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Letter

Synthetic Approach toward Enantiopure Cyclic Sulfinamides

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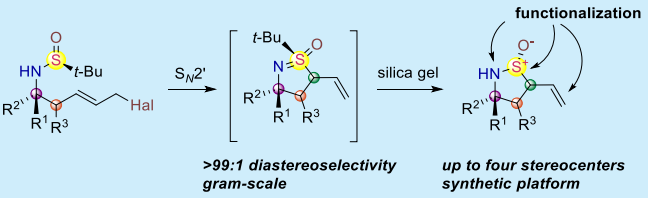
ABSTRACT: A synthetic approach toward densely substituted enantiopure cyclic sulfinamides possessing up to four consecutive stereogenic centers was developed based on a completely diastereoselective S_N2' cyclization/*tert*-Bu cleavage sequence. Diastereospecific transformation of the obtained scaffold into chiral S^{VI} derivatives such as sulfoximines and sulfonimidamides is demonstrated.



General utility of sulfinamides[1] may be largely obscured by the amount and versatility of synthetic applications[2] developed around Ellman's and Davis' chiral auxiliaries (Figure 1). Yet the sulfinamide moiety has also found use in asymmetric

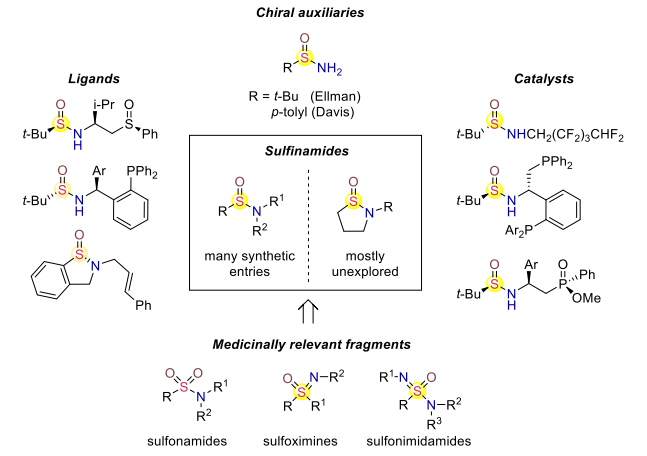
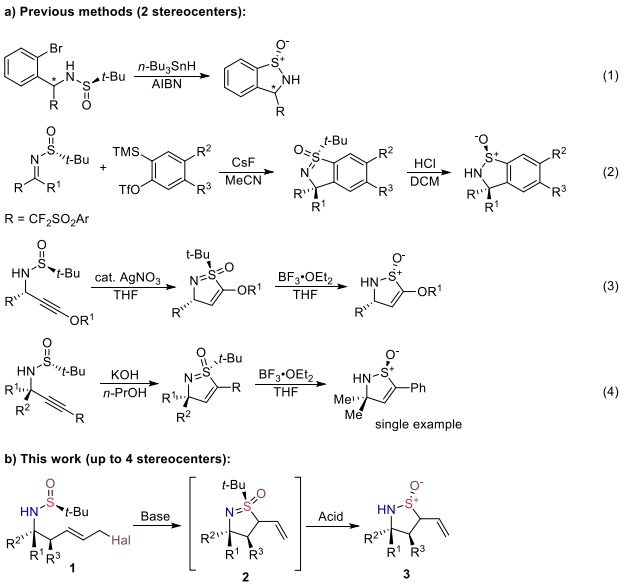


Figure 1. Utility of enantiopure sulfinamides.

synthesis as an integral part of organocatalysts[3] and ligands in metallocatalysis.[4] Although underappreciated[5] as structural fragments in drug discovery, sulfinamides have been established as a convenient synthetic platform[6] for more medicinally acknowledged sulfonamides and chiral S^{VI}-compounds. In particular, recently developed stereoselective methodologies toward increasingly more popular[7] sulfoximines and sulfonimidamides rely on enantiopure sulfinamides as synthetic precursors.[8] The fact that the general value of enantiopure sulfinamides has been long recognized is eloquently demonstrated by the sheer effort dedicated to their preparation over the years.[9]

However, despite a considerably wide scope existing entries are generally[10] inapplicable to cyclic structures. Hence the library of known enantiopure cyclic sulfinamides so far is limited to six- and five-membered congeners. Whereas the former have been approached[11] via hetero Diels–Alder reaction of *N*-sulfinyl dienophiles, the latter have been obtained[12] exclusively from Ellman's sulfinamide derivatives (Scheme 1a) exploiting the lability of the *t*-Bu-substituent. Thus, the susceptibility of the *t*-Bu-group to radical scission was used in the synthesis of benzo-fused scaffolds.[12a] Radical S_Hi substitution at the S-atom directly delivers sulfinamides with configurational inversion at the *S*-

Scheme 1. Entries toward Enantiopure Five-Membered Cyclic Sulfinamides



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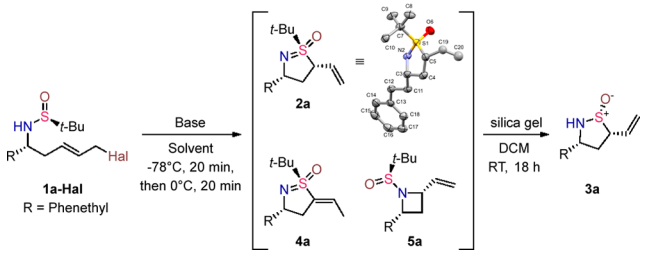
stereocenter (eq 1, Scheme 1a). The rest of the known methods are based on stereoretentive acid-induced cleavage of *S-tert*-butylated sulfoximines. The sulfoximines in turn have been synthesized via [3 + 2] cycloaddition of *N*-sulfinyl imines with benzynes (eq 2),[12b,c] $AgNO_3$-catalyzed cyclization[12d] of ynol ethers (eq 3), and base-mediated cyclization[12e] of acetylenes (eq 4, Scheme 1a).

The common feature of the listed approaches consists of the limited capacity to introduce new stereocenters due to unsaturation dictated by the structure of the substrate. On the other hand, denser stereodefined substitution would be not only highly desirable by modern diversity-oriented synthesis[13] but also rather realistic considering the richness of chemistry[2a] around Ellman's auxiliary. Therefore, we envisioned a transformation starting with a novel 5-*exo*-*trig* cyclization of sulfinamides **1** to sulfoximines **2** (Scheme 1b). The intended *S*-allylation via S_N2' substitution would simultaneously install a new stereocenter and a synthetically useful vinyl handle. Subsequently, already well precedented *t*-Bu-removal would deliver sulfinamides **3** potentially accommodating up to four consecutive stereocenters. Previous success[14] in *S*-alkylation of *N*-alkyl *t*-Bu-sulfinamides added soundness to the hypothesis and encouraged us to put it to practical scrutiny.

The investigation began with the cyclization of the iodide **1a-I** (Table 1). Gratifyingly, deprotonation of **1a-I** with non-

Table 1. Optimization of Reaction Conditions[a]



Entry	Hal	Base	Solvent	2a (%)[b]	4a (%)[b]	5a (%)[b]	3a (%)[c]
1	I	NaH	THF	60	5		
2	I	LiHMDS[d]	THF	20	5	20	
3	I	NaHMDS[d]	THF	64	4		60
4	I	KHMDS[d]	THF	18	36		
5	I	NaHMDS[d]	Et_2O	62	4		
6	I	NaHMDS[d]	DCM	79			
7	I	NaHMDS[d]	Toluene	80			75
8	I	NaHMDS[e]	Toluene	85			80
9	Br	NaHMDS[e]	Toluene	84			80
10	Cl	NaHMDS[e]	Toluene	71			
11	Cl	KOH	DMA		26	57	

[a]Performed on 0.15 mmol scale with 2.2 equiv of base in 15 mL of solvent. [b]^{1}H NMR yield measured against mesitylene as internal standard. [c]Isolated yield. [d]In THF. [e]In toluene.

nucleophilic NaH indeed led to the requisite sulfoximine **2a** in moderate yield accompanied by the isomeric **4a** (entry 1). More importantly **2a** was formed as a single diastereomer, and its structure could be unambiguously determined by X-ray crystallographic analysis. Configuration of the S-atom in **2a** was apparently retained with respect to the precursor **1a-I**, while the newly installed vinyl opposed the *t*-Bu-group. On the other hand, independent conversion of **2a** to **4a** upon exposure to NaH ascertained that deprotonation at the allylic position should be responsible for the observed isomerization. While attempting chromatographic purification of **2a**, we also determined that the intended *t*-Bu-cleavage leading to sulfinamide **3a** is quite facile and can be accomplished with as weak an acid as silica gel. Therefore, the outcome of subsequent cyclization experiments was assessed by ^{1}H NMR and sulfinamide **3a** was isolated only in selected entries.

In order to explore the counterion effect we switched to hexamethyldisilamide bases conveniently available as THF solutions (Table 1, entries 2−4). Reaction with LiHMDS reflected the usual[15] propensity of sulfinamides for *N*-alkylation manifested in formation of azetidine **5a**. While KHMDS produced a dramatically increased amount of isomerization, NaHMDS performed similarly to NaH. The degree of NaHMDS aggregation has been reported to depend significantly on the solvent.[16] Therefore, we speculated that excessive basicity leading to poorly separable **4a** could be mitigated by weaker coordinating media (entries 5−7). Although Et_2O failed to improve the situation, DCM and toluene performed equally well affording **2a** with markedly improved yields without formation of **4a**. Additional improvement was obtained by complete exclusion of THF from the reaction media utilizing NaHMDS in toluene (entry 8). Thus, the yield of the intermediate **2a** was increased to 85% and subsequent *t*-Bu-cleavage delivered sulfinamide **3a** with 80% yield. Finally, bromide **1a-Br** was found to be an equally competent substrate in the cyclization (entry 9), while chloride **1a-Cl** displayed slightly inferior behavior (entry 10). Interestingly, the selectivity of cyclization with **1a-Cl** could be largely reversed in favor of *N*-alkylation (entry 11).

In view of the limited stability of allylic iodides, the scope of the transformation was explored using bromide substrates **1-Br** (Scheme 2). Excellent reactivity was observed in the case of monoalkyl substituted **1a−d-Br**. Aryl containing precursors **1e−g-Br** were also efficiently converted to the corresponding sulfinamides **3e−g**. The crystal structure[17] obtained for **3e** decisively confirmed the stereoretentive character of the *t*-Bu-cleavage. Notably, the developed standard conditions were successfully applied in a gram-scale synthesis of **3g**. However, for reasons not fully understood heteroaryl-containing sulfinamides **3h,i** were obtained with considerably lower yields. Quaternary centers in **3j,k** and additional substitution at the double bond in **3l** were found to be a small hurdle for the transformation. Importantly, no loss of enantiopurity could be detected in the corresponding conversion of **1k-Br** to **3k**. Furthermore, the crystal structure obtained for **3k** mirrored *syn S-O* and vinyl alignment already established for **3e**. Successful preparation of sulfinamide **3m** conformed well to our declared aim at densely substituted structures.

Finally, transformation of epimers *epi*-**1a-Br** and *epi*-**1d-Br** addressed the influence of stereocenters next to the N-atom. The respective sulfinamides *iso*-**3a** and *epi*-**3d** were obtained with the *anti* arrangement of the vinyl and *α*-*N*-substituent contrary to **3a** and **3d**. Complementary to the case of **3k**, this observation concludes that the new stereocenter must be controlled solely by the initial configuration at the *S*-atom placing the vinyl *syn* to S−O in an entirely stereospecific manner. Of additional note may be the attempt to expand the cyclization scope to the 6-*exo*-*trig* mode using homologous substrate **6**. Despite favorable all equatorial positioning of substituents in the speculative *S*-alkylation product, only the five-membered *N*-alkylation **7** was obtained. This result suggests that the dominant *S*- instead of *N*-

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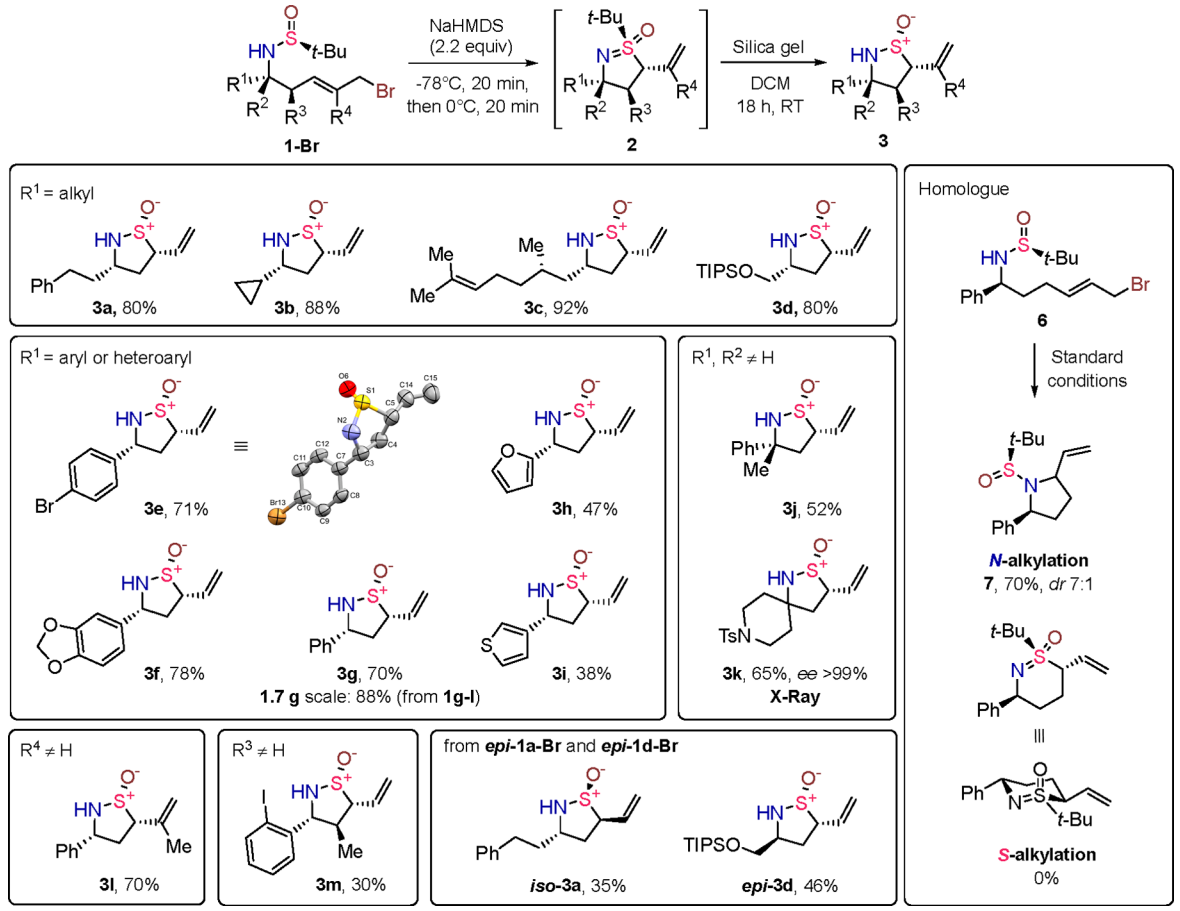
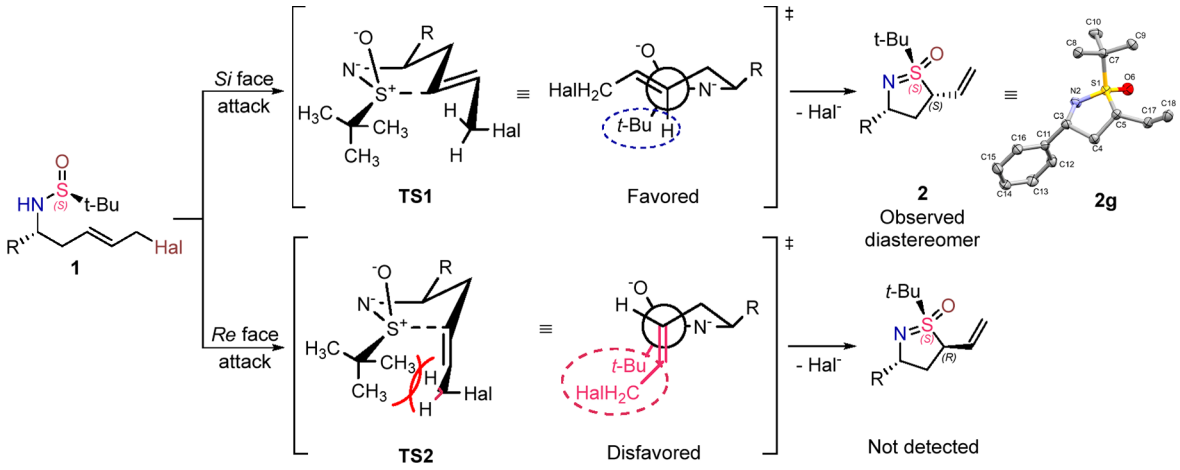
Scheme 2. Transformation Scope



Scheme 3. Stereochemical Model



alkylation in the case of substrates **1** is most likely determined by the typical kinetic preference[18] for five-membered cycles.

Analysis of the acquired data allowed us to devise a stereochemical model accounting for the net stereochemical outcome of the transformation (Scheme 3).[19] The envelope geometry of the transition state proposed for the cyclization step may be derived from the crystal structures obtained for sulfoximines **2a** and **2g**. Nucleophilic *Si* attack of the S-lone pair on the double bond of **1** leads to the favored **TS1** and consequently to **2** with the vinyl opposed to the *t*-Bu-group. Subsequent stereoretentive removal of the latter affords sulfinamides **3** with the observed *syn* vinyl and S−O arrangement. Conversely, *Re* attack would result in congested **TS2** featuring pronounced steric clash between the *t*-Bu-group and the halomethylene unit of **1**. Hence, the corresponding *anti* vinyl and S−O alignment has not been detected in either sulfoximines **2** or sulfinamides **3**.

Since the chemistry of cyclic sulfinamides like **3** is scarcely presented in literature, we decided to screen the behavior of the obtained scaffold in relevant synthetic transformations using **3g** as a typical representative (Scheme 4). Thus, chemoselective *S*-oxidation[20] delivered sulfonamide **8**, which belongs to the class

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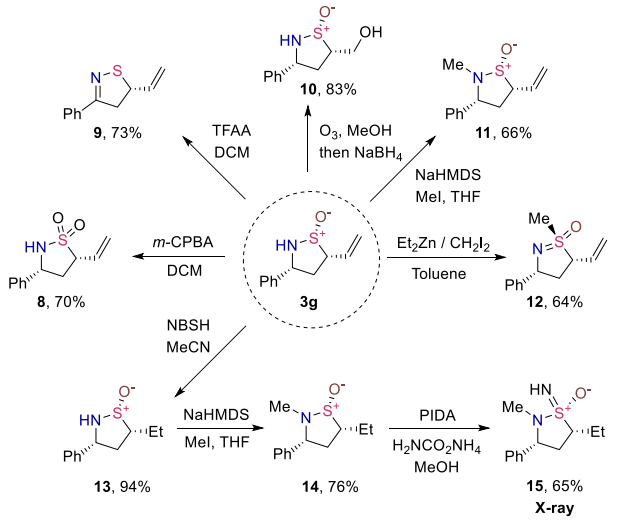
Scheme 4. Synthetic Modifications of the Product Scaffold



of medicinally privileged γ-sultams.[21] Another modification at the S-atom resulted in sulfenimine **9** in the course of a Pummerer-like reaction.[22] The reactivity of the double bond was probed in reductive ozonolysis cleanly affording **10**. In spite of the previously noted base-induced isomerization of **2a**, *N*-alkylation of **3g** leading to **11** could be accomplished with a synthetically useful yield. As an alternative option to utilize the double bond in **3g** we considered Simmons−Smith cyclopropanation.[23] Surprisingly, the respective fairly standard conditions delivered sulfoximine **12** as the major product rather than the expected cyclopropane. The single comparable example of such atypical reactivity was reported by Zercher et al. and regarded primarily as an undesirable synthetic obstacle.[24] Meanwhile, intrigued by the chemo- and stereospecificity observed in the formation of **12** we plan to explore this valuable transformation in greater detail. Further modifications of **3g** included diimide reduction[25] to **13**, which in turn was smoothly converted to the tertiary sulfinamide **14**. Finally, electrophilic NH transfer under reported conditions[26] resulted in stereospecific formation of sulfonimidamide **15** with anticipated configurational retention at S-atom as confirmed by X-ray crystallographic analysis.

In summary, the transformation presented herein opens access to enantiopure sulfinamide scaffold **3** via a facile cyclization−deprotection sequence. The cyclization proceeds with retention of configuration at the S-atom and stereospecific introduction of the additional vinyl substituent, while subsequent mild deprotection completely preserves the installed stereochemical arrangement. These features enable synthesis of densely substituted structures accommodating up to four consecutive stereocenters. Complementary to the existing methods[12] our methodology considerably enriches the library of yet underexplored cyclic sulfinamides. Moreover, disclosed additional modifications at S- and N-atoms as well as at the vinyl handle suggest the promising potential of the obtained scaffold in synthetic and medicinal chemistry. Specific relevance for the latter is demonstrated by preparation of γ-sultam **8**, sulfoximine **12**, and sulfonimidamide **15**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c01738.

Experimental procedures, analytical and spectroscopic data for new compounds, copies of NMR spectra, and X-ray crystallographic data for **2a**, **2g**, **3e**, **3k**, and **15** (PDF)

Accession Codes

CCDC 2173342−2173346 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

During the preparation of this manuscript, a complementary methodology toward cyclic sulfinamides via radical cyclization was reported by Chen, Y.; Wu, X.; Yang, S.; Zhu, C. Asymmetric Radical Cyclization of Alkenes by Stereospecific Homolytic Substitution of Sulfinamides. *Angew. Chem., Int. Ed.* **2022**, *Just Accepted*: anie.202201027.

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■ REFERENCES

(1) Zhang, Q.; Xi, J.; Ze, H.; Qingle, Z. Syntheses and Transformations of Sulfinamides. *Synthesis* **2021**, *53*, 2570−2582.

(2) (a) Robak, M. T.; Herbage, M. A.; Ellman, J. A. Synthesis and Applications of *Tert*-Butanesulfinamide. *Chem. Rev.* **2010**, *110*, 3600−3740. (b) Davis, F. A. Adventures in Sulfur−Nitrogen Chemistry. *J. Org. Chem.* **2006**, *71* (24), 8993−9003.

(3) For a comprehensive review, see: (a) Otocka, S.; Kwiatkowska, M.; Madalińska, L.; Kiełbasiński, P. Chiral Organosulfur Ligands/Catalysts with a Stereogenic Sulfur Atom: Applications in Asymmetric Synthesis. *Chem. Rev.* **2017**, *117*, 4147−4181. (b) Zhou, W.; Su, X.; Tao, M.; Zhu, C.; Zhao, Q.; Zhang, J. Chiral Sulfinamide Bisphosphine

Catalysts: Design, Synthesis, and Application in Highly Enantioselective Intermolecular Cross-Rauhut−Currier Reactions. *Angew. Chem., Int. Ed.* **2015**, *54*, 14853−14857.

(4) (a) Borrego, L. G.; Recio, R.; Álvarez, E.; Sánchez-Coronilla, A.; Khiar, N.; Fernández, I. Steric Tuning of Sulfinamide/Sulfoxides as Chiral Ligands with C_1, Pseudo- *Meso*, and Pseudo-C_2 Symmetries: Application in Rhodium(I)-Mediated Arylation. *Org. Lett.* **2019**, *21*, 6513−6518. (b) Wen, Q.; Zhang, L.; Xiong, J.; Zeng, Q. A New Type of Chiral Cyclic Sulfinamide−Olefin Ligands for Rhodium-Catalyzed Asymmetric Addition. *Eur. J. Org. Chem.* **2016**, *2016*, 5360−5364. (c) Zhang, Z.-M.; Chen, P.; Li, W.; Niu, Y.; Zhao, X.-L.; Zhang, J. A New Type of Chiral Sulfinamide Monophosphine Ligands: Stereodivergent Synthesis and Application in Enantioselective Gold(I)-Catalyzed Cycloaddition Reactions. *Angew. Chem., Int. Ed.* **2014**, *53*, 4350−4354.

(5) Single example of biological activity: Finn, P., Charlton, M., Edmund, G., Jirgensons, A., Loza, E. WO2018065611A1, 2018.

(6) Wojaczyńska, E.; Wojaczyński, J. Modern Stereoselective Synthesis of Chiral Sulfinyl Compounds. *Chem. Rev.* **2020**, *120*, 4578−4611.

(7) For the utility of sulfoximines and sulfonimidamides in medicinal and agricultural chemistry, see: (a) Mäder, P.; Kattner, L. Sulfoximines as Rising Stars in Modern Drug Discovery? Current Status and Perspective on an Emerging Functional Group in Medicinal Chemistry. *J. Med. Chem.* **2020**, *63*, 14243−14275. (b) Han, Y.; Xing, K.; Zhang, J.; Tong, T.; Shi, Y.; Cao, H.; Yu, H.; Zhang, Y.; Liu, D.; Zhao, L. Application of Sulfoximines in Medicinal Chemistry from 2013 to 2020. *Eur. J. Med. Chem.* **2021**, *209*, 112885. (c) Frings, M.; Bolm, C.; Blum, A.; Gnamm, C. Sulfoximines from a Medicinal Chemist's Perspective: Physicochemical and in Vitro Parameters Relevant for Drug Discovery. *Eur. J. Med. Chem.* **2017**, *126*, 225−245. (d) Chinthakindi, P. K.; Naicker, T.; Thota, N.; Govender, T.; Kruger, H. G.; Arvidsson, P. I. Sulfonimidamides in Medicinal and Agricultural Chemistry. *Angew. Chem., Int. Ed.* **2017**, *56*, 4100−4109.

(8) (a) Aota, Y.; Kano, T.; Maruoka, K. Asymmetric Synthesis of Chiral Sulfoximines through the S-Alkylation of Sulfinamides. *Angew. Chem., Int. Ed.* **2019**, *58*, 17661−17665. (b) Greed, S.; Briggs, E. L.; Idiris, F. I. M.; White, A. J. P.; Lücking, U.; Bull, J. A. Synthesis of Highly Enantioenriched Sulfonimidoyl Fluorides and Sulfonimidamides by Stereospecific Sulfur−Fluorine Exchange (SuFEx) Reaction. *Chem.—Eur. J.* **2020**, *26*, 12533−12538. (c) Feng, J.; Liu, H.; Yao, Y.; Lu, C.-D. Synthesis of Enantioenriched Primary *Tert*-Butanesulfonimidamides via Imination−Hydrazinolysis of *N′-Tert* -Butanesulfinyl Amidines. *J. Org. Chem.* **2022**, *87*, 5005−5016.

(9) (a) For methods based on asymmetric S-oxidation, biocatalytic resolution and the use of chiral auxiliaries, see ref 6. Sulfinamides via catalytic asymmetric preparation of alkyl sulfinates followed by amidation: (b) Zhang, X.; Ang, E. C. X.; Yang, Z.; Kee, C. W.; Tan, C.-H. Synthesis of Chiral Sulfinate Esters by Asymmetric Condensation. *Nature* **2022**, *604*, 298−303.

(10) Except for a single example of asymmetric S-oxidation of a six-membered sulfenimine: Guigen, L., Yucheng, W., Xiao, H. CN1537851 A, 2004.

(11) (a) Endeshaw, M. M.; Bayer, A.; Hansen, L. K.; Gautun, O. R. Catalytic Asymmetric Hetero Diels−Alder Reactions of N-Sulfinyl Dienophiles with Chiral Bis(Oxazoline)Copper(II) and -Zinc(II) Triflates. *Eur. J. Org. Chem.* **2006**, *2006*, 5249−5259. (b) Remiszewski, S. W.; Yang, J.; Weinreb, S. M. Enantioselective N-Sulfinyl Dienophile Diels-Alder Cycloadditions. *Tetrahedron Lett.* **1986**, *27*, 1853−1856.

(12) (a) Fernández-Salas, J. A.; Rodríguez-Fernández, M. M.; Maestro, M. C.; García-Ruano, J. L. Stereochemical Aspects and the Synthetic Scope of the S H i at the Sulfur Atom. Preparation of Enantiopure 3-Substituted 2,3-Dihydro-1,2-Benzoisothiazole 1-Oxides and 1,1-Dioxides. *Chem. Commun.* **2014**, *50*, 6046−6048. (b) Rong, J.; Ni, C.; Gu, Y.; Hu, J. Synthesis of Enantiopure Benzo Fused Cyclic Sulfoximines Through Stereoselective [3 + 2] Cycloaddition between *N-Tert* -Butanesulfinyl [(2-Pyridyl)Sulfonyl]-difluoromethyl Ketimines and Arynes. *Helv. Chim. Acta* **2021**, *104*, No. e2100019. (c) Ye, W.; Zhang, L.; Ni, C.; Rong, J.; Hu, J. Stereoselective [3 + 2] Cycloaddition of N-Tert-Butanesulfinyl Imines to Arynes Facilitated by a Removable $PhSO_2CF_2$ Group: Synthesis and Transformation of Cyclic Sulfoximines. *Chem. Commun.* **2014**, *50*, 10596−10599. (d) Cividino, P.; Verrier, C.; Philouze, C.; Carret, S.; Poisson, J. Accessing Enantiopure Endocyclic Sulfoximines Through Catalytic Cycloisomerization of Oxygenated Propargyl-Sulfinamides. *Adv. Synth. Catal.* **2019**, *361*, 1236−1240. (e) Aota, Y.; Maeda, Y.; Kano, T.; Maruoka, K. Efficient Synthesis of Cyclic Sulfoximines from N-Propargylsulfinamides through Sulfur−Carbon Bond Formation. *Chem.—Eur. J.* **2019**, *25*, 15755−15758. (f) Feng, J.; Liu, H.; Yao, Y.; Lu, C.-D. Mannich-Type Reaction of α-Sulfanyl *N-Tert*-Butanesulfinylimidates: Diastereoselective Access to α-Mercapto-β-Amino Acid Derivatives. *J. Org. Chem.* **2021**, *86*, 3049−3058. (g) Hsung, R. P.; Wang, X.-N.; Fox, S. K.; Qi, R.; Lv, M.-C. Synthesis of de Novo Chiral γ-Amino-Ynamides Using Lithiated Ynamides. Observation of a Unique 5-Endo-Dig Cyclization with an Inversion of S-Center. *Heterocycles* **2014**, *88*, 1233−1254.

(13) Galloway, W. R. J. D.; Isidro-Llobet, A.; Spring, D. R. Diversity-Oriented Synthesis as a Tool for the Discovery of Novel Biologically Active Small Molecules. *Nat. Commun.* **2010**, *1*, 80.

(14) (a) Martjuga, M.; Belyakov, S.; Liepinsh, E.; Suna, E. Asymmetric Synthesis of 1,3-Diamines. II: Diastereoselective Reduction of Atropisomeric *N-Tert* -Butanesulfinylketimines. *J. Org. Chem.* **2011**, *76*, 2635−2647. (b) Kazak, M.; Priede, M.; Shubin, K.; Bartrum, H. E.; Poisson, J.-F.; Suna, E. Stereodivergent Synthesis of Pseudotabersonine Alkaloids. *Org. Lett.* **2017**, *19*, 5356−5359.

(15) Mendes, J. A.; Costa, P. R. R.; Yus, M.; Foubelo, F.; Buarque, C. D. *N-Tert* -Butanesulfinyl Imines in the Asymmetric Synthesis of Nitrogen-Containing Heterocycles. *Beilstein J. Org. Chem.* **2021**, *17*, 1096−1140.

(16) (a) Woltornist, R. A.; Collum, D. B. Sodium Hexamethyldisilazide: Using $^{15}N-^{29}Si$ Scalar Coupling to Determine Aggregation and Solvation States. *J. Am. Chem. Soc.* **2020**, *142* (15), 6852−6855. (b) Woltornist, R. A.; Collum, D. B. Aggregation and Solvation of Sodium Hexamethyldisilazide: Across the Solvent Spectrum. *J. Org. Chem.* **2021**, *86*, 2406−2422.

(17) Thermal displacement ellipsoids are drawn at the 50% probability level and hydrogen atoms are omitted for clarity in X-ray crystal structures for **2a** (Table 1), **2g** (Scheme 3), and **3e** (Scheme 2).

(18) Di Martino, A.; Galli, C.; Gargano, P.; Mandolini, L. Ring-Closure Reactions. Part 23. Kinetics of Formation of Three- to Seven-Membered-Ring N-Tosylazacycloalkanes. The Role of Ring Strain in Small- and Common-Sized-Ring Formation. *J. Chem. Soc., Perkin Trans.* **1985**, *2*, 1345−1349.

(19) The same model may address lower yields of *iso*-**3a**/*epi*-**3d** compared to the epimeric **3a**/**3d**: see SI (page S2) for details.

(20) García Ruano, J.; Parra, A.; Yuste, F.; Mastranzo, V. Mild and General Method for the Synthesis of Sulfonamides. *Synthesis* **2008**, *2008*, 311−319.

(21) Okwuchukwu, P. M.; Bandyopadhyay, D. Medicinally Privileged Sultams: Synthesis and Mechanism of Action. *MRMC* **2021**, *20*, 2193−2206.

(22) Isola, M.; Ciuffarin, E.; Sagramora, L.; Niccolai, C. Pummerer-like Reaction of Sulphinamides. *Tetrahedron Lett.* **1982**, *23*, 1381−1384.

(23) Charette, A. B.; Beauchemin, A. Simmons−Smith Cyclopropanation Reaction. In *Organic Reactions*; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2001; pp 1−415.

(24) Jacobine, A. M.; Puchlopek, A. L. A.; Zercher, C. K.; Briggs, J. B.; Jasinski, J. P.; Butcher, R. J. Tandem Chain Extension−Mannich Reaction: An Approach to β-Proline Derivatives. *Tetrahedron* **2012**, *68*, 7799−7805.

(25) Marsh, B. J.; Carbery, D. R. One-Pot *o*-Nitrobenzenesulfonylhydrazide (NBSH) Formation−Diimide Alkene Reduction Protocol. *J. Org. Chem.* **2009**, *74* (8), 3186−3188.

(26) Izzo, F.; Schäfer, M.; Stockman, R.; Lücking, U. A New, Practical One-Pot Synthesis of Unprotected Sulfonimidamides by Transfer of Electrophilic NH to Sulfinamides. *Chem.—Eur. J.* **2017**, *23*, 15189−15193.

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