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Base-mediated intramolecular one-pot double-cyclization of epoxide-tethered 2-fluorobenzenesulfonamides: an avenue to 1,4-benzoxazine-fused benzothiaoxazepine-1,1-dioxides†

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Herein, we describe the synthesis of hitherto unknown 1,4-benzoxazine-fused benzothiaoxazepine-1,1-dioxides by a NaH-promoted intramolecular one-pot double-cyclization of epoxide-tethered 2-fluorobenzene sulfonamides. Mechanistically, the reactions proceed *via* an intramolecular epoxide ring-opening followed by an intramolecular nucleophilic aromatic substitution. The high yields, mild conditions, complete regio- and diastereoselectivity, and a wide substrate scope render this protocol well suited for drug discovery efforts.

Nucleophilic aromatic substitution (S_NAr) is one of the most frequently used reactions that stand tall amongst many recent innovative reactions.[1] Epoxide ring-opening reaction is another major workhorse in synthetic organic chemistry.[2] Despite these attributes, however, a major drawback is that these two reactions in the intermolecular mode often suffer from one or more of the following drawbacks: harsh reaction conditions, excess of reagents, low product yields and long reaction times. On the other hand, their intramolecular counterparts not only circumvent these hurdles, but also often enjoy high to complete regio- and stereocontrol to furnish ring systems in a straightforward fashion.[3,4] In this context, intramolecular one-pot double-cyclization involving epoxide ring-opening followed by S_NAr would be a very interesting and useful method for accessing fused ring systems. Considering the too frequent usage of S_NAr and epoxide ring-opening reactions, one would expect a number of synthetic reports based on this concept. However, to the best of our knowledge, such an idea is unprecedented in the chemical literature.

As members of the privileged N-heterocycles, the 3,4-dihydro-2*H*-1,4-benzoxazine and benzothiaoxazepine-1,1-dioxide scaffolds are ubiquitous in a wide range of natural and/or synthetic compounds.[5,6] Fig. 1a and b show some prominent representative examples of compounds based on these two core structures. Owing to their demonstrated pharmacological uses, extensive efforts have been devoted to the development of synthetic methods for diverse 3,4-dihydro-2*H*-1,4-benzoxazines and benzothiaoxazepine-1,1-dioxides.[7,8]

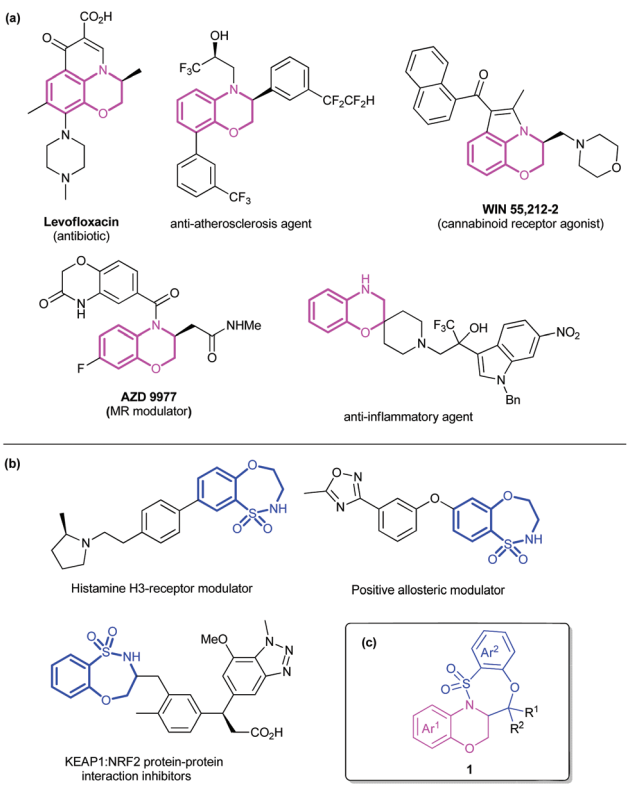

Fig. 1 (a) Representative bioactive 3,4-dihydro-2*H*-1,4-benzoxazines. (b) Representative bioactive benzothiaoxazepine-1,1-dioxides. (c) Designed fused 3,4-dihydro-2*H*-1,4-benzoxazine–benzothiaoxazepine-1,1-dioxide hybrids.

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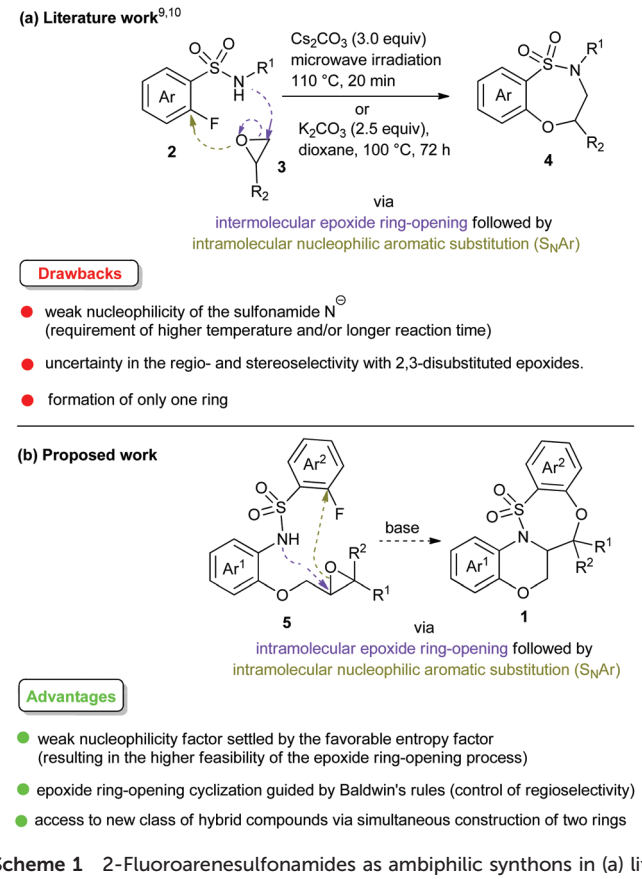
†Electronic supplementary information (ESI) available: Experimental details, X-ray crystallographic data, figures of ^1H, ^{13}C and ^{19}F NMR spectra, and HRMS. CCDC 1966259. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9ob02377a

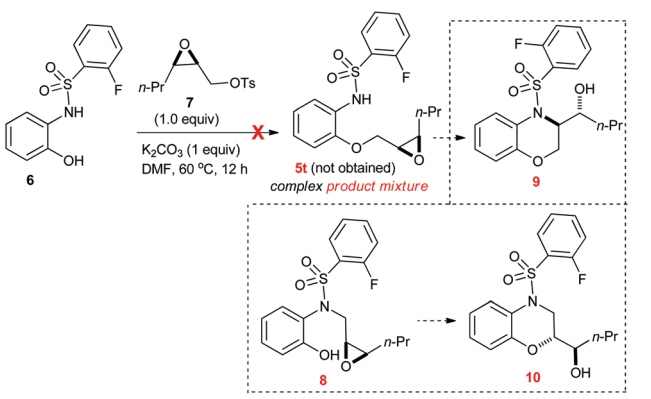
However, the synthesis of hybrid molecules by the combination of these two privileged scaffolds remains unreported, despite holding great potential to furnish compounds of new biological profiles. More specifically, synthetic studies to construct benzothiaoxazepine-1,1-dioxide fused 3,4-dihydro-2*H*-1,4-benzoxazines such as **1** (Fig. 1c) remain elusive. From the vantage point of interest in both synthetic and medicinal chemistry settings, access to such hybrid compounds is highly desirable.

Meanwhile, in 2010, the research groups of Hanson and Cleator almost simultaneously reported the synthesis of diverse benzosultams **4** using 2-fluoroarenesulfonamides **2** as ambiphilic synthons and terminal epoxides **3** as masked ambiphilic synthons under harsh reaction conditions and without addressing the issues of regio- and diastereoselectivity (Scheme 1a).[9,10] We felt that this 2-fluoroarenesulfonamide–epoxide pairing strategy should be studied further in organic synthesis to explore the unaddressed issues and could be implemented in an intramolecular one-pot double cyclization fashion to access fused benzosultams like **1** from glycidyl ether-tethered 2-fluoroarenesulfonamide **5** (Scheme 1b). Herein, we present the realization of this novel concept.

At the beginning, we focused on the development of an effective synthetic route for the double-cyclization precursors **5**. However, in contrast to the synthesis of substrates for the intermolecular 2-fluoroarenesulfonamide–epoxide pairing strategy (Scheme 1a), we believed that accomplishing this task for its intramolecular counterpart (Scheme 1b) would not be as simple as it might seem, since it would need tethering of two reactive ambiphilic synthons in a single molecule. For example, when we attempted the synthesis of **5t** from compound **6** using epoxy tosylate **7** under typical K_2CO_3-mediated monoalkylation reaction conditions, we were disappointed to obtain a complex product mixture (Scheme 2). This failure to obtain **5t** as a major isolated product might be attributed to the non-selective generation of sulfonamide N^- and phenoxide anions as nucleophiles, resulting in the formation of both *N*- and *O*-alkylated products (**5t** and **8**), which in turn might have undergone further intramolecular cyclization reactions to provide compounds **9** and **10**. Thus, the complex mixture possibly consisted of unreacted **6**, and compounds **5t** and **8–10**. Moreover, changing the base and other reaction parameters also did not bring any synthetically acceptable result. Therefore, at this stage, we were forced to use an alternative strategy involving a late-stage epoxidation strategy. Starting from 2-nitrophenol **11a**, first we conducted a three step reaction sequence involving sequential allylation/prenylation, chemoselective reduction of the NO_2 group and 2-fluorobenzenesulfonylation of the NH_2 group to swiftly generate epoxide-precursor **12a** in a high overall yield of 75% (Table 1, entry 1, column 7). However, epoxidation of **12a** using *m*-CPBA (1.15 equiv.) in CH_2Cl_2 at rt failed miserably, resulting in a complete recovery of **12a** (not shown in Table 1). This observation is consistent with the absence of literature reports (to our knowledge) on the epoxidation of aryl allyl ethers bearing an *ortho*-benzenesulfonamide moiety with *m*-CPBA. The exact reason for the observed unreactivity is unclear at present, but possibly the sulfonamide moiety has a detrimental effect. Delightfully, however, epoxidation of **12a** using excess *m*-CPBA (2.5 equiv.) and under more forcing reaction conditions in 1,2-dichloroethane (DCE) at 80 °C generated **5a**, albeit in a moderate yield of 65% (Table 1, entry 1, column 8). Nevertheless, additional substrates **5b–p**, bearing substituents at different positions of the two benzene rings, were prepared following the optimized route (Table 1, entries 2–16).

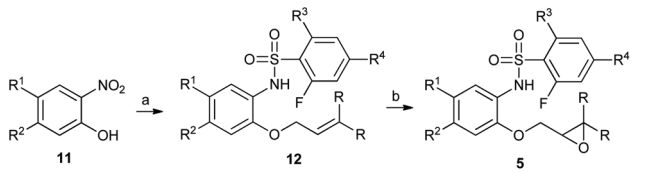


Scheme 1 2-Fluoroarenesulfonamides as ambiphilic synthons in (a) literature reports and (b) our proposed work.



Scheme 2 Attempted synthesis of **5t**.

Table 1 Synthesis of epoxide substrates of **5** [a]

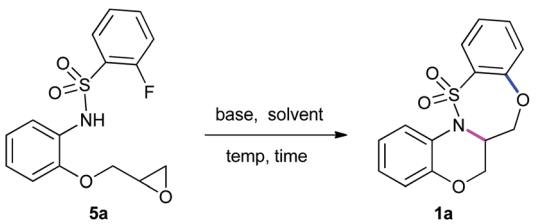


Entry	R	R^1	R^2	R^3	R^4	Yield[b]	
1	H	H	H	H	H	**12a** (75%)	**5a** (65%)
2	H	H	H	H	F	**12b** (74%)	**5b** (62%)
3	H	H	H	F	H	**12c** (71%)	**5c** (64%)
4	Me	H	H	H	H	**12d** (75%)	**5d** (75%)
5	Me	H	H	H	F	**12e** (73%)	**5e** (73%)
6	Me	H	H	F	H	**12f** (70%)	**5f** (72%)
7	H	Me	H	H	H	**12g** (69%)	**5g** (62%)
8	H	Me	H	H	F	**12h** (70%)	**5h** (64%)
9	Me	H	Me	H	H	**12i** (71%)	**5i** (70%)
10	Me	H	Me	H	F	**12j** (69%)	**5j** (72%)
11	Me	H	Me	F	H	**12k** (68%)	**5k** (70%)
12	Me	H	Me	H	Br	**12l** (70%)	**5l** (73%)
13	Me	OMe	H	H	H	**12m** (71%)	**5m** (74%)
14	Me	OMe	H	H	F	**12n** (75%)	**5n** (74%)
15	Me	Br	H	H	H	**12o** (73%)	**5o** (71%)
16	Me	Br	H	H	F	**12p** (74%)	**5p** (69%)

[a] Reaction conditions: (a) (i) allyl/prenyl bromide, K_2CO_3, acetone, 65 °C, 12 h; (ii) Fe powder, NH_4Cl, $EtOH/H_2O$, reflux, 2 h; (iii) 2-fluorobenzenesulfonyl chlorides, pyridine, 12 h. (b) *m*-CPBA (2.5 equiv.), DCE, 80 °C, 12 h. [b] The values in parentheses indicate the isolated yields.

From here, we chose compound **5a** as the model substrate for screening bases and optimizing the reaction conditions required for probing the envisioned double cyclization reaction. The results are summarized in Table 2.

Table 2 Screening of the reaction conditions for the one-pot double-cyclization of **5a** [a]



Entry	Base (equiv.)	Solvent	Temp. (°C)	Time (h)	Yield[b] (%)
1	K_2CO_3 (1.5)	MeCN	rt	16	nr[c]
2	K_2CO_3 (1.5)	MeCN	80	16	20
3	K_2CO_3 (1.5)	Dioxane	80	16	22
4	K_2CO_3 (1.5)	DMF	80	16	24
5	Cs_2CO_3 (1.5)	Dioxane	80	16	35
6	Cs_2CO_3 (1.5)	DMF	80	16	42
7	**NaH (1.5)**	**DMF**	**rt**	**4**	**85**
8	NaH (1.5)	DMF	80	4	67
9	NaH (0.5)	DMF	rt	6	40

[a] All reactions were conducted with 0.2 mmol of **5a** in 2.0 mL of solvent. [b] The values in parentheses indicate the isolated yields. [c] No reaction.

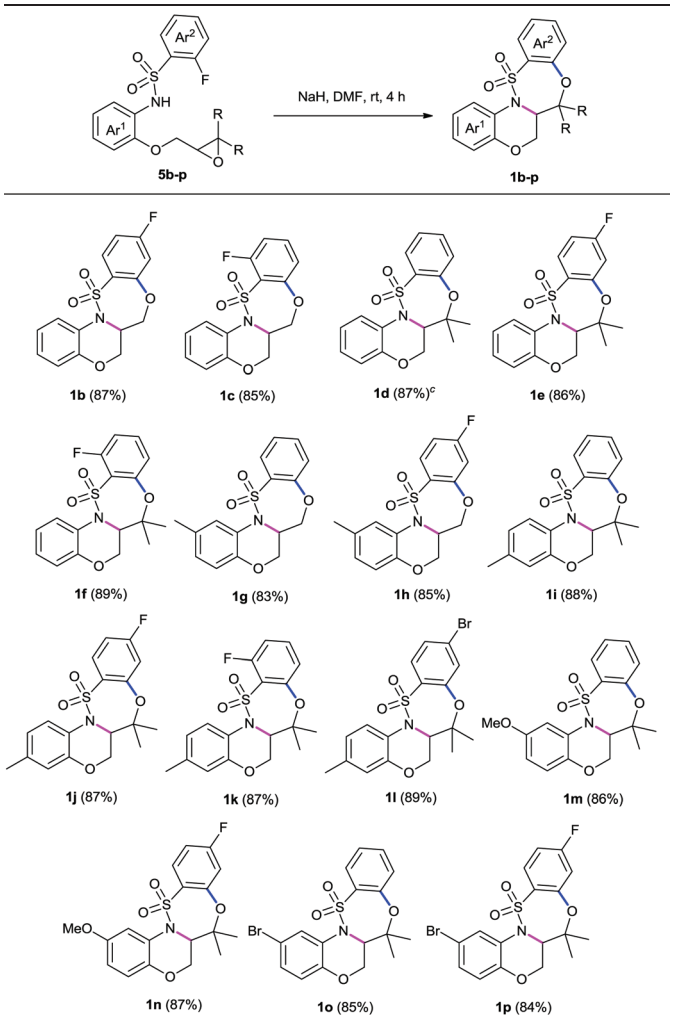
The reaction was initially conducted in the presence of anhydrous K_2CO_3 (1.5 equiv.) as a base in acetonitrile (MeCN) at room temperature for 16 h. The desired product **1a** was not detected under these conditions (Table 2, entry 1). However, increasing the reaction temperature to 80 °C afforded **1a**, albeit in a poor yield of 20% (entry 2). Changing the solvent to 1,4-dioxane (entry 3) or DMF (entry 4) failed to show any significant improvements. At 80 °C, the use of stronger and more soluble but expensive base Cs_2CO_3 (1.5 equiv.) in 1,4-dioxane (entry 5) or DMF (entry 6) resulted in improved but still synthetically unsatisfactory yields. Next, we attempted to utilize strong bases to facilitate the present domino transformation in a more efficient way. Delightfully, the treatment of **5a** with NaH (1.5 equiv.) in DMF at rt for 4 h gave **1a** in 85% yield (entry 7). It is worth mentioning that with NaH (1.5 equiv.) as the base, increasing the reaction temperature to 80 °C (entry 8) decreased the yield, as did decreasing the amount of NaH to 0.5 equiv. at rt (entry 9). Thus, the use of NaH (1.5 equiv.) as the base in DMF at rt for 4 h (Table 2, entry 7) proved to be the best choice among all the conditions that we employed for the optimization studies.

With the optimized conditions in hand, we set out to investigate the substrate scope of the reaction using the remaining substrates **5b–p** (Table 3). The electronic effect of the substituent on the Ar^1-ring did not significantly affect the reaction efficiency as evidenced by the fact that substrates **5g–n** bearing an electron-donating methyl or methoxy group or substrates **5o** and **5p** with an electron-withdrawing bromo substituent on the Ar^1-ring were transformed smoothly into the corresponding tetracyclic hybrid compounds (Table 3, products **1g–p**). We also observed similar efficiency of the reaction with the introduction of additional F or Br atoms on the Ar^2-ring (products **1b** and **1c**, **1e** and **1f**, **1h**, **1j–l**, and **1n** and **1p**). Products bearing a Br-substituent (**1l**, **1o** and **1p**) hold great potential for further derivatization using diverse palladium-catalyzed coupling chemistry. Similarly, products bearing a fluoro-substituent at the *ortho*- or *para*-position with respect to the electron withdrawing sulfonamide group (products **1b** and **1c**, **1e** and **1f**, **1h**, **1j** and **1k**, and **1n** and **1p**) should be useful in further elaboration *via* the intermolecular S_NAr reaction protocol.[8] Nevertheless, when the H atoms at the alkene terminus were changed to methyl groups, no significant changes in the product yields were observed (products **1d–f** and **1i–p**). This indicates that the reaction efficiency was insensitive to the steric hindrance of the geminal methyl groups around the *in situ* generated alkoxy moiety.

Meanwhile, to demonstrate the synthetic practicality of this intramolecular one-pot double-cyclization method, a scale-up experiment with 5.0 mmol of **5d** was performed, affording the desired product **1d** in 78% yield.

It is to be mentioned that the structures of tetracyclic products **1a–p** were confirmed by the ^1H NMR, ^{13}C NMR and HRMS data. X-ray single-crystal diffraction analysis of representative compound **1l** was performed to further confirm their structures (Fig. 2).

Table 3 Substrate scope of the intramolecular one-pot double-cyclization of **5a** [a,b]



[a] Reactions were conducted with 0.2 mmol of **5b–p** in 2.0 mL of DMF at rt under a N_2 atmosphere. [b] The values in parentheses indicate the isolated yields. [c] 78% yield was observed when the reaction was conducted with 5 mmol of **5d**.

Now, our methodology in principle should be applicable to benzothiaoxazepine-1,1-dioxides fused to various other azaheterocycles such as pyrrolidines, piperidines, indolines, tetrahydroquinolines *etc*. To delineate one of many such possibilities, we further extended the strategy to the synthesis of indoline-fused benzothiaoxazepine-1,1-dioxides (Scheme 3). Thus, compound **13** was converted into epoxides **5q–s** *via* intermediate alkenes **12q–s** following a sequential chemoselective NO_2-reduction–2-fluorophenylsulfonylation–epoxidation reaction sequence (Scheme 3). The intramolecular one-pot double-cyclization of **5q–s** proceeded efficiently under the standard conditions, affording indoline-fused benzothiaoxazepine-1,1-dioxides **12q–s** in high isolated yields.

Although we could successfully carry out the double cyclization, we sensed that the incorporation of a stereodefined epoxide moiety into the substrate might be troublesome owing to the already-described difficulty in the late stage epoxidation process. Thus, despite our initial failure as shown in Scheme 1, the focus of our study then turned back again towards the desire of using a preformed epoxide building block in the synthesis. Along this line, we performed alkylation of **11a** with epoxy tosylate **7** furnishing **14** in excellent yield (Scheme 4). Chemoselective reduction of the NO_2 group of **14** under transfer hydrogenation conditions (Et_3SiH, Pd–C)[11] followed by 2-fluorobenzenesulfonylation of the resulting crude amine provided the corresponding glycidyl ether-tethered 2-fluoroarenesulfonamide **5t** which, without purification, was treated with NaH under the optimized reaction conditions to afford the corresponding diastereomerically pure tetracyclic product **1t** in a high overall yield.

In summary, we have established a base-mediated one-pot double cyclization of glycidyl ether-tethered 2-fluoroarenesulfonamides to furnish 1,4-benzoxazine-fused benzothiaoxazepine-1,1-dioxides as a new class of hybrid compounds. Mechanistically, the reaction involves an intramolecular epoxide ring-opening followed by an intramolecular nucleophilic aromatic substitution – a scenario unprecedented in the chemical literature. The notable features of this protocol com-

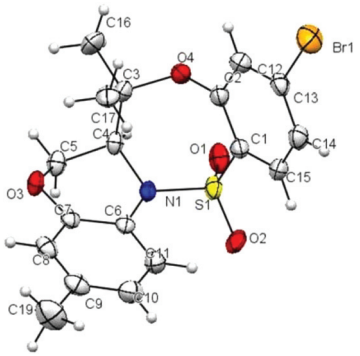
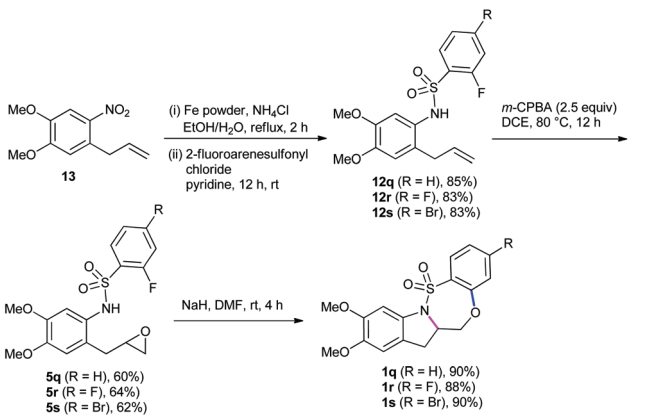
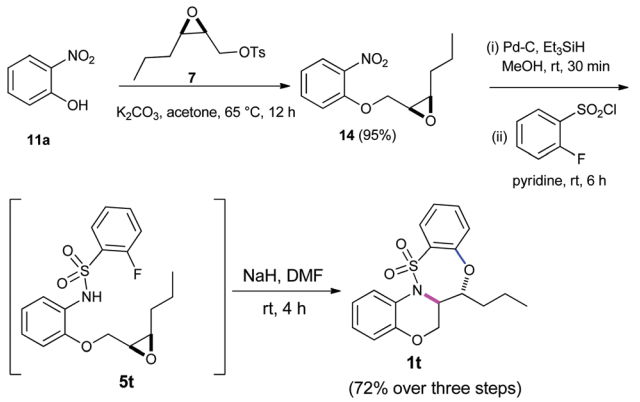


Fig. 2 ORTEP diagram of compound **1l** as determined by X-ray analysis (ellipsoid contour probability, 35%).



Scheme 3 Synthesis of indoline-fused benzothiaoxazepine-1,1-dioxides.



Scheme 4 Diastereoselective synthesis of **1t**.

prise mild conditions, a broad substrate scope (multiple diversification points), complete regio- and diastereoselectivity, and high yields.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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