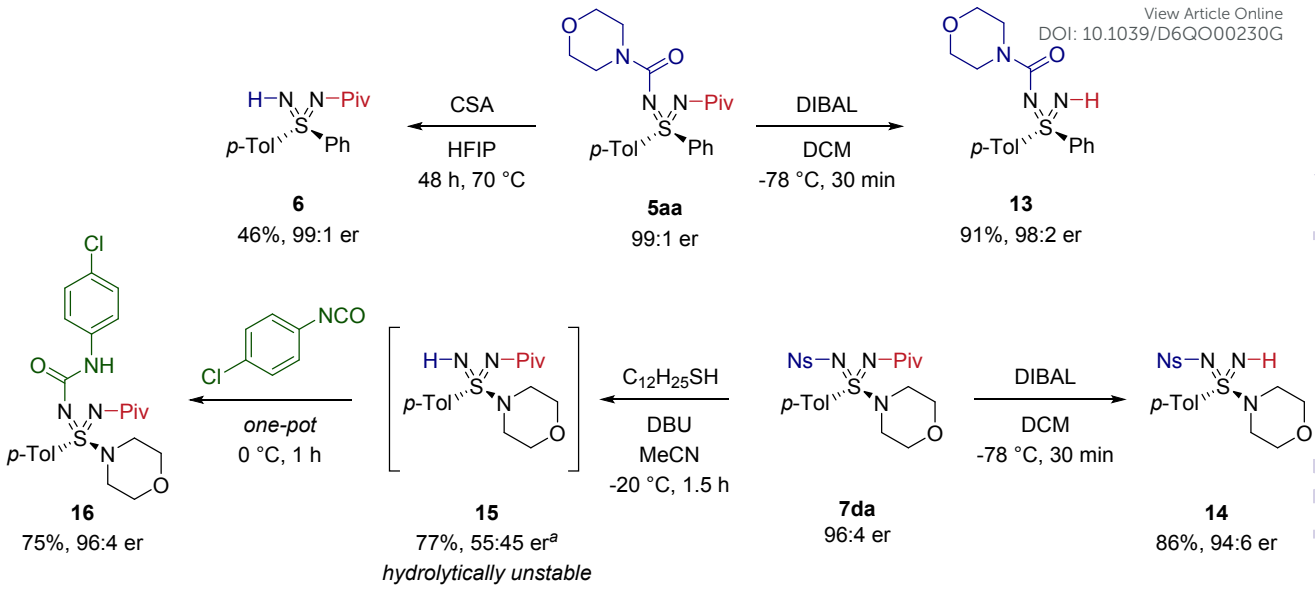

Scheme 8. Orthogonal deprotection of the obtained scaffolds; (a) Enantiomer ratio measured for isolated **15**.

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 a 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.

Data availability

Crystallographic data for **2**, **4d**, **5ae**, **5ah**, **5ao**, and **7ae** have been deposited at the Cambridge Crystallographic Data Centre under 2531871-2531876

Experimental details, characterization data, HPLC/csp chromatograms, and NMR spectra have been included in the ESI.

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

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There are no conflicts to declare.

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38 Although aliphatic alcohols can serve as *O*-nucleophiles in reactions with sulfondiimidoyl fluorides, the resulting *O*-alkyl sulfondiimidoates are highly unstable, owing to the electrophilic nature of the *O*-alkyl group and excellent leaving group ability of sulfonimidamide; see for example: E. Friedrich, P. Freund, C. Lorenz, T. Heinrich, D. Didier and M. Reggelin, Synthesis of Sulfondiimidoates by Desoxychlorination of Sulfonimidamides, *Org. Lett.*, 2025, **27**, 11673–11677. Consistent with these observations, attempts to isolate the corresponding sulfondiimidate ester from the reaction of sodium or lithium menthoxide with fluoride **4a** were unsuccessful.

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Data availability

Crystallographic data for **2**, **4d**, **5ae**, **5ah**, **5ao**, and **7ae** have been deposited at the Cambridge Crystallographic Data Centre under 2531871-2531876

Experimental details, characterization data, HPLC/csp chromatograms, and NMR spectra have been included in the ESI.