Harnessing strain-release driven reactivity of a chiral SuFEx reagent: Stereocontrolled access to sulfinamides, sulfonimidamides, and sulfoximines

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Abstract

Efforts aimed at enriching the chemical and structural diversity of small molecules have invigorated synthetic exploration in the last two decades. Spatially defined molecular functionality serves as the foundation to construct unique chemical space to further advance discovery science. The chiral SuFEx reagent *t*-BuSF provides a modular platform for the stereocontrolled bifunctionalization of sulfur. Here we report a third functional feature of *t*-BuSF enabled by carbamoyl torsional strain-release that further expands the S(IV) and S(VI) chemical space accessible as showcased in over seventy examples, multiple applications in medicinal chemistry, organocatalysis, and diversity-oriented synthesis. The methods presented herein allow for rapid asymmetric diversification around a stereodefined sulfur center with readily available building blocks, improving upon the current state-of-the-art for sulfinyl and sulfonimidoyl synthesis.
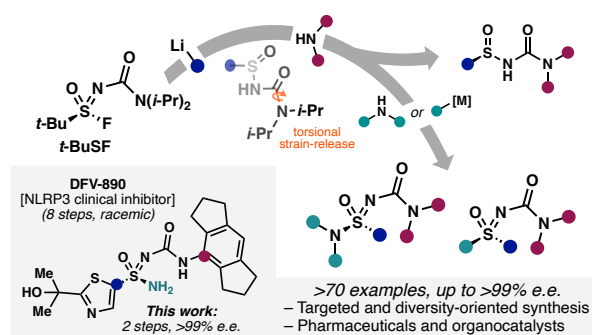
Introduction

Sulfur in its range of oxidation states is ubiquitous in nature and the modern industrial world. From the organosulfur compounds found in essential biomolecules such as amino acids (cysteine and methionine) and vitamins (biotin), to life saving antibiotics (penicillin) and antidiabetic medicines (glibenclamide), sulfur's rich chemical and structural diversity has profound impacts on all living organisms.[1-3] Sulfonylureas, such as glibenclamide, represent an important class of S(VI) functionality that are found in pharmaceuticals and agrochemicals (Figure 1A).[4-6] Recent medicinal chemistry efforts towards the investigation of bioisosteric replacement groups and the exploration of more sp³-rich chemical space have led to an increased interest in multi-dimensional groups such as sulfonimidoyls (**1**, **2**), the aza-derivatives of sulfonyls.[7-13] These S(VI) groups consist of an additional spatial vector and stereogenic sulfur center, have served as bioisoteres for carboxylic acids and sulfonamides,[7,14] and are known to have favorable physiochemical properties such as permeability and total polar surface area,[10-13] making them advantageous for pharmaceutical development.

One of the first bioactive sulfonimidoyl ureas was reported by Eli Lilly where the observed oncolytic activity was determined to be dependent on the *S*-chirality of **1**.[15] More recently, sulfonimidoyl ureas have taken center stage in the development of NLRP3 inhibitors as immunomodulators,[16] garnering attention from companies such as Genentech (**2**)[17] and Novartis (DFV-890)[18-20]—with DFV-890 currently under clinical evaluation in multiple USFDA trials.[21] In addition to promising therapeutics, the S(IV) derivatives have been developed as highly enantioselective organocatalysts for asymmetric aza-Henry reactions (**3**),[22] 1,4-conjugate additions,[23] and β-amino olefin reductions (**4**).[24,25]

Conventional synthetic approaches for sulfonyl and sulfonimidoyl ureas rely on the addition of the S(VI) functionality to isocyanates at the final stage of a synthesis, prohibiting subsequent derivatization at sulfur (Figure 1B).[15-20,26,27] The requisite sulfonimidamides are obtained as racemates through the S(VI) interconversion of *N*-protected sulfonamides (**5**) via deoxychlorination and amine addition,[28] or treatment with
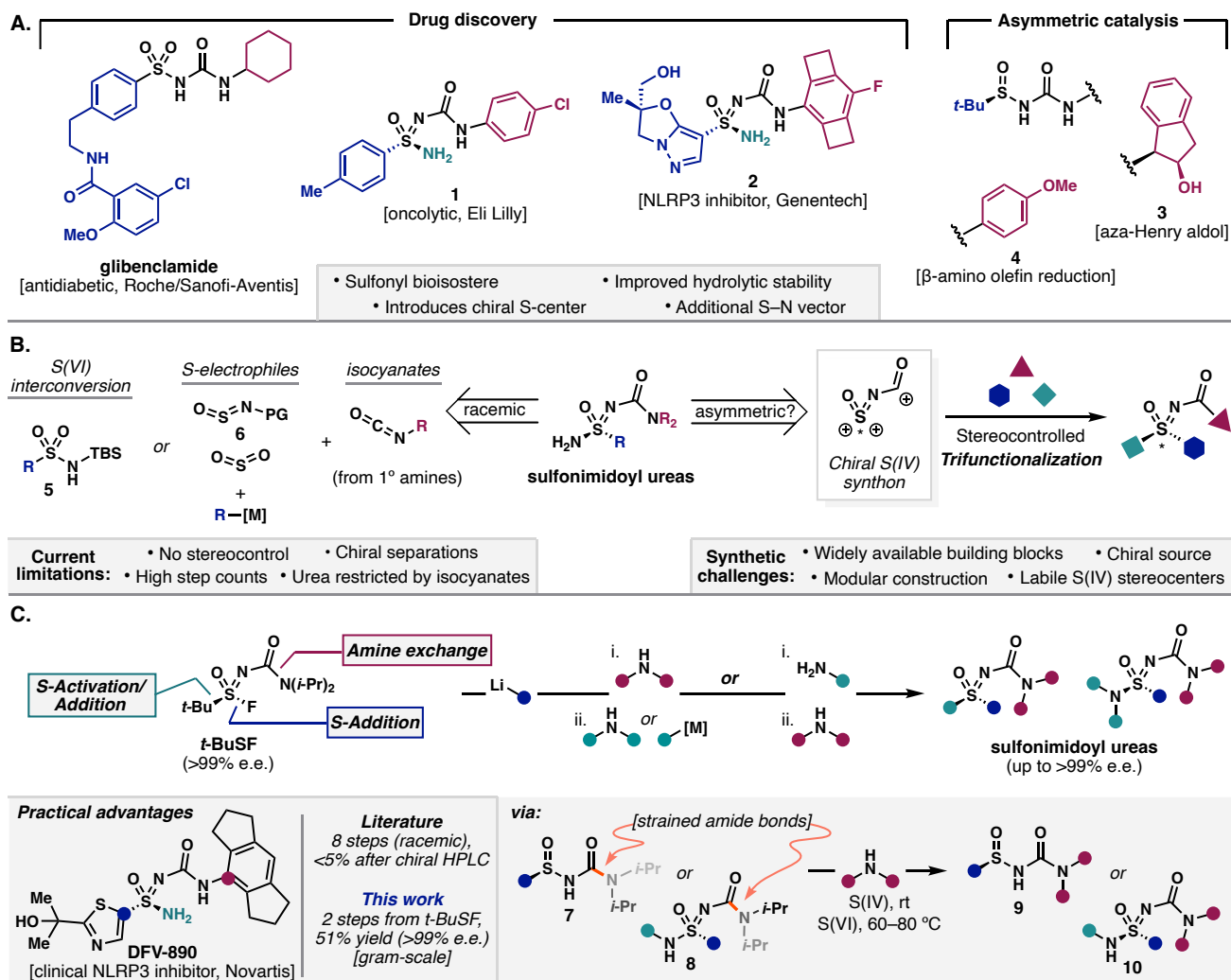
Figure 1: Introduction and background of sulfinyl and sulfonimidoyl functionality. A) Pharmaceutical and catalysis examples. B) Synthetic strategies of sulfonimidoyl ureas. C) Utilizing *t*-BuSF as a trifunctional reagent for the asymmetric synthesis of sulfinyl and sulfonimidoyl ureas (this work).

organolithium and Grignard reagents to achiral S(IV) electrophiles (e.g. **6**, SO$_2$)[29-32] followed by oxidative amination and *N*-protection. Although additional methods for the synthesis of sulfonimidamides exist,[33-38] they are not commonly employed for sulfonimidoyl ureas. The relatively high step count to key precursors, lack of stereochemical control, and the synthetic restrictions related to isocyanates, make these routes less tractable for future discoveries and manufacturing of this important compound class. Therefore, there is an unmet need to develop practical and modular methods that utilize diverse and readily available building blocks with stereocontrol at sulfur, which was surmised to be possible using a trifunctional chiral S(IV) synthon that can be fully elaborated with carbon and nitrogen nucleophiles (Figure 1B, right).

Inspired by our chiral bifunctional SuFEx reagent ***t*-BuSF**,[39] we envisioned switching the role of the *N,N*-diisopropyl urea protecting group through an activation strategy that would introduce a third functional feature of this reagent platform, increasing the overall utility and addressing the current synthetic limitations of sulfonimidoyl ureas (Figure 1C). Here we disclose an additional reactivity mode of ***t*-BuSF** in which the bulky *N,N*-diisopropylurea serves as an enabling group and undergoes facile amine exchange as sulfinamides (**7**) and sulfonimidamides (**8**), providing two independent routes for rapid diversification around the S(IV) (**9**) and S(VI) (**10**) core with stereochemical control. Moreover, *tert*-butyl sulfoximines derived from ***t*-BuSF** serve as stereogenically stable S(IV) surrogates that circumvent the traditional stereochemical lability associated with sulfinamides[40,41] by direct conversion to sulfonimidoyl ureas in a single step. The methods herein have expanded the accessible S(IV) and S(VI) chemical space from ***t*-BuSF**, as demonstrated in over seventy examples, have provided significant improvements in the targeted synthesis of clinical candidates and

pharmaceutical derivatives, and were applied to a combinatorial chemistry approach for rapid generation of 75 diverse S(IV) and S(VI) derivatives within one workday for a single chemist.

Results and Discussion

Reaction discovery. The successful development of **t-BuSF** as a chiral SuFEx reagent was contingent on an imido protecting group that provided selective *S*-reactivity as well as reagent and product stability.[39] By employing a sterically encumbered and electron rich *N,N*-diisopropyl carbamoyl group, bifunctional asymmetric manipulation at sulfur became possible via sulfinyl urea intermediates, such as **7** (Figure 2A). The ease in which the protecting group is removed, especially for 2° sulfonimidamides **8** (DMSO/H₂O, 60 °C), prompted further investigations into its reactivity and structural features as an additional point of diversification.

Conformational analysis of *N,N*-diisopropyl sulfinyl and sulfonimidoyl ureas revealed out-of-plane distortions about the amide bonds as a result of torsional strain induced by two *N*-isopropyl substituents (dihedral angle of 159°). In the presence of an α-NH proton, the inherent strain and increased N-pyramidalization[42-45] converts the carbamoyl protecting group (PG) to a strain-activated enabling group (EG) for facile

A.

B.

R¹, R² =	Me, Me	Et, Et	*i*-Pr, Me	*i*-Pr, *i*-Pr	*i*-Pr, *t*-Bu	TMP
Conversion (%)[a]	5	7	10	94	—	—
Dihedral angle (°)[b]	177	175	172	159	139	106

C.

S(IV) Enantiostability (% e.e.)[c]

Temp.	Time	9a	9b
23 °C	3 h	>99%	>99%
60 °C	1 h	>99%	>99%
80 °C	8 h	72%	93%
80 °C	24 h	ND	40%

9a
(89%, >99% e.e.)[d]
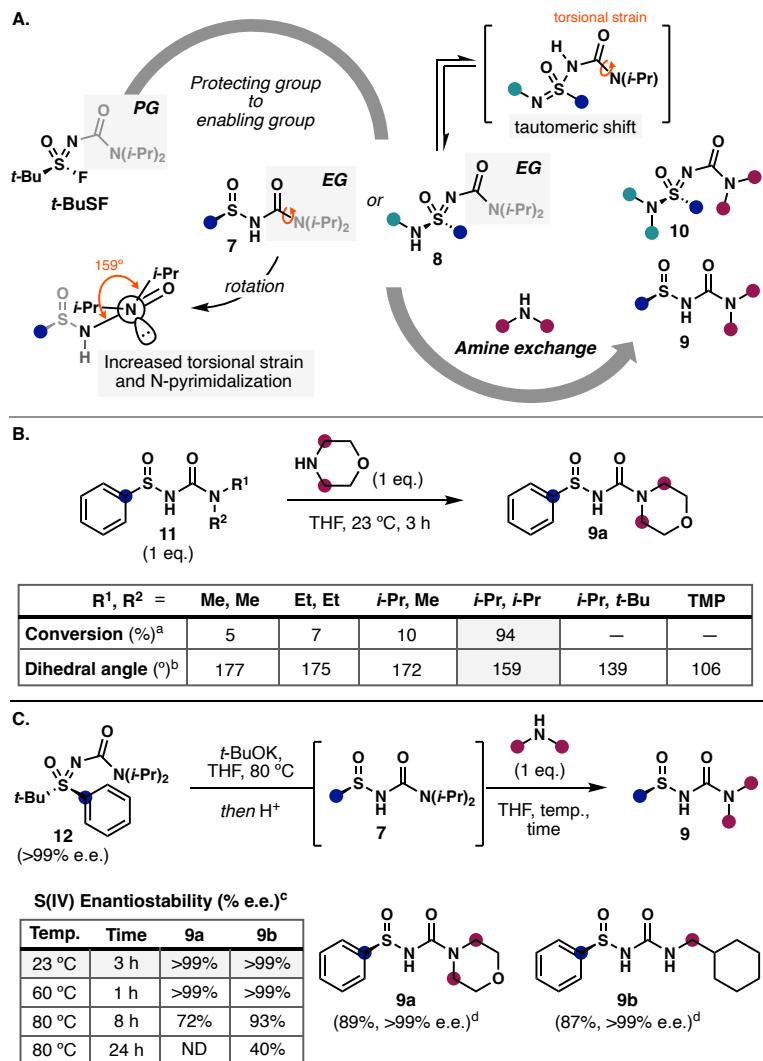
9b
(87%, >99% e.e.)[d]

Figure 2: The *N,N*-diisopropyl carbamoyl enabled S(IV)/(VI) amine exchange. A) Switching the roles of the *t*-BuSF protecting group. B) Investigating amine exchange efficiency of sulfinyl ureas with *N,N*-substituents of varying size. [a]Conversion to **9a** was determined by LC–MS. [b]Dihedral angle was calculated in Maestro after energy minimizations were performed using MacroModel. C) One-pot *S*-activation and amine exchange of *tert*-butyl sulfoximines and evaluation of S(IV) sulfinyl urea enantiostability. [c]Enantiomeric excess (e.e.) was determined by chiral HPLC. [d]Amine exchange was performed for 3 hours at 23 °C. ND = not detected.

amine exchange—providing entry to S(IV) (**9**) and S(VI) (**10**) derivatives. The torsional strain-release promoted by 1° and 2° amines was found to be highly efficient with *N,N*-diisopropyl sulfinyl ureas, exhibiting nearly full conversions in three hours at room temperature, while heating (60–80 °C) was required for sulfonimidoyl ureas. The observed thermodynamic barrier for S(VI) amine exchange is presumably due to the tautomeric shift required for *N,N*-diisopropyl carbamoyl activation along with the decreased amide torsional strain relative to S(IV) variant.

To investigate this reactivity, a series of phenyl sulfinyl ureas (**11**) were used to evaluate the amine exchange with respect to torsional strain and steric bulk around the tertiary amide bond (Figure 2B). Smaller substituents, such as *N,N*-dimethyl and -diethyl, adopt a near-planar conformation (dihedral angles of 177–175°) and exhibit low reactivity (5–7% conversion to **9a** within 3 hours) in the presence of morpholine (1 eq.) at room temperature. Conversely, the larger *N*-isopropyl-*N*-methyl group's increased torsional strain (dihedral angle of 172°) revealed slightly higher conversion (10%). The strain-release reactivity trend continued with symmetrical *N,N*-diisopropyl substituent having the largest change in dihedral angle (159°) and subsequently increasing amine exchange conversion to 94%. Attempts to exaggerate the torsional strain further with *N-tert*-butyl-*N*-isopropyl (dihedral angle of 139°) and 2,2-6,6-tetramethylpiperidine (TMP) (dihedral angle of 105°) proved impractical due to product instability.

Based on our current understanding of the sulfinyl urea amine exchange in conjunction with similar studies of sterically congested electron deficient amides[43] and ureas,[44,45] an addition-elimination pathway at the crowded urea carbonyl is unlikely. Alternatively, elimination of *N,N*-diisopropyl amine in the presence of a protic amine to form a sulfinyl isocyanate intermediate followed by addition of the less bulky amine is more plausible; although our attempts to identify such an intermediate by analytical or synthetic means have proven unfruitful. Aside from the reaction mechanism, the capriciousness of S(IV) stereocenters under neutral conditions[38,39] implored us to examine the effects, if any, this transformation has on the distal chiral center. Enantiopure *tert*-butyl phenyl sulfoximine **12** was thermally activated using *t*-BuOK over two hours then neutralized to give sulfinyl urea intermediate **7** that was subsequently treated with morpholine (**9a**) or aminomethylcyclohexane (**9b**) at varying temperatures and reaction times (Figure 2C). To our delight, the stereogenic sulfur center was unaffected during the amine exchange at room temperature (23 °C) or 60 °C. Although not required, prolonged heating at 80 °C resulted in stereochemical erosion for secondary and tertiary sulfinyl urea derivatives, and eventual decomposition (see Supplementary Information S14 for additional details). This S(IV) stereochemical fidelity analysis during the amine exchange suggested enantiopurity would be conserved when the reactions were conducted at room temperature. The balanced steric influence of *N,N*-diisopropyl ureas on amine exchange, SuFEx chemistry, and overall stability offers a unique versatile synthetic handle for sulfinyl and sulfonimidoyl synthesis.

Sulfinyl urea scope. With optimal reaction conditions in hand, the scope of the S(IV) reaction was evaluated (Table 1). Aryl, heteroaryl and alkyl *tert*-butyl sulfoximines were prepared from ***t*-BuSF** and used as models for scope analysis. Following S-activation of their respective *t*-Bu sulfoximines, the resulting sulfinyl urea intermediates were treated at room temperature for three to four hours with amines of varying complexity, from building blocks to advanced pharmaceutical intermediates and drugs. Additionally, the enantiopurity for each class of sulfinyl derivative was determined after isolation.

Primary aliphatic amines were first evaluated using less sterically hindered benzylic amines and aminomethyl cyclic amines which exchanged smoothly to provide sulfinyl ureas **9b**–**9e** in excellent yields (86–98%), with no observable change in enantiomeric excess (>99% e.e.). Furthermore, amino oxetane **9f** and N-Boc protected azetidine **9g** were prepared uneventfully, representing common medicinal chemistry fragments. Interestingly, *tert*-butyl amine exchanged with *N,N*-diisopropyl amine in nearly quantitative yield (**9h**), revealing no steric limitation for primary amine substrates. In addition to primary aliphatic amines, 1-amino piperidine was also a compatible nucleophile giving rise to **9i** in 85% yield and providing entry to an underexplored class of sulfinyl ureas.

The decreased basicity and nucleophilicity of aromatic amines contributed to lesser reactivity under optimized conditions, reaching an equilibrium with the starting *N,N*-diisopropyl sulfinyl ureas and diminished yields (ca. 50–60%). Gratifyingly, Brønsted acid additives were found to accelerate amine exchange with less basic amines and improving target yields up to 88%. Trifluoroacetic acid (TFA) was selected as the ideal additive due to its role in S-activation and observed reactivity enhancement, making it suitable for one-pot and telescoped protocols. When optimal conditions were employed for aromatic amine substrates (1 eq. of TFA, 2-MeTHF or THF, rt), S(IV) derivatives **9j**–**9m** bearing electron withdrawing/donating groups and *ortho*-substituents were obtained in 79–88% yields with no erosion of enantiopurity. Additionally, heteroaryl amines, 3-aminopyridine **9n** and 2-aminothiazole **9o**, were obtained in high yields. Secondary aliphatic amines rapidly underwent S(IV) amine exchange within three hours at room temperature and in high yields without consequence for enantiopurity, as demonstrated by morpholine and N-hexynyl piperazine derivatives **9a**, **9b**, and **9q**. In addition, unsymmetrical secondary amines provide sulfinyl ureas **9r** and **9s** with functional alkynyl and hydroxy handles suitable for further downstream manipulation.
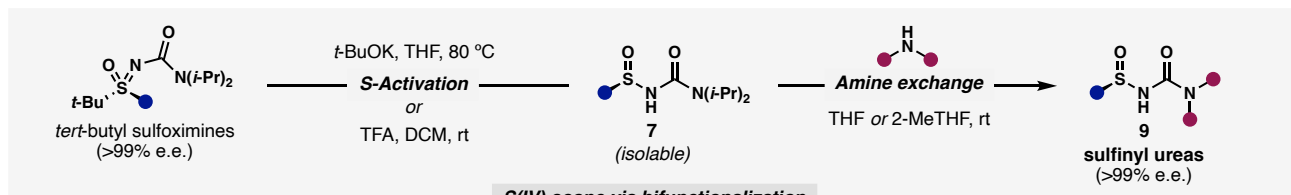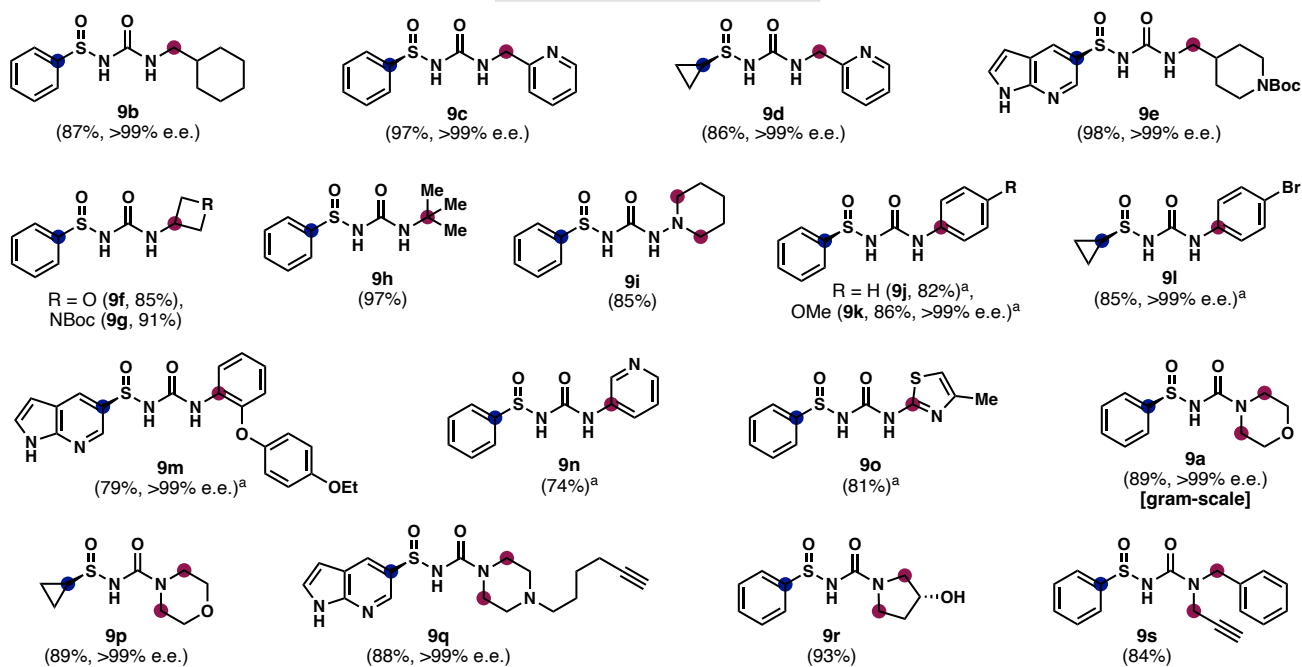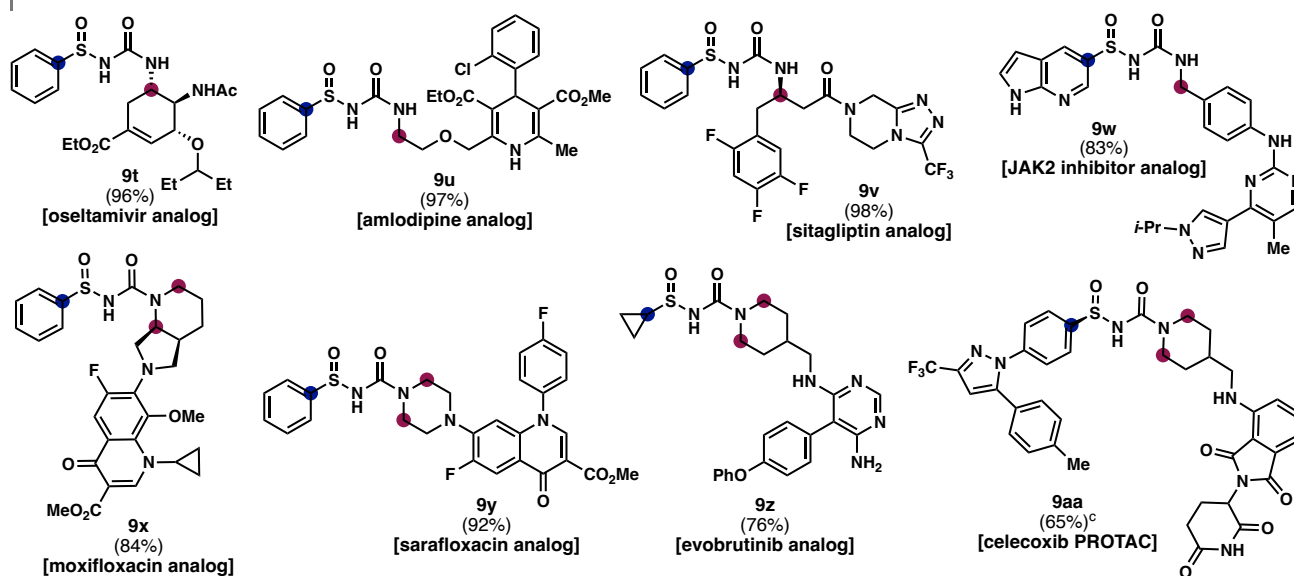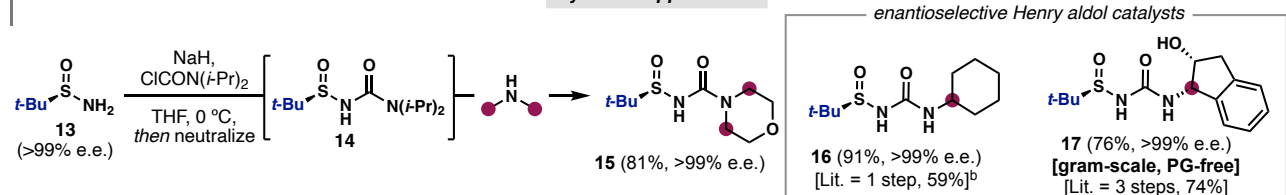
Table 1: Reaction scope and application of *N,N*-diisopropyl sulfinyl urea amine exchange. All reactions were performed on 0.1–0.25 mmol scales unless otherwise stated. Isolated yields are reported. Enantiomeric excess (% e.e.) was determined by chiral HPLC. [a]TFA (1 eq.) was used as an additive. [b]Commercial cyclohexyl isocyanate was used. [c]Isolated as a mixture of diastereomers at the epimeric carbon.

Late-stage compatibility and (real-world) functional group tolerance were exemplified using eight pharmaceutically relevant amines of varying complexity. The primary amines of the antiviral oseltamivir, and

calcium channel blocker amlodipine, performed exceptionally well giving sulfinyl urea derivatives **9t** and **9u** exclusively in the presence of esters, secondary amides and 1,4-dihydropyridine. Additionally, the β-amine of sitagliptin was successfully functionalized to **9v** in nearly quantitative yield. An aza-indole sulfinyl urea derivative of a JAK2 inhibitor[46] (**9w**) was made readily accessible through *N,N*-diisopropyl amine exchange, introducing S(IV) functionality to commonly encountered kinase pharmacophores. Antibiotic analogs of moxifloxacin (**9x**) and sarafloxacin (**9y**) were readily obtainable by engaging their 1*H*-pyrrolo[3,4-*b*]pyridine and piperazine motifs respectfully. Notable site selectivity was observed for evobrutinib, favoring the piperidine over a diaminopyrimidine leading to the sulfinyl derivative **9z** in good yield (76%). Lastly, S(IV) amine exchange was employed as a bimolecular linking strategy between a sulfinyl urea analog of celecoxib and an E3 ligase ligand (**9aa**) that could be leveraged for the development of proteolysis targeting chimeras (PROTACs).

Synthetic applications of S(IV) amine exchange. Sulfinyl urea organocatalysts impart asymmetric control through chiral hydrogen–bonding environments and have been largely restricted to *tert*-butyl S-substituents.[21-24] These limitations are due in part to the steric bulk offered by the *tert*-butyl group, availability of the sulfinamide starting material, and most notably, a lack of synthetic methods to efficiently introduce structural and electronic diversity around the chiral S-center. Although **t-BuSF** could serve as the chiral template for catalyst design, enantiopure (*R*)-*tert*-butyl sulfinamide **13** was employed to prepare sulfinyl urea organocatalysts in a single step. Carbamoylation of sulfinamide **13** affords diversifiable intermediate **14** that was directly treated with amines to give sulfinyl ureas **15–17**, improving the yield of **16** by 32% and providing a protecting group-free synthesis of **17**—subsequently reducing the overall step count.[22] The practicality and scalability of this method was demonstrated in the gram-scale preparation of **17** and by replacing isocyanates with widely available amine building blocks.

Sulfonimidoyl urea scope. After establishing the S(IV) amine exchange, our focus shifted to the analogous S(VI) transformation of sulfonimidamides. Two secondary sulfonimidamides, N-alkyl **8a** and N-aryl **8b**, were chosen to examine the reaction scope due to their differences in structure and tautomerization potential (Table 2). In general, sulfonimidoyl ureas are less reactivate than their S(IV) counterparts and require elevated temperatures to undergo the desired amine exchange. A similar set of structurally diverse primary and secondary amines were evaluated under thermal conditions (60–80 °C) in THF and MeCN. It was quickly determined that N-aryl derivative **8a** undergoes the exchange more readily at 60 °C while N-alkyl derivative **8b** required a slightly more elevated temperature (80 °C). Despite the known stereogenic stability of sulfonimidamides,[47,48] enantiopurity was assessed for each class of sulfonimidoyl ureas.

Both N-substituted *N,N*-diisopropyl sulfonimidoyl derivatives (**8a** and **8b**) readily undergo amine exchange with primary aliphatic amines (**10a–10h**) in good to excellent yields (72–96%) without impacting enantiopurity (>99% e.e.). Benzylic amines and heterocycle-containing primary amines afforded **10a–10c** and **10d–10f** respectively. Sterically congested valinol provided sulfonimidoyl urea **10g** preferentially via amine exchange in 84% yield with no observed reactivity at the less hindered alcohol. An arene bioisostere was introduced as a bicyclopentyl (BCP) unit via amine exchange to give S(VI) derivative **10h** in high yield. Aromatic amines exhibited similar reactivity trends to the analogous S(IV) amine exchange, therefore the same tactic was employed using TFA as an additive. Even though diminished reactivity was observed, good to high yields (56–85%) were achievable for anilinic substrates **10i–10l** with no effect on the S-stereocenter. On the other hand, secondary amines readily exchange with *N,N*-diisopropyl amine producing **10m** and **10n** uneventfully while maintaining enantiopurity (>99% e.e.). N-Substituted piperazines **10o–10q**, 3-hydroxypyrrolidine **10r**, and 3-N-Boc-piperidine **10s** all delivered the desired sulfonimidoyl ureas in excellent yields. Venturing further away from "flat-land" chemical space, sp³-rich spirocyclic amines were successfully introduced granting access to **10t–10w**, which represent untapped chemical space.
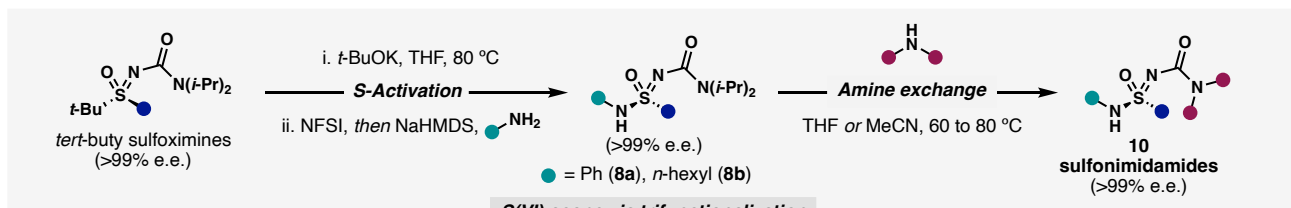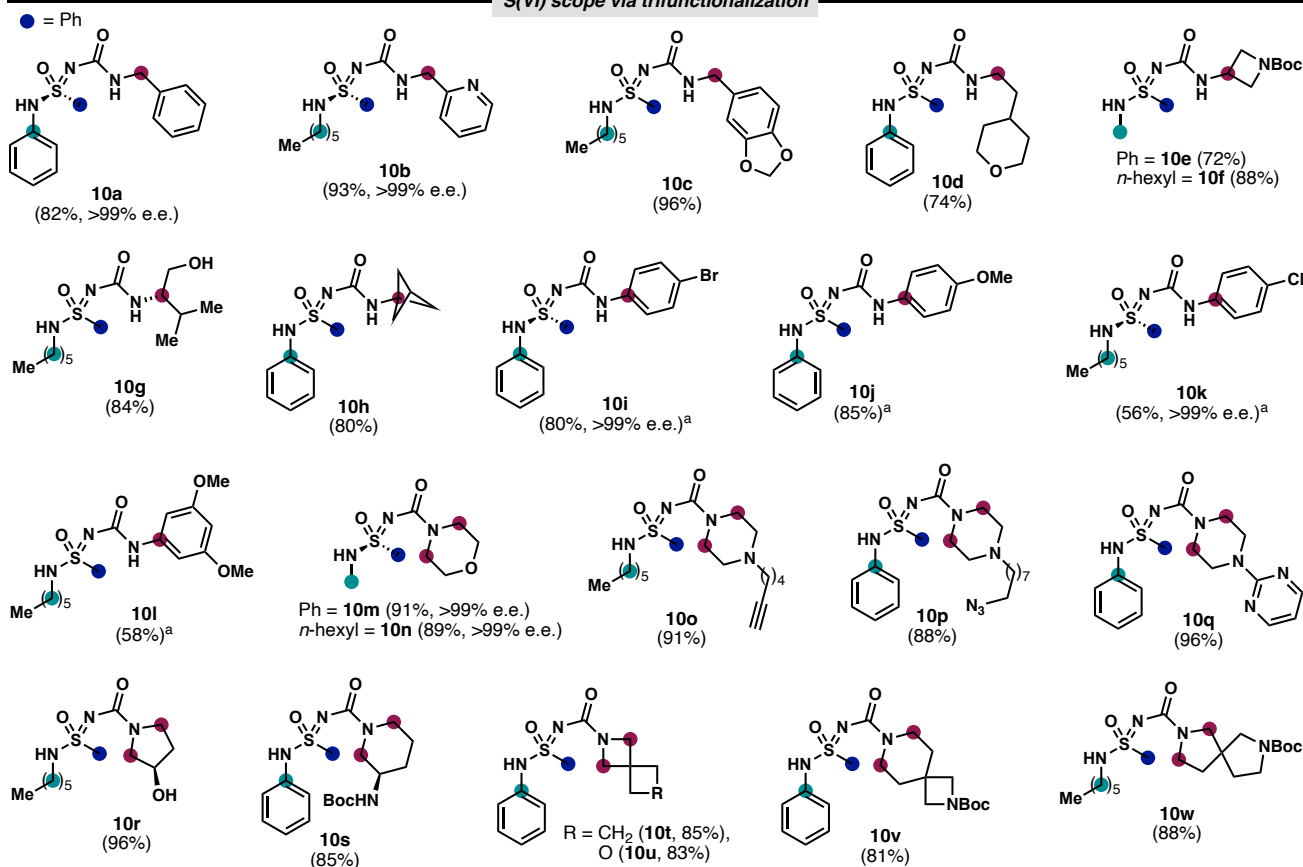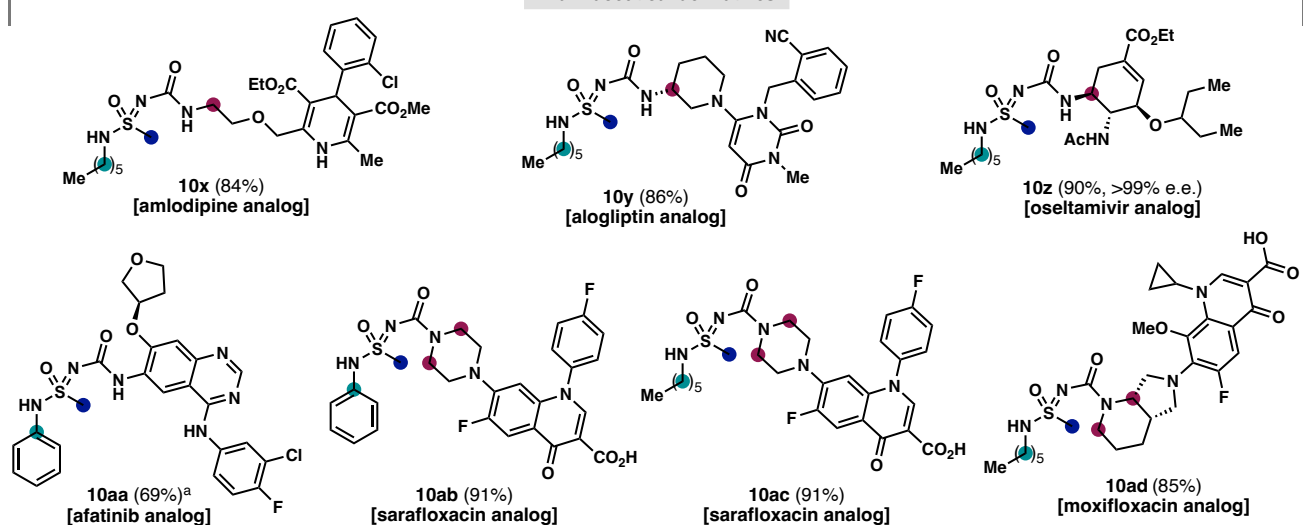
Table 2: Reaction scope of *N,N*-diisopropyl sulfonimidoyl urea amine exchange. All reactions were performed on 0.1–0.25 mmol scales. Isolated yields are reported. Enantiomeric excess (e.e.) determined by chiral HPLC. [a]TFA (1 eq.) was used as an additive.

The S(VI) amine exchange scope was further expanded to encompass the complexity often encountered in drug discovery programs and to verify late-stage introduction of sulfonimidoyl functionality. Amlodipine, alogliptin, and oseltamivir were efficiently exchanged with *N,N*-diisopropylamine to afford **10x**, **10y**, and **10z** as their respective sulfonimidoyl urea derivatives in the presence of esters, nitriles, amides, and α,β-unsaturated

esters. Additionally, the primary aromatic amine of afatinib's pharmacophore underwent the S(VI) amine exchange (**10aa**) despite the large *o*-substituent and weak nucleophilicity. Sarafloxacin and moxifloxacin exhibited exclusive reactivity at the secondary amine over condensation with carboxylic acids or 1,4-additions, providing both **10ab** and **10ac** in 91% yield and **10ad** in 85% yield. These representative pharmaceutical examples highlight the selectivity and utility of the sulfonimidoyl amine exchange, revealing opportunities for late-stage diversification and derivatization of clinically optimized scaffolds.

While secondary sulfonimidoyl ureas can be functionalized under mild conditions, tertiary substrates were unreactive at elevated temperatures (120 °C, dioxane) or with the addition of Brønsted and Lewis acids (see Supplementary Information S57 for more information). To capture this class of sulfonimidoyl ureas, the S(IV) amine exchange and *S*-activation of sulfinyl ureas was leveraged (Figure 3). A practical one-pot procedure was developed as a streamlined approach that mitigates the handling of reactive and less stable intermediates while showcasing the degree of modularity and diversity accessible. Tertiary sulfonimidamide **18** was prepared in enantiopure form from the corresponding *tert*-butyl sulfoximine in a single step (56% yield) via the sulfonimidoyl chloride intermediate. Alternatively, S(IV) amine exchanged intermediates (**9**) can be fluorinated to provide isolable bifunctionalized S(VI) electrophiles, as demonstrated by sulfonimidoyl fluoride **19**, that can undergo additional functionalization. A minor decrease in enantiopurity (>99% to 99% e.e.) was observed
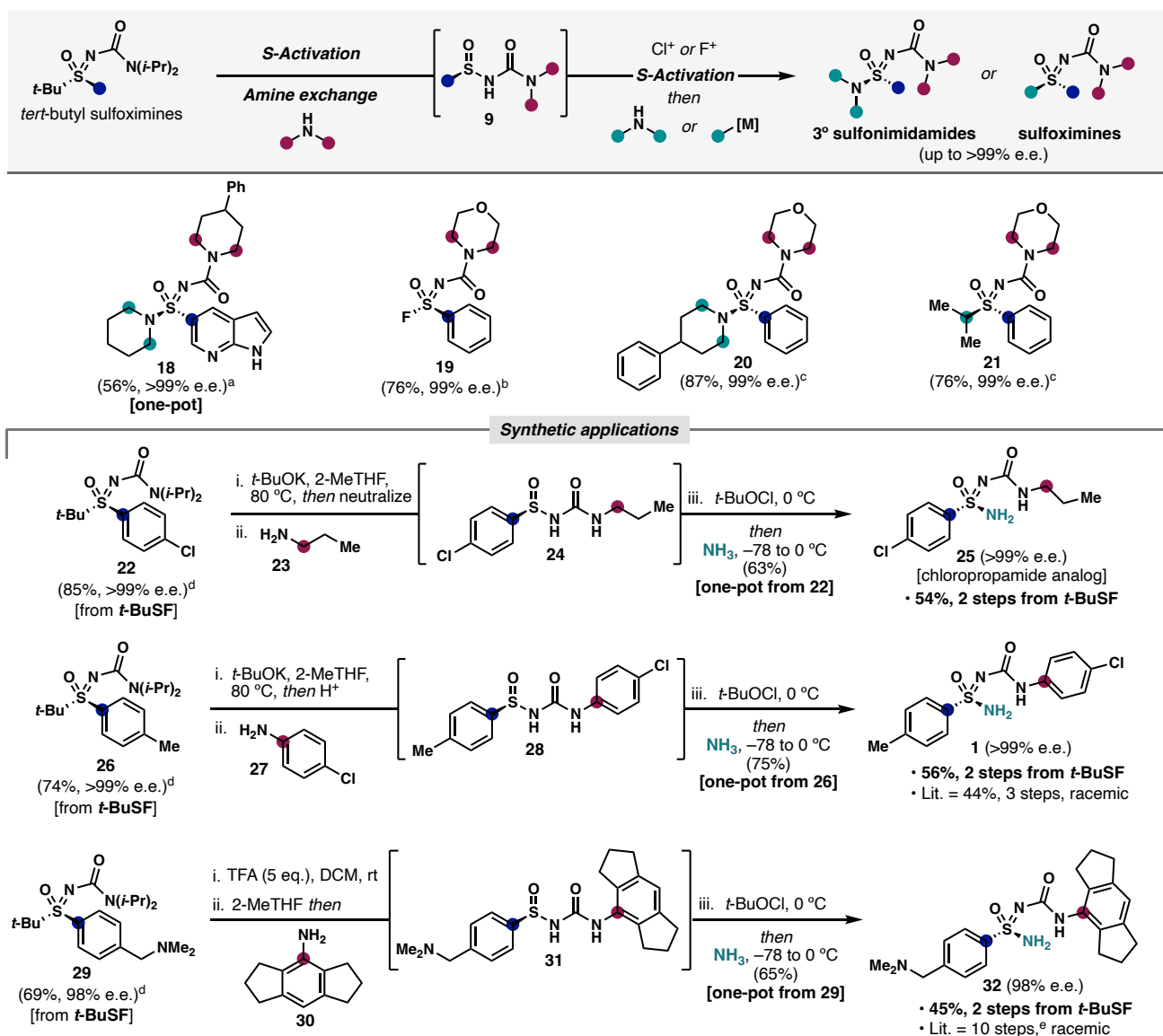

Figure 3: Direct asymmetric functionalization of *tert*-butyl sulfoximines to sulfonimidoyl ureas. Enantiomeric excess (e.e.) was determined by chiral HPLC. [a]Isolated yield from *tert*-butyl sulfoximine via sulfonimidoyl chloride. [b]Isolated yield from *S*-activation/flourination of a *tert*-butyl sulfoximine. [c]Isolated yield from sulfonimidoyl fluoride **19** using a turbo-amide or turbo-Grignard. [d]Isolated yield from *t*-BuSF SuFEx. [e]Yields for each step were not reported.

during the fluorination event for **19**, however, the stereospecific addition of an amine and turbo-Grignard reagent afforded **20** and **21** in 87% and 76% yield, respectively.

Synthetic applications. The practical utility and versatility of the amine exchange method was further demonstrated in target- and diversity-oriented syntheses of clinically relevant sulfonimidoyl ureas. In two steps, ***t*-BuSF** was trifunctionally elaborated in an asymmetric fashion (Figure 3). An aza-analog of the sulfonylurea antidiabetic drug chloropropamide was prepared in 54% yield from ***t*-BuSF** via an *S*-activation and amine exchange strategy leveraging sulfoximine **22** and *n*-propyl amine (**23**). The corresponding S(IV) intermediate **24** was subjected to oxidative amination with *t*-BuOCl and ammonia providing enantiopure **25** in 63% yield from sulfoximine **22** in a single step. To our knowledge, this is the first example of S-chlorination with secondary sulfinyl ureas. The same tactic was applied in a targeted asymmetric synthesis of sulfonimidoyl stereoisomer **1** reported by Eli Lilly.[15] Starting from ***t*-BuSF**, enantiopure sulfoximine **26** was prepared in 74% yield after recrystallization, which was subsequently transformed to **1** in one step (75% yield, >99% e.e.)—providing an asymmetric route with a decreased step count and improved overall yield. Furthermore, an NLRP3 inhibitor developed by Genentech[16] was prepared asymmetrically from sulfoximine **29** that was obtained from ***t*-BuSF** in 98% e.e. without recrystallization. Upon *S*-activation of sulfoximine **29** with TFA, sulfinyl urea **31** was directly exchanged with aniline **30** followed by oxidative amination. This one-step protocol gave rise to sulfonimidoyl urea **32** in 65% yield (45% from ***t*-BuSF**) and excellent enantiopurity (98% e.e.), significantly improving the reported 10 step racemic synthesis[17] while affording a derivatization platform for future analog development.
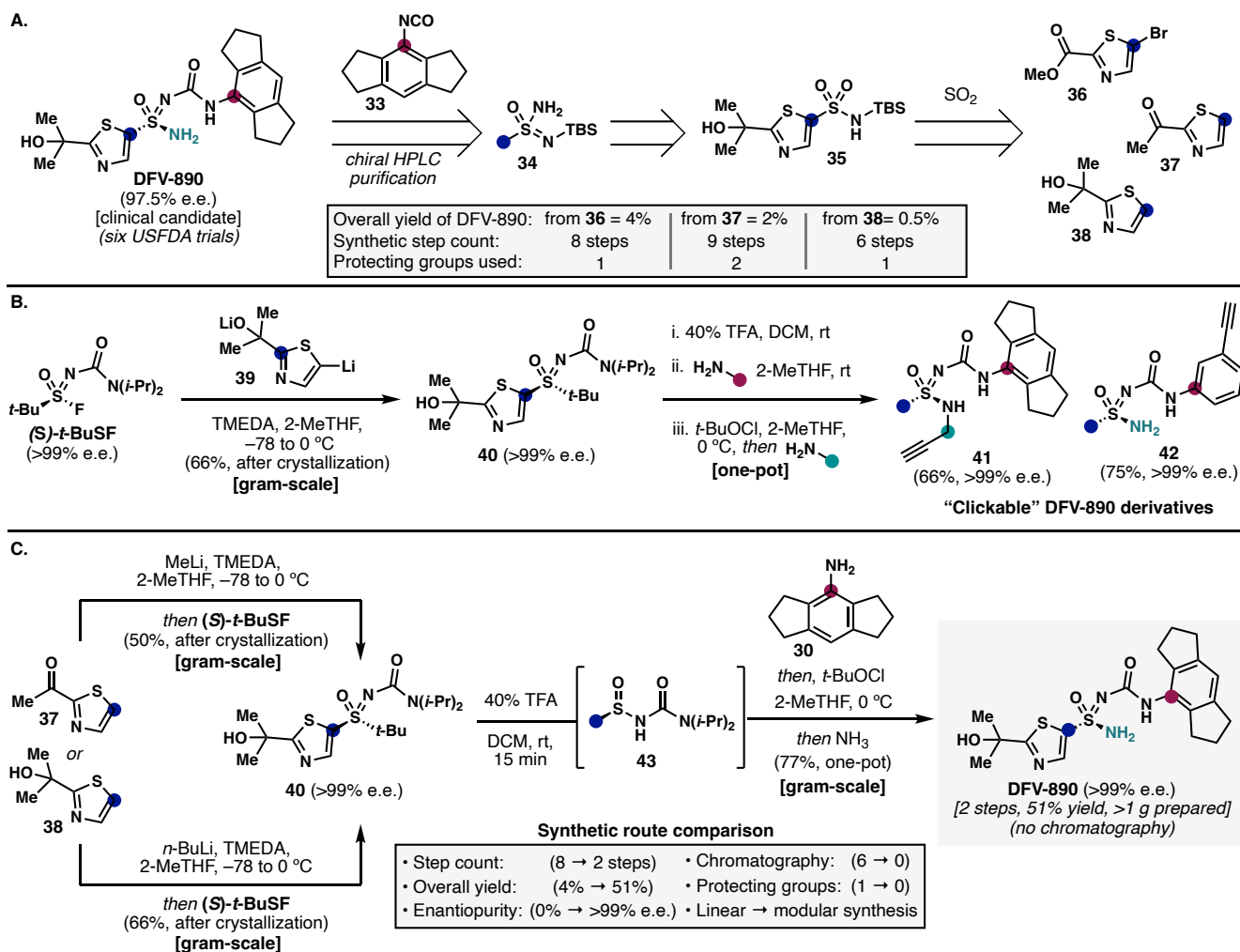

Figure 4: Application of *t*-BuSF trifunctionalization for the preparation of clinical inhibitor DFV-890 and derivatives. A) Analysis of reported synthetic routes for DFV-890. B) A medicinal chemistry route for the asymmetric synthesis of DFV-890 derivatives from *t*-BuSF. C) A scalable targeted asymmetric synthesis of DFV-890 as a "mock process" route.

One of the most clinically significant sulfonimidoyl compounds to date is Novartis' NLRP3 inhibitor DFV-890, which is currently under evaluation in six USFDA clinical trials across multiple indications including cancer, heart disease, osteoarthritis, auto-inflammatory syndromes, and COVID-19.[21] The reported routes to DFV-890 rely on preparative chiral HPLC, isocyanate **33**, and sulfonyl to sulfonimidoyl (**34**) interconversion (Figure 4A). The requisite sulfonamide **35** is prepared from three different thiazole building blocks (**36–38**) and sulfur dioxide in varying yields and step counts. Depending on the initial heterocycle chosen, DFV-890 can be prepared in 6–9 steps using at least one protecting group with an overall yield of 0.5–4% and 97.5% e.e. after chiral chromatography.

To address the synthetic drawbacks associated with DFV-890, the trifunctionalization of **t-BuSF** was applied. Starting from enantiopure (**S**)-**t-BuSF**, SuFEx using lithiated thiazole **39** (1st point of diversification) provided *tert*-butyl sulfoximine **37** with >99% e.e. in 66% yield after recrystallization on gram-scale (Figure 4B). It is worth noting that the sulfonimidoyl transfer reaction deviated from previously reported conditions[39] and was conducted in 2-MeTHF with TMEDA as an additive to aid in dianion formation. Sulfoximine **40** was then subjected to TFA mediated *S*-activation followed by amine exchange (2nd point of diversification), then oxidative amination with propargyl amine or ammonia (3rd point of diversification) to deliver clickable chemical probe derivatives of DFV-890 **41** and **42** in good yields as single stereoisomers, illustrating an advantageous medicinal chemistry route. The same strategy was used in a target-oriented, "mock process" approach for the gram-scale synthesis of DFV-890 (Figure 4C). Two different thiazoles (**37**, **38**) were used to prepare gram quantities of enantiopure sulfoximine **40** with no chromatography. *S*-Activation followed by S(IV) amine exchange with aniline **30** afforded a sulfinyl urea intermediate **43** that was oxidatively aminated in situ providing over a gram of DFV-890 (>99% e.e.) in 77% yield without the need for chromatographic purification. This modular two-step asymmetric synthesis of DFV-890 reduced the overall synthetic step count (8 to 2 steps), improved the yield 10-fold, provided the target compound in enantiopure form, and removed the need for both protecting groups and chromatography.

Combinatorial trifunctionalization of *t*-BuSF. The modularity, efficiency, and chemical space accessible from **t-BuSF** was further demonstrated by applying the methods herein to a combinatorial chemistry workflow as a diversity-oriented synthesis platform for S(IV) and S(VI) library generation (Figure 5A). *tert*-Butyl sulfoximines (from **t-BuSF**) serve as the central building block (**A**) to which the remaining diversity is introduced during amine exchange (**B**) and subsequent *S*-activation/additions with amines (**C**) or turbo-Grignards (**D**). For this compound set, the S-substituent was fixed to phenyl and representatives for building blocks **B** (maroon), **C** and **D** (teal) are shown in Figure 5A. Individual reactions were set to specific time points (eight total hours, representing a typical workday for a single chemist) and were not independently optimized. Analysis was performed by LC–MS to monitor conversions for yield estimations of target compounds, which were cross-checked by isolation.

Starting from *tert*-butyl sulfoximine **A**, *S*-activation was carried out on a gram-scale using *t*-BuOK in 2-MeTHF at 80 °C for 2 hours then partitioned into four quadrants (Q1–Q4) throughout a 48-well reaction block. The S(IV) amine exchange was initiated by the addition of 22 amine building blocks (**B**). After three hours, the newly formed sulfinyl ureas could be split, purified, or further transformed via *S*-activation; in this proof-of-concept experiment, 44 unique S(VI) products were targeted. Quadrant 1 was subjected to oxidative amination with *t*-BuOCl and NH₃ to obtain 10 primary sulfonimidamides, while quadrant 2 was designed to give 12 products captured in the S(VI) amine exchange scope (Table 2) as controls for method validation. Quadrant 3 contained a diverse set of 12 secondary and tertiary sulfonimidamides, and quadrant 4 was devoted to the synthesis of sulfoximine derivatives via sulfonimidoyl fluorides and turbo-Grignards **D1** and **D2**.

Estimated yields (with the overall mass of target compounds) after four transformations are colored coded within the 48 well plate according to the legend in Figure 7A. Two examples from each quadrant were isolated and shown to be in agreement with the estimated yields (Figure 7B). To our delight, 42 examples out of 44 were estimated to have >50% yield (from building block **A**). The two examples that fell short of the 50%
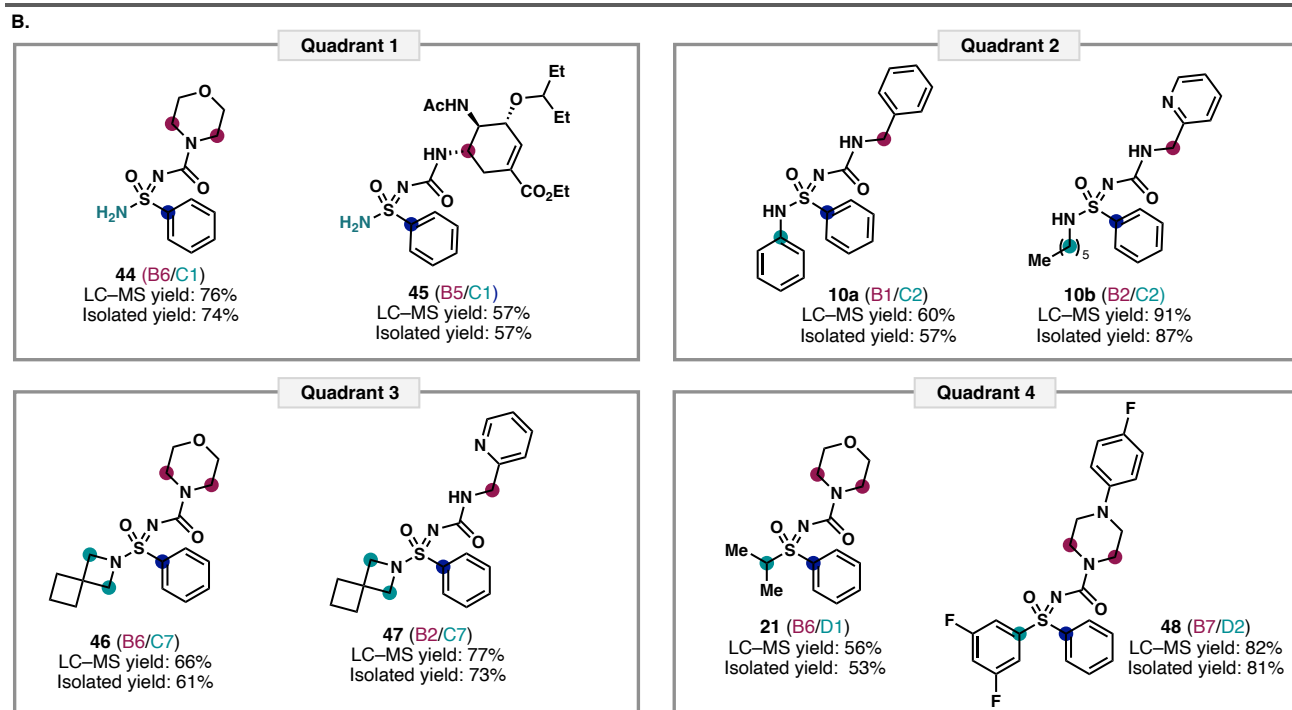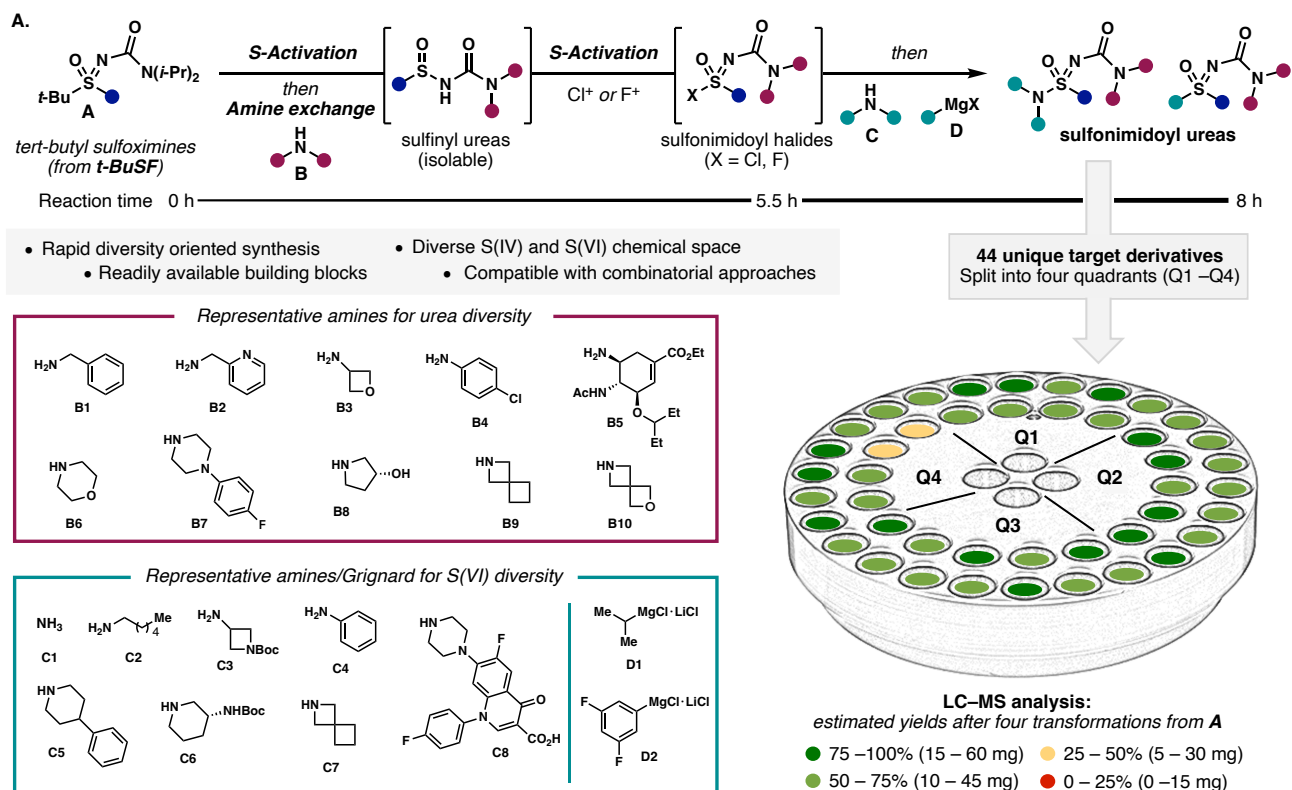
Figure 5: Applying the trifunctionalization of *t*-BuSF to a combinatorial workflow. A) Combinatorial approach to sulfonimidoyl ureas from *t*-BuSF. Representative nucleophile building blocks used and reaction profile analysis performed by LC–MS. B) Structural representatives for the sulfonimidoyl classes obtained from each quadrant.

cut off were Q4 sulfoximines treated with **D1** having estimated yields of 40%. Within the course of eight hours, 34 sulfonimidamides and 10 sulfoximines were prepared, including 25 sulfinyl ureas, 34 sulfonimidoyl chlorides, and 5 sulfonimidoyl fluoride intermediates. The chemical and structural diversity created within this proof-of-concept workflow signifies the impact **t-BuSF** will have in the chemical sciences. With the translation to automated liquid handling coupled with the wide variety of available amine building blocks, it is anticipated that high-throughput variations of this approach will be feasible.

Conclusion

A new functional feature of ***t*-BuSF** has been developed resulting in a trifunctional chiral SuFEx reagent platform. The key *N,N*-diisopropyl urea protecting group of ***t*-BuSF** was transformed to an enabling group that promotes torsional strain-release driven amine exchange for the asymmetric synthesis of sulfinyl and sulfonimidoyl ureas. This reactivity mode allows for selective and efficient carbamoyl derivatization with amines at either the S(IV) or S(VI) stage, providing multiple synthetic route options that negates the need for isocyanates and laborious functional group interconversions. The reaction compatibility was explored using myriad amines ranging in structural complexity offering over seventy sulfinamide, sulfonimidamide, and sulfoximine examples with enantiopurities up to >99% e.e. Scalable one-pot protocols were established for rapid construction of the target sulfur functionality in two steps (five transformations) from ***t*-BuSF** that were highlighted in five synthetic applications and successfully applied to a combinatorial chemistry workflow. Most notably, the significant synthetic improvements these methods provide for important clinical candidates and derivatives illustrates the impact that the ***t*-BuSF** SuFEx platform will have on the discovery sciences. Additional reactivity modes and activation strategies of ***t*-BuSF** and intermediates are currently under investigation and will be reported in due course.

Data availability

All data including experimental procedures, compound characterization data, and stability analysis data are available within the article and its Supplementary Information file.

Author contributions

P.A., Z.P.S., and J.M.L. conceived and designed the project. P.A., Z.P.S., A.S. and Y.H. performed the experimental studies. P.A., Z.P.S., and J.M.L. analyzed and interpreted experimental data. Z.P.S., P.A., and J.M.L. wrote the manuscript. ‡These authors contributed equally to this work.

Competing interests

A patent application naming J.M.L, Z.P.S., and P.A. as inventors has been filed by H. Lee Moffitt Cancer Center & Research Institute, which covers the synthetic methods and development regarding the trifunctionalization of an S(VI) reagent for the asymmetric synthesis of sulfur-containing functional groups.

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References

1. Ingenbleek, Y.; Kimura, H., Nutritional essentiality of sulfur in health and disease. *Nutr. Rev.* **2013,** *71* (7), 413-432.
2. Hill, C. R.; Shafaei, A.; Balmer, L.; Lewis, J. R.; Hodgson, J. M.; Millar, A. H.; Blekkenhorst, L. C., Sulfur compounds: From plants to humans and their role in chronic disease prevention. *Crit. Rev. Food Sci. Nutr.* **2023,** *63* (27), 8616-8638.
3. Feng, M.; Tang, B.; Liang, H. S.; Jiang, X., Sulfur Containing Scaffolds in Drugs: Synthesis and Application in Medicinal Chemistry. *Curr. Top. Med. Chem.* **2016,** *16* (11), 1200-1216.
4. Luzi, L.; Pozza, G., Glibenclamide: an old drug with a novel mechanism of action? *Acta Diabetol.* **1997,** *34* (4), 239-244.

5. Sola, D.; Rossi, L.; Schianca, G. P.; Maffioli, P.; Bigliocca, M.; Mella, R.; Corlianò, F.; Fra, G. P.; Bartoli, E.; Derosa, G., Sulfonylureas and their use in clinical practice. *Arch. Med. Sci.* **2015,** *11* (4), 840-848.

6. Liu, Y.-F.; Wen, Z.-F.; Bian, Y.; Zhou, Y.; Liu, Z.-F.; Zhang, Y.; Feng, X.-S., A Review on Recent Innovations of Pretreatment and Analysis Methods for Sulfonylurea Herbicides. *Crit. Rev. Anal. Chem.*, 1-30.

7. Sehgelmeble, F.; Janson, J.; Ray, C.; Rosqvist, S.; Gustavsson, S.; Nilsson, L. I.; Minidis, A.; Holenz, J.; Rotticci, D.; Lundkvist, J.; Arvidsson, P. I., Sulfonimidamides as Sulfonamides Bioisosteres: Rational Evaluation through Synthetic, in Vitro, and in Vivo Studies with γ-Secretase Inhibitors. *ChemMedChem* **2012,** *7* (3), 396-399.

8. Lücking, U., Sulfoximines: A Neglected Opportunity in Medicinal Chemistry. *Angew. Chem. Int. Ed.* **2013**, *52* (36), 9399-9408.

9. 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* (15), 4100-4109.

10. 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.

11. Lücking, U., Neglected sulfur(vi) pharmacophores in drug discovery: exploration of novel chemical space by the interplay of drug design and method development. *Org. Chem. Front.* **2019,** *6* (8), 1319-1324.

12. 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* (23), 14243-14275.

13. Izzo, F.; Schäfer, M.; Lienau, P.; Ganzer, U.; Stockman, R.; Lücking, U., Exploration of Novel Chemical Space: Synthesis and in vitro Evaluation of N-Functionalized Tertiary Sulfonimidamides. *Chem. Eur. J.* **2018,** *24* (37), 9295-9304.

14. Borhade, S. R.; Svensson, R.; Brandt, P.; Artursson, P.; Arvidsson, P. I.; Sandström, A., Preclinical Characterization of Acyl Sulfonimidamides: Potential Carboxylic Acid Bioisosteres with Tunable Properties. *ChemMedChem* **2015,** *10* (3), 455-460.

15. Toth, J. E.; Grindey, G. B.; Ehlhardt, W. J.; Ray, J. E.; Boder, G. B.; Bewley, J. R.; Klingerman, K. K.; Gates, S. B.; Rinzel, S. M.; Schultz, R. M.; Weir, L. C.; Worzalla, J. F., Sulfonimidamide analogs of oncolytic sulfonylureas. *J. Med. Chem.* **1997,** *40* (6), 1018-1025.

16. Agarwal, S.; Sasane, S.; Shah, H. A.; Pethani, J. P.; Deshmukh, P.; Vyas, V.; Iyer, P.; Bhavsar, H.; Viswanathan, K.; Bandyopadhyay, D.; Giri, P.; Mahapatra, J.; Chatterjee, A.; Jain, M. R.; Sharma, R., Discovery of N-Cyano-sulfoximineurea Derivatives as Potent and Orally Bioavailable NLRP3 Inflammasome Inhibitors. *ACS Med. Chem. Lett.* **2020,** *11* (4), 414-418.

17. Lai, K. W.; Nilewski, C.; Pastor, R. M.; Stivala, C. Preparation of sulfonimidamide compounds and uses thereof. Patent WO 2023/004257, **2023**.

18. Franchi, L.; Ghosh, S.; Glick, G.; Katz, J.; Opipari, A. W., Jr.; Roush, W.; Seidel, H. M.; Shen, D.-M.; Venkatraman, S.; Winkler, D. G. Preparation of sulfonylurea compound and compositions for treating conditions associated with NLRP activity. Patent WO 2020/102576, **2020**.

19. Coleman, L.; Farady, C.; Gatlik, E.; Schieker, M. Dosing regimen for an NLRP3 inhibitor in the treatment of osteoarthritis. Patent WO 2023/002399, **2023**.

20. Farady, C. J.; Gatlik, E.; Waldron-Lynch, F. D. Dosing regimen for a NLRP3 inhibitor for treatment of auto-inflammatory syndrome. Patent WO 2024/023696, **2024**.

21. *Clinical trials using NLRP3 Inhibitor DFV-890* (National Institute of Health, accessed 14 March 2024); https://clinicaltrials.gov/study/NCT04868968?term=DFV890&rank=1, https://clinicaltrials.gov/study/NCT06031844?term=DFV890&rank=2, https://clinicaltrials.gov/study/NCT04886258?term=DFV890&rank=3, https://clinicaltrials.gov/study/NCT06097663?term=DFV890&rank=4, https://clinicaltrials.gov/study/NCT05552469?term=DFV890&rank=5, https://clinicaltrials.gov/study/NCT04382053?term=DFV890&rank=6,

22. Robak, M. T.; Trincado, M.; Ellman, J. A., Enantioselective Aza-Henry Reaction with an N-Sulfinyl Urea Organocatalyst. *J. Am. Chem. Soc.* **2007,** *129* (49), 15110-15111.

23. Kimmel, K. L.; Robak, M. T.; Ellman, J. A., Enantioselective Addition of Thioacetic Acid to Nitroalkenes via N-Sulfinyl Urea Organocatalysis. *J. Am. Chem. Soc.* **2009,** *131* (25), 8754-8755.

24. Liu, X. W.; Yan, Y.; Wang, Y. Q.; Wang, C.; Sun, J., Highly enantioselective reduction of β-amino nitroolefins with a simple N-sulfinyl urea as bifunctional catalyst. *Chem. Eur. J.* **2012,** *18* (30), 9204-9207.

25. Miller, D.; Thom, S.; St-Gallay, S.; Shannon, J.; Leeson, P. Preparation of to sulfoximine ureas and sulfoximine thioureas comprising a cyclic group substituted at the α-position useful inhibiting NLRP3. Patent WO 2019/068772, **2019**.

26. 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* (5), 4147-4181.

27. De Ventura, T.; Zanirato, V., Recent Advances in the Synthesis of Sulfonylureas. *Eur. J. Org. Chem.* **2021,** *2021* (8), 1201-1214.

28. Chen, Y.; Gibson, J., A convenient synthetic route to sulfonimidamides from sulfonamides. *RSC Adv.* **2015,** *5* (6), 4171-4174.

29. Davies, T. Q.; Hall, A.; Willis, M. C., One-Pot, Three-Component Sulfonimidamide Synthesis Exploiting the Sulfinylamine Reagent N-Sulfinyltritylamine, TrNSO. *Angew. Chem. Int. Ed.* **2017,** *56* (47), 14937-14941.

30. Davies, T. Q.; Tilby, M. J.; Ren, J.; Parker, N. A.; Skolc, D.; Hall, A.; Duarte, F.; Willis, M. C., Harnessing Sulfinyl Nitrenes: A Unified One-Pot Synthesis of Sulfoximines and Sulfonimidamides. *J. Am. Chem. Soc.* **2020,** *142* (36), 15445-15453.

31. Lo, P. K. T.; Willis, M. C., Nickel(II)-Catalyzed Addition of Aryl and Heteroaryl Boroxines to the Sulfinylamine Reagent TrNSO: The Catalytic Synthesis of Sulfinamides, Sulfonimidamides, and Primary Sulfonamides. *J. Am. Chem. Soc.* **2021,** *143* (38), 15576-15581.

32. Ding, M.; Zhang, Z.-X.; Davies, T. Q.; Willis, M. C., A Silyl Sulfinylamine Reagent Enables the Modular Synthesis of Sulfonimidamides via Primary Sulfinamides. *Org. Lett.* **2022,** *24* (8), 1711-1715.

33. García Mancheño, O.; Bolm, C., Synthesis of sulfonimidamides from sulfinamides by oxidation with N-chlorosuccinimide. *Beilstein J. Org. Chem.* **2007,** *3*, 25.

34. Gao, B.; Li, S.; Wu, P.; Moses, J. E.; Sharpless, K. B., SuFEx Chemistry of Thionyl Tetrafluoride (SOF₄) with Organolithium Nucleophiles: Synthesis of Sulfonimidoyl Fluorides, Sulfoximines, Sulfonimidamides, and Sulfonimidates. *Angew. Chem. Int. Ed.* **2018,** *57* (7), 1939-1943.

35. Yu, H.; Li, Z.; Bolm, C., Copper-Catalyzed Transsulfinamidation of Sulfinamides as a Key Step in the Preparation of Sulfonamides and Sulfonimidamides. *Angew. Chem. Int. Ed.* **2018,** *57* (47), 15602-15605.

36. 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* (55), 12533-12538.

37. Luisi, R.; Bull, J. A., Synthesis of Sulfoximines and Sulfonimidamides Using Hypervalent Iodine Mediated NH Transfer. *Molecules* **2023,** *28* (3), 1120.

38. Nandi, G. C.; Arvidsson, P. I., Sulfonimidamides: Synthesis and Applications in Preparative Organic Chemistry. *Adv. Synth. Catal.* **2018,** *360* (16), 2976-3001.

39. Teng, S.; Shultz, Z. P.; Shan, C.; Wojtas, L.; Lopchuk, J. M., Asymmetric synthesis of sulfoximines, sulfonimidoyl fluorides and sulfonimidamides enabled by an enantiopure bifunctional S(VI) reagent. *Nat. Chem.* **2024,** *16*, 183-192.

40. Booms, R. E.; Cram, D. J., Stereochemistry of sulfur compounds. III. Radical-chain mechanism for racemization of sulfinamides. *J. Am. Chem. Soc.* **1972,** *94* (15), 5438-5446.

41. Wojaczyńska, E.; Wojaczyński, J., Modern Stereoselective Synthesis of Chiral Sulfinyl Compounds. *Chem. Rev.* **2020,** *120* (10), 4578-4611.

42. Winkler, F. K.; Dunitz, J. D., The non-planar amide group. *J. Mol. Biol.* **1971,** *59* (1), 169-182.

43. Hutchby, M.; Houlden, C. E.; Haddow, M. F.; Tyler, S. N.; Lloyd-Jones, G. C.; Booker-Milburn, K. I., Switching pathways: room-temperature neutral solvolysis and substitution of amides. *Angew. Chem. Int. Ed.* **2012,** *51* (2), 548-551.

44. Hutchby, M.; Houlden, C. E.; Ford, J. G.; Tyler, S. N.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I., Hindered ureas as masked isocyanates: facile carbamoylation of nucleophiles under neutral conditions. *Angew. Chem. Int. Ed.* **2009,** *48* (46), 8721-8724.

45. Ying, H.; Cheng, J., Hydrolyzable Polyureas Bearing Hindered Urea Bonds. *J. Am. Chem. Soc.* **2014,** *136* (49), 16974-16977.

46. Chen, L. Preparation of the 2,4-disubstituted pyrimidine derivative and their medical applications. Patent WO 2020/259683, **2020**.

47. Zhao, P.; Zeng, Q., Progress in the Enantioselective Synthesis of Sulfur (VI) Compounds. *Chem. Eur. J.* **2023,** *29* (47), e202302059.

48. Zhang, X.; Wang, F.; Tan, C.-H., Asymmetric Synthesis of S(IV) and S(VI) Stereogenic Centers. *JACS Au* **2023,** *3* (3), 700-714.