Heteroaryl sulfonamide synthesis: Scope and limitations

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Abstract: Heteroaryl sulfonamides are important structural motifs in the medicinal and agrochemical industries. However, their synthesis often relies on the use of heteroaryl sulfonyl chlorides, which are unstable and toxic reagents. Herein, we report a protocol that allows direct oxidative coupling of heteroaryl thiols and primary amines, readily available and inexpensive commodity chemicals. The transformation proceeds under mild reaction conditions and yields the desired *N*-alkylated sulfonamides in good yields. *N*-alkyl heteroaryl sulfonamides can be further transformed using a microwave-promoted Fukuyama-Mitsunobu reaction to *N,N*-dialkyl heteroaryl sulfonamides. Developed protocols enable the synthesis of previously difficult-to-prepare sulfonamides (toxic reagents, harsh conditions, and low yields) under mild conditions.

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General information

All starting materials were purchased from commercial suppliers and used without further purification, unless otherwise stated. All reactions were performed in round-bottom flasks fitted with rubber septa using standard laboratory techniques under positive pressure of argon. Anhydrous Tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), and 1,2-dichloroethane (1,2-DCE) were purchased from Sigma-Aldrich. The purification of the reaction products was carried out by column chromatography using Standard Grade silica gel (60 Å, 230–400 mesh), by preparative thin layer chromatography glass plates precoated with silica gel (silica gel G-200 F_{254}), or by column chromatography using C18 silica gel. Analytical thin-layer chromatography was performed on a thin-layer chromatography (TLC) aluminum plates precoated with silica gel (silica gel 60 F_{254}). Visualization was accomplished with UV light, phosphomolybdic acid, and potassium permanganate stains, followed by heating.

The determination of melting points was done on a Büchi melting point apparatus. All microwave irradiation experiments were carried out on a dedicated CEM-Discover monomode microwave apparatus. The reactor was used in the standard configuration as delivered, including proprietary software. The reactions were carried out in 10- or 35-mL glass vials that were sealed with silicone/PTFE caps, which can be exposed to a maximum of 250 °C and 20 bar internal pressure. The temperature was measured with an IR sensor on the outer surface of the process vial. After the irradiation period, the reaction vessels were cooled to ambient temperature by gas jet cooling. The ^{1}H NMR and ^{13}C $\{^{1}H\}$ NMR spectra were measured on Jeol ECA400II (400 and 101 MHz) or Jeol 500 ECA (500 and 126 MHz) in $CHCl_3$. Chemical shifts are reported in ppm, and their calibration was performed (a) in case of ^{1}H NMR experiments on the residual peak of non-deuterated solvent δ ($CHCl_3$) = 7.26 ppm, in case of ^{13}C NMR experiments on the middle peak of the ^{13}C signal in deuterated solvent δ ($CHCl_3$) = 77.16 ppm. Proton coupling patterns are represented as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), triplet of triplet (tt), and multiplet (m). High-resolution mass spectrometry (HRMS) on Agilent 6230 high-resolution mass spectrometer with electrospray ionization (ESI) and a time-of-flight analyzer operating in a positive or negative full scan mode in the range of 100− 1700 m/z. High-performance liquid chromatography (HPLC) was performed using an Agilent 1290 Infinity II system with UV-VIS detector and an Agilent InfinityLab LC/MSD mass detector. The purification using semiprep HPLC was carried out on Agilent 1290 Infinity II with UV-VIS and the Agilent InfinityLab LC / MSD mass detector using the C18 reverse phase column (Agilent 5Prep-C18 10x21.2 mm). The gradient was formed from 15 mM aqueous ammonium acetate (buffer) and methanol with a flow rate of 20 mL/min. Optical rotation for selected compounds was measured on a Perkin Elmer Polarimeter 241 Automatic (Massachusetts, USA). SFC chiral analyzes were performed using an Acquity UPC2 system (Waters) consisting of a binary solvent manager, sample manager, column manager, column heater, convergence manager, PDA detector 2998, QDa mass detector and chiral analytical column Chiralpak IA3 (4.6 mm × 100 mm, 3 µm particle size). Chromatographic runs were carried out at a flow rate of 2.2 mL/min, column temperature of 38 °C, and ABPR 2000 psi. HPLC chiral analyses were performed using an Alliance 2695 system (Waters) consisting of a binary solvent manager, separation module, sample manager, column manager, PDA detector 2996, and a chiral analytical column YMC Chiral ART Amylose SA (4.6 mm × 250 mm, 5 µm particle size). Solvent (A) consisted of n-hexane, and solvent (B) consisted of isopropanol. The chromatographic runs were carried out at a flow rate of 0.5 mL/min, following binary gradient was used: 0 min, 10 % B; 0-8 min. linear gradient to 90 % B; 8-15 min. isocratic elution of 90 % B; 15-16 min. linear gradient to 10 % B; 16-26 min. isocratic elution of 10 % B. The effluent was then introduced to the PDA detector (scanning range 210-700 nm with 1.2 nm resolution. Potentiometric

titration for the determination of dissociation constant was carried out using a benchtop meter pH 50+ DHS (Instruments XS, Italy) equipped with an ATC glass electrode (for the determination of pKa in H_2O) or with the glass electrode ScienceLine N 6480 eth (SI Analytics™, Germany), electrolyte solution L 5034 – LiCl in ethanol (SI Analytics, Germany) (for the determination of pKa in EtOH). Before each measurement, a pH meter was calibrated with buffer solutions of pH 4.01 and 7.00. The titration was performed using Titronic® basic piston burette (Schott Instruments, Germany). A 0.01 M basic solution in water was prepared by dissolving an appropriate amount of 50% aqueous sodium hydroxide solution (w/V) purchased from Sigma-Aldrich in deionized water (Merck Millipore, USA) and a 0.05 M basic solution in EtOH was prepared by dissolving an appropriate amount of KOH (Penta Chemicals) in absolute ethanol (>99,7%, VWR Chemicals). The titrant was added in increments of 0.02 or 0.01 mL. Dissociation constants were calculated from titration curves.

Oxazole-2-thiol[1], caffeine-SH[2] and sulfenamides **9p** and **q**[3] were synthesized according to published procedures.

Computational Details

All quantum chemical calculations were performed using the Gaussian 16 software package.[4] Sulfonamide geometries were optimized using Density Functional Theory at the B3LYP/cc-pVDZ level of theory with Grimme's D3 dispersion correction and Becke-Johnson damping function.[5–9] At the same level of theory, subsequent frequency calculations were carried out to ensure that all geometries are minima on the potential energy surface. This hybrid functional is known to perform well for geometry optimizations with a low computational cost.[10] To account for the solvent interactions, an implicit continuum solvent model, more precisely the SMD model, was introduced with tetrahydrofuran (THF) as solvent.[11]

Three indices are put forward to estimate the local reactivity of the sulfonamide's C_α atom. To probe for electrostatic interactions, so-called hard-hard interactions, an NBO analysis was carried out as implemented in Gaussian 16 to obtain the Natural Population Analysis (NPA) charges.[12–15] We also probed the soft-soft reactivity[16] associated with the frontier orbital interactions through the local Fukui function for the nucleophilic attack $f^+(\mathbf{r})$ as defined in Equation 1.[17]

$$f^+(\mathbf{r}) = \left(\frac{\partial \rho(\mathbf{r})}{\partial N}\right)^+_{v(\mathbf{r})} \approx \rho_{N+1}(\mathbf{r}) - \rho_N(\mathbf{r}) \quad (1)$$

Equation 1 relies on the Finite Differences Approximation (FDA), where $\rho_{N+1}(\mathbf{r})$ (r) and $\rho_N(\mathbf{r})$ represent the electron densities of the anionic and neutral systems computed at the geometry of the neutral sulfonamides. The Fukui function can be condensed to atoms using the NPA partitioning (Equation 2):

$$f_k^+ = N_k[N+1] - N_k[N] \quad (2)$$

where N_k is the number of electrons assigned to atom *k* of the molecular system. This atom condensation methodology based on the NPA charges has already proven its reliability for the calculation of the Fukui functions.[18]

Since Fukui functions are local descriptors used primarily to evaluate the reactivity of regions or sites within a given system, they are not ideal when a series of molecules need to be compared. We therefore opted

for the local electrophilicity index, which involves a distribution of the global electrophilicity index via the Fukui function $f^+(\mathbf{r})$. The global electrophilicity index ω was proposed by Parr et al.[19] as:

$$\omega = \frac{\mu^2}{2\eta} \approx \frac{(IE + EA)^2}{8(IE - EA)} \quad (3)$$

where μ is the electronic chemical potential, η the chemical hardness, *IE* the vertical ionization energy and *EA* the vertical electron affinity. It measures the energy stabilization when an electrophile gets saturated with electrons. The local electrophilicity index (ω^+) based on the global index is then defined as the global electrophilicity index multiplied with the Fukui function for the nucleophilic attack (Equation 4).[20,21]

$$\omega^+(\mathbf{r}) = \omega f^+(\mathbf{r}) \quad (4)$$

DFT calculation of the local electrophilicity index ($\omega_{C_\alpha}^{+}$) and partial charge at C_α of selected heteroaryl sulfonamides

The purpose of the DFT calculations was to evaluate the tendency of the C_α carbon atom in heteroaryl sulfonamides to undergo nucleophilic addition (Figure S1D). We considered this preliminary step as important, since we previously faced some problems during the isolation of selected heteroaryl sulfonamides due to their instability during column chromatography on silica gel.

In silico evaluation revealed that sulfonamides **1a-10a** (Figure 1E) can be found in two types of conformation, linear and sandwich-like ($\pi-\pi$ stacking interactions), where the sandwich-like conformation has lower energy (Figure SDFT1 and 2). Since the observed $\pi-\pi$-conformation is presumably specific to the *N*-benzyl substitution in sulfonamides, both conformers were considered when the local electrophilicity index and partial charge at C_α were calculated (Figure S1A). The Gibbs free energy difference between both conformations is listed in Figure S1B. In all cases, the sandwich-like conformation is the most stable. Furthermore, the case of protonated sulfonamides **2a-10a** was considered (Figure S1C) due to the expected instability of generated sulfonamides in protic solvents, on silica gel or in the presence of Lewis or Brønsted acid.

A. Calculated local electrophilicity $\omega^{+}_{C\alpha}$ values and partial charges at C_α for linear and sandwich conformer

	linear		*sandwich*	
	$\omega^{+}_{C\alpha}$	q (NPA)	$\omega^{+}_{C\alpha}$	q (NPA)
1a	0.19	-0.30	0.17	-0.31
1b	0.18	-0.32	0.15	-0.32
1c	0.27	-0.27	0.25	-0.27
2a	0.19	0.00	0.20	-0.01
3a	0.06	0.26	0.07	0.25
4a	0.18	0.22	0.18	0.20
5a	0.07	0.13	0.07	0.13
6a	0.15	0.18	0.15	0.15
7a	0.25	0.34	0.25	0.43
8a	0.23	0.31	0.18	0.40
9a	0.27	-0.18	0.25	-0.16
10a	0.25	-0.23	0.21	-0.18

B. Gibbs free energy difference between the linear and the sandwich conformations in kJ mol^{-1}

	$\Delta G_{linear/sandwich}$ [kJ/mol]
1a	3.40
1b	2.82
1c	6.78
2a	5.33
3a	7.94
4a	9.04
5a	-0.61
6a	7.93
7a	12.26
8a	6.60
9a	1.55
10a	8.94

C. Comparison of calculated local electrophilicity $\omega^{+}_{C\alpha}$ values at Cα and global ω values for sandwich and protonated sandwich conformer

	sandwich		*H$^+$-sandwich*	
	$\omega^{+}_{C\alpha}$	ω	$\omega^{+}_{C\alpha}$	ω
2a	0.20	1.45	0.44	3.15
3a	0.07	1.60	0.32	3.58
4a	0.18	1.38	0.50	2.63
5a	0.07	1.04	0.44	2.01
6a	0.15	1.16	0.54	2.63
7a	0.25	1.58	0.69	3.09
8a	0.18	1.23	0.68	2.61
9a	0.25	1.73	0.64	3.63
10a	0.21	1.51	0.67	3.19

D. Unprotonated and protonated sulfonamides evaluated *in silico*, carbon C_α =

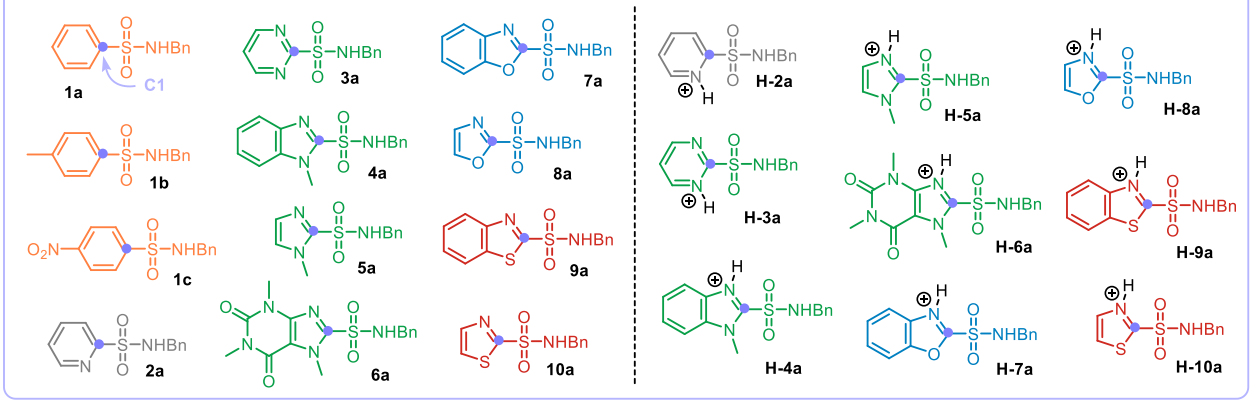


Figure S1. *In silico* evaluation of sulfonamides **1a-10a**. (A) Calculated values of the local electrophilicity index $\omega^{+}_{C\alpha}$ and partial charges at carbon Cα for the two most stable conformations found during geometry optimization. (B) Calculated Gibbs free energy difference between the linear and sandwich-like conformations. (C) Comparison of the $\omega^{+}_{C\alpha}$ and partial charges at Cα for the neutral and protonated form of **2a-10a** sulfonamides. (D) Overview of *in silico* evaluated sulfonamides **1a-10a** and **H-1a-H10a**.

Table S1. Gibbs free energy difference between the protonated linear and the protonated sandwich-like conformations in kJ mol^{-1}.

Heterocycle	$\Delta G_{\text{open-π-π-stacked}}$
H-2a	15.41
H-3a	9.92
H-4a	9.42
H-5a	8.75
H-6a	15.94
H-7a	17.31
H-8a	18.74
H-9a	15.00
H-10a	15.49

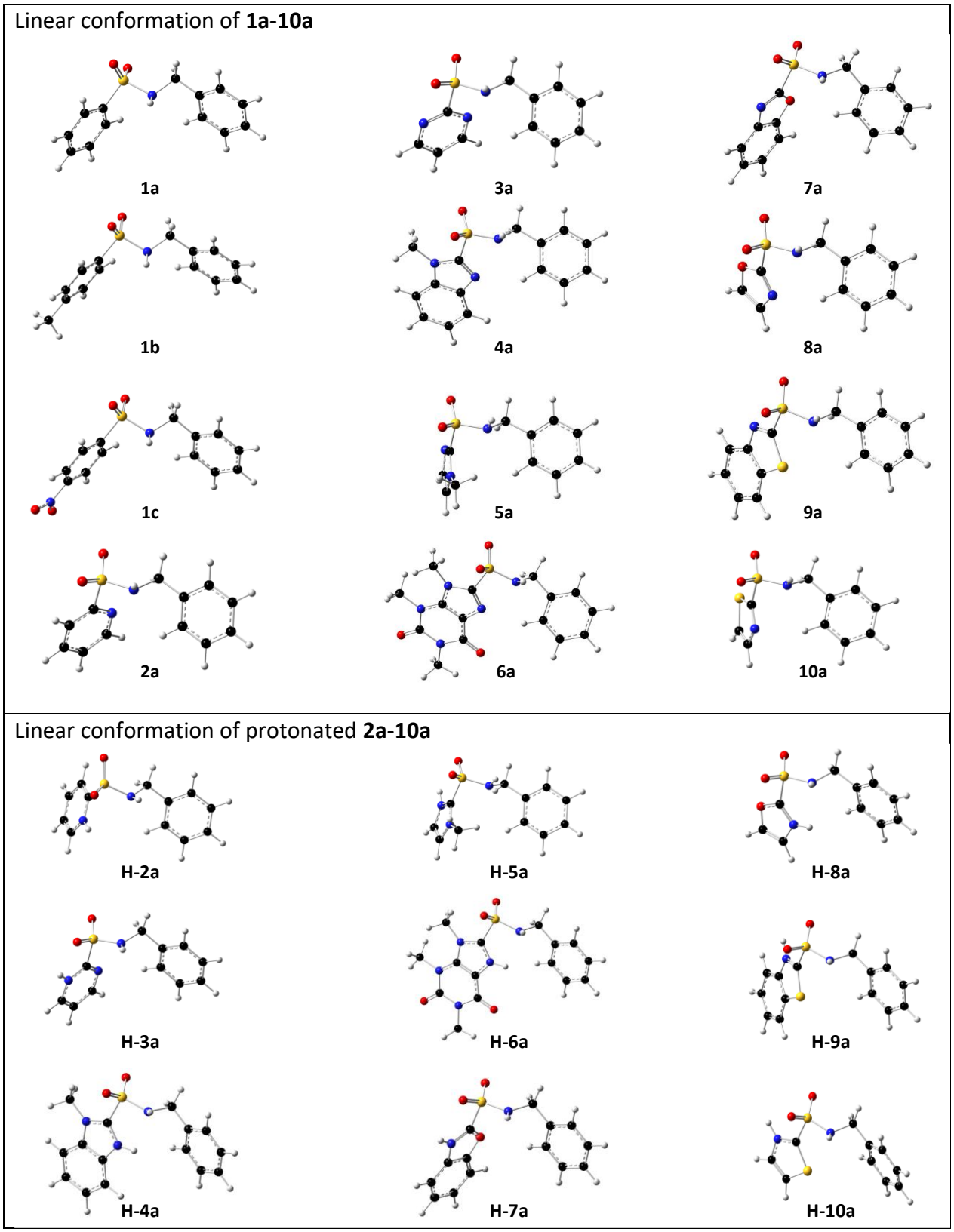


Figure SDFT1: 3D representation of the linear conformation of **1a**–**10a** and protonated **2a**–**10a**. *Color code: black = carbon, blue = nitrogen, red = oxygen, yellow = sulfur, and white = hydrogen.*

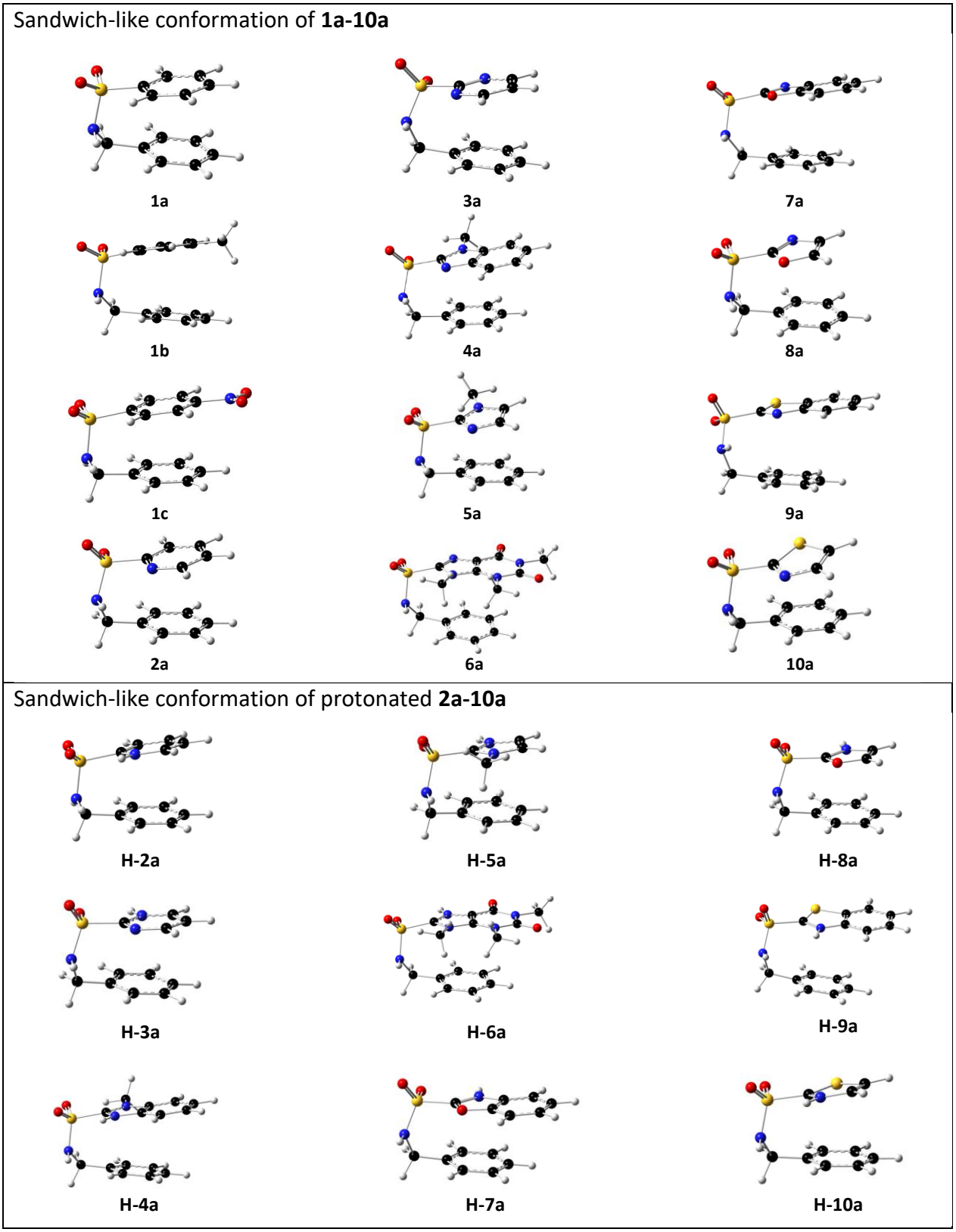


Figure SDFT2: 3D representation of the sandwich-like conformation of **1a**–**10a** and the protonated **2a**–**10a**. *Color code: black = carbon, blue = nitrogen, red = oxygen, yellow = sulfur, and white = hydrogen.*

Tables S2 and S3 list the partial charge at C_α ($q_{C_\alpha}^{NPA}$), the Fukui function for a nucleophilic attack condensed at C_α ($f_{C_\alpha}^{+}$), which, when multiplied with the global electrophilicity index ω, yields the local electrophilicity index, $\omega_{C_\alpha}^{+}$, for the sandwich-like and linear conformations of **2a**-**10a**, respectively. Both unprotonated and protonated sulfonamides are considered.

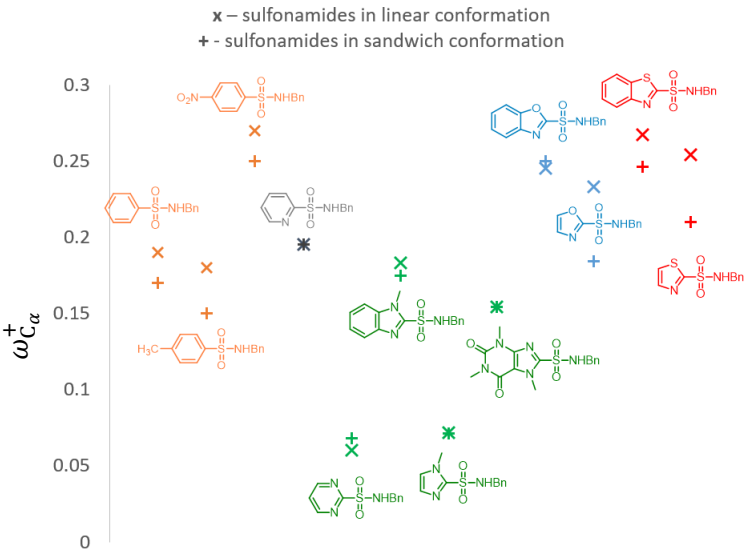
Graphs S1-5 offer a more visual representation of the data in Tables S2 and S3. A color code was used according to the type of heterocycle synthesized.

Table S2. Computed NPA charges, $f_{C_\alpha}^{+}$, ω and $\omega_{C_\alpha}^{+}$ at the sulfonamides' C_α carbons of the sandwich-like conformations.

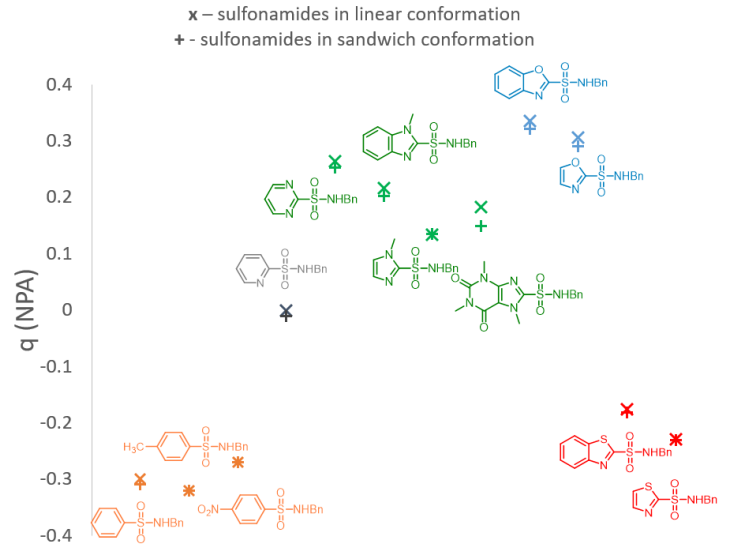
Heterocycle	unprotonated				protonated			
	$q_{C_\alpha}^{NPA}$	$f_{C_\alpha}^{+}$	ω	$\omega_{C_\alpha}^{+}$	$q_{C_\alpha}^{NPA}$	$f_{C_\alpha}^{+}$	ω	$\omega_{C_\alpha}^{+}$
2a	-0.011	0.135	1.45	0.195	0.018	0.138	3.15	0.436
3a	0.253	0.042	1.60	0.068	0.294	0.089	3.58	0.319
4a	0.202	0.127	1.38	0.175	0.259	0.191	2.63	0.501
5a	0.135	0.068	1.04	0.071	0.213	0.218	2.01	0.436
6a	0.148	0.133	1.16	0.154	0.235	0.205	2.63	0.540
7a	0.321	0.158	1.58	0.250	0.427	0.223	3.09	0.691
8a	0.290	0.150	1.23	0.184	0.400	0.258	2.61	0.675
9a	-0.182	0.142	1.73	0.246	-0.161	0.175	3.63	0.637
10a	-0.231	0.139	1.51	0.210	-0.173	0.211	3.19	0.673

Table S3. Computed NPA charges, $f_{C_\alpha}^{+}$, ω and $\omega_{C_\alpha}^{+}$ at the sulfonamides' C_α carbons of the linear conformations.

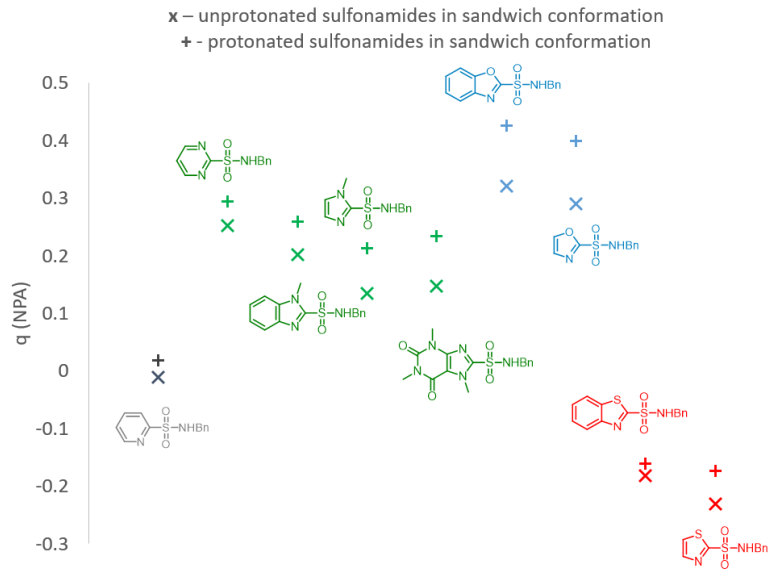
Heterocycle	unprotonated				protonated			
	$q_{C_\alpha}^{NPA}$	$f_{C_\alpha}^{+}$	ω	$\omega_{C_\alpha}^{+}$	$q_{C_\alpha}^{NPA}$	$f_{C_\alpha}^{+}$	ω	$\omega_{C_\alpha}^{+}$
2a	-0.001	0.134	1.45	0.195	0.029	0.137	3.25	0.444
3a	0.264	0.038	1.60	0.060	0.307	0.086	3.71	0.319
4a	0.216	0.139	1.31	0.183	0.278	0.198	2.46	0.486
5a	0.133	0.068	1.06	0.072	0.215	0.236	2.09	0.493
6a	0.182	0.145	1.07	0.154	0.259	0.213	2.42	0.516
7a	0.335	0.159	1.54	0.245	0.437	0.237	3.14	0.743
8a	0.306	0.191	1.22	0.233	0.415	0.275	2.61	0.718
9a	-0.176	0.152	1.76	0.267	-0.152	0.185	3.71	0.686
10a	-0.230	0.159	1.60	0.254	-0.167	0.208	3.20	0.666



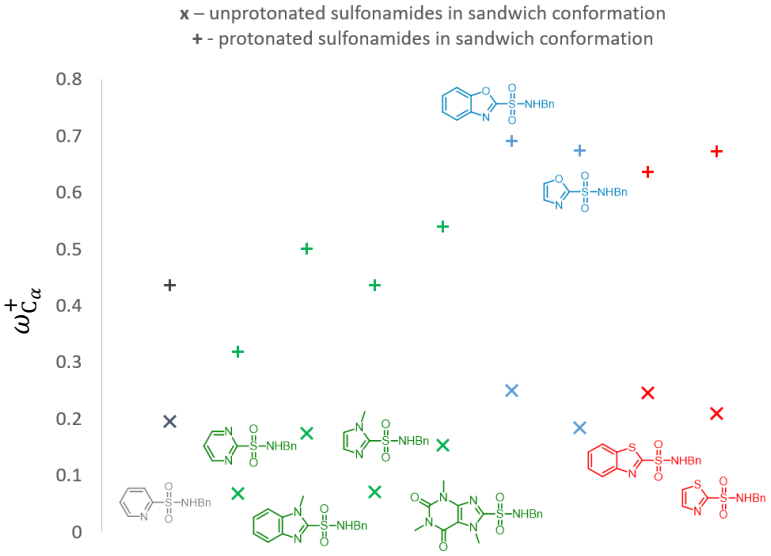
Graph S1. Comparison of the calculated local electrophilicity index $\omega^{+}_{C_\alpha}$ values at carbon C_α of sulfonamides **1a-10a** for both linear (**x**) and sandwich (**+**) conformers.



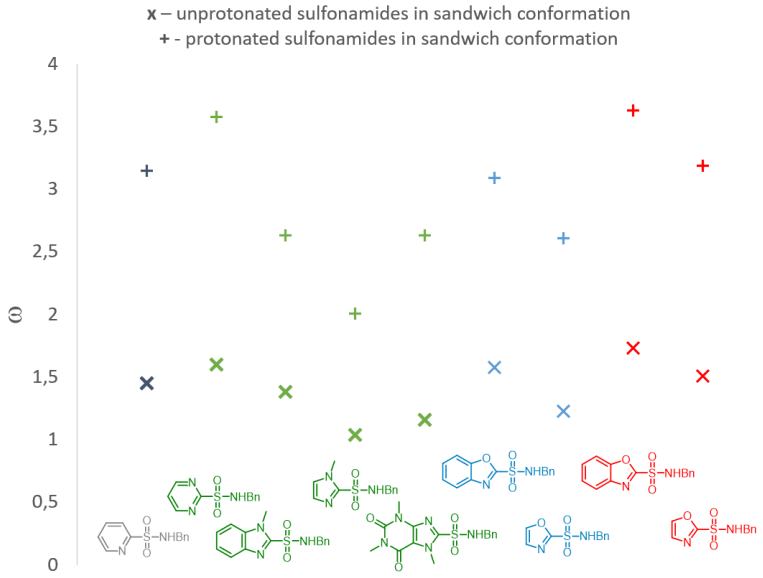
Graph S2. Comparison of the calculated partial charges at carbon C_α of sulfonamides **2a-10a** for both linear (**x**) and sandwich (**+**) conformers.



Graph S3. Comparison of the calculated partial charges at carbon C_α of sulfonamides **1a-10a** for unprotonated sandwich (**x**) and the protonated sandwich (**+**) conformer.



Graph S4. Comparison of the calculated local electrophilicity index $\omega^+_{C_\alpha}$ values at carbon C_α of sulfonamides **2a-10a** for unprotonated sandwich (**x**) and protonated sandwich (**+**) conformers.



Graph S5. Comparison of the calculated global electrophilicity index ω values of sulfonamides **2a-10a** for unprotonated sandwich (**x**) and protonated sandwich (**+**) conformers.

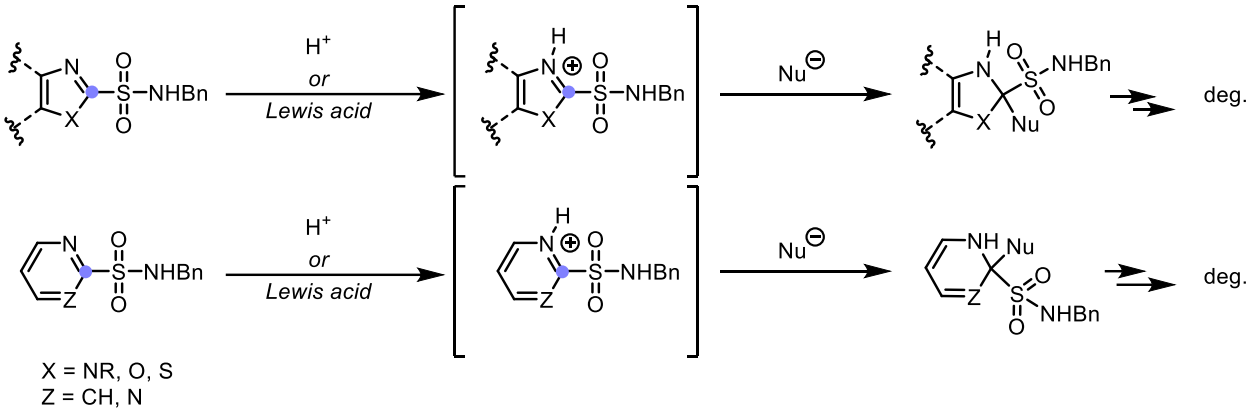
Based on the calculated $\omega_{C_\alpha}^{+}$ values, evaluated sulfonamides were divided into two groups. In the first, sulfonamides with relatively high affinity towards the nucleophiles at C_α atom (nitro-aryl (**1c**), N,O-containing (**7a** and **8a**) and N,S-containing (**9a** and **10a**) heteroaryl sulfonamides) are included. In these cases, small or insignificant differences of $\omega_{C_\alpha}^{+}$ values between the two investigated conformers were observed (Graph S1, in case of small differences, sandwich-like conformers had higher $\omega_{C_\alpha}^{+}$ values). Interestingly, when partial charges of C_α were evaluated, the C_α carbon atom in N,O-heteroaryl sulfonamides **7a** and **8a** had a substantially higher partial charge (is more electrophilic) than those of **1c** and **9a** and **10a** (Graph S2). The second group of sulfonamides consists of aryl (**1a,b**), 2-pyridinyl (**2a**), and *N,N*-heteroaryl (**3a** - **6a**) sulfonamides with medium to low affinity towards nucleophiles at C_α. In addition, in these cases, no significant differences in C_α local electrophilicity index values were observed in the case of the linear and sandwich-like conformation.

Much to our surprise, the C_α electrophilicity of aryl sulfonamides was similar to that calculated for heteroaryl derivatives (Graph S1). Based on our experience with the instability of various benzothiazole-2-yl sulfones and sulfonamides on silica gel we expected that the C_α electrophilicity index value would be substantially higher than that of aryl sulfonamides. Thus, we speculate that the observed (and presumed) instability of various heteroaryl sulfonamides is caused by the additional *in situ* activation of the heterocyclic ring (increase of the electrophilicity) towards the nucleophilic attack (Scheme S1).

As a consequence, we expected that other heteroaryl sulfonamides, especially those containing the oxazole ring, might be highly unstable on silica gel and/or in the presence of acid (Scheme S1).

To shed some light on this problem, an *in silico* evaluation of global and C_α electrophilicity of protonated forms of sulfonamides **2a-10a** was carried out (Figure S1C). Again, two conformations were examined, of which sandwich-like structures are substantially more stable (Table S1). Not surprisingly, protonated sulfonamides were observed to be more electrophilic (global electrophilic index ω, Figure S1C, Graph S5) than the corresponding unprotonated (data shown only for more stable sandwich conformer). In all

calculated cases, the values of the local electrophilicity index values on carbon C_α, $\omega^+_{C_\alpha}$, in protonated sulfonamides **2a-10a** in their sandwich conformation are significantly higher than the unprotonated (Graph S4), suggesting that the stability of heteroaryl sulfonamides generated in a strong protic environment could be an issue. Interestingly, the local partial charges of the protonated and unprotonated forms were not as significantly different (Graph S3).



Scheme S1. Proposed method of degradation of *N*-containing heteroaryl sulfonamides via proton/Lewis acid activation (demonstrated for H^+ activation).

Optimization of the oxazole sulfonamide 7a synthesis

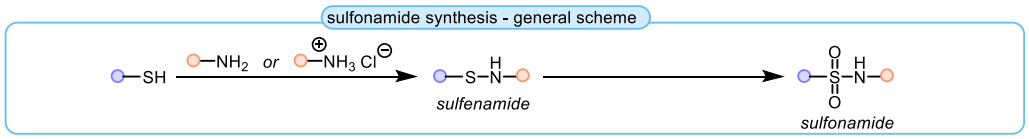
Our attempts toward sulfonamide **7a** synthesis started with optimization of the reaction conditions. Sulfonamide **7a** was selected as a target due to its presumable instability (see above) and / or incompatibility with previously developed reaction conditions. Very quickly it was observed that the originally developed reaction conditions[3] are far from being optimal (Figure 2C, entry 1). Thus, we have decided to evaluate both steps of the sequence with the aim of optimizing the reaction yield.

First, we focused on the formation of sulfenamide (Figure S2). The reaction mechanism that includes the best starting ratio thiol/amine was already previously studied[3]; therefore, we focused mainly on the role of NCS equivalents and solvent in the case of two heteroaryl thiols, pyrimidine-2-thiol (Figure S2A) and benzo[d]oxazole-2-thiol (Figure S2B). In both cases, the reaction work-up was minimalized with simple filtration and washing of the filtrated solid (generated ammonium salt) with CH_2Cl_2 and the results obtained are reported based on the crude reaction mixture ^{1}H NMR spectra analysis. In both cases, the main and only side product formed during the transformation was a heteroaryl disulfide **S2**. Thus, our efforts were directed to diminish the amount of disulfide formation (for the mechanism of disulfide formation see[3]). After some evaluation of various solvents, reaction temperatures and equivalents of NCS (use of more equivalents of NCS than 1.0 equiv had no effect on the reaction), the combination of 1,2-DCE as a solvent and room temperature as a reaction temperature proved to give the best reaction yields of sulfenamide **S1**.

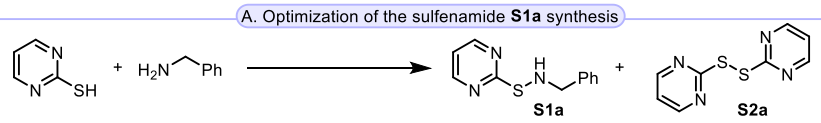
Having in hands straightforward approach to sulfenamide **S1b** (crude mixture of **S1b** included disulfide **S2b**), its oxidation to sulfonamide **7a** was attempted. Various standard oxidation reagents were evaluated; however, only in the case of H_2O_2 (30% aq. sol.)/$(NH_4)_6MoO_4{\cdot}4H_2O$ (30 mol%) was compound **7a** formation observed (Figure S2C, entries 6 and 7). In this case, the use of 30mol% of molybdate proved to be sufficient (higher catalyst loading had no effect on reaction yield or kinetics, and lower catalyst loading prolonged

the reaction time but did not significantly influence reaction yield) and had little impact on the reaction outcome. On the other hand, the amount of H_2O_2 used had a crucial effect on the reaction yield of product **7a.** Although 10 equiv of H_2O_2 was necessary to achieve complete conversion of sulfenamide **S1b**, 20 equiv of peroxide led to a lower reaction yield of **7a** (Figure S2C, entries 6 and 7). The reason behind the lower reaction yield of **7a** observed in the case of a higher peroxide loading can be found in the degradation of **7a** under the reaction conditions to benzo[d]oxazol-2(3H)-one **S3** (for a control experiment, see Scheme S2A). The same compound is also formed through the oxidative decomposition of disulfide **S2b** (for a literature precedent see[22]).

Having these results in hands, the isolation of sulfonamide **7a** was attempted. Unfortunately, most standard chromatography techniques (various sorbents used – SiO_2, Florisil®, basic alumina, etc.) produced the desired sulfonamide **7a** as an inseparable mixture with compound **S3**, presumably due to partial hydrolysis of **7a** to **S3** (Scheme S2B). At this stage, crystallization proved to be the best separation techniques and the desired compound **7a** was isolated in 35% yield (Figure S2C, entry 7). Unfortunately, the crystallization technique proved to be inefficient in the case of some other benzoxazolsulfonamides (e.g. **7b, c**), which did not allow us to prepare those compounds in analytically pure form. Interestingly, when *N,N*-disubstituted sulfonamide (–)-**17f** was prepared by Mitsunobu alkylation, no decomposition was observed during purification on C18-SiO_2 (see experimental part).

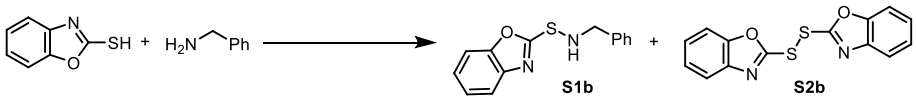


A. Optimization of the sulfenamide **S1a** synthesis



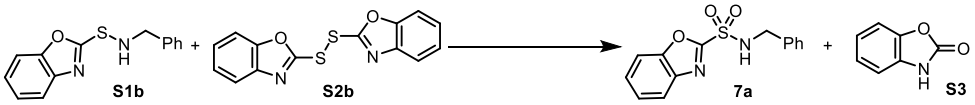
Entry	NCS (equiv)	Solvent	Temperature (Reaction time)	**S1a/S2a** ratio	**S1a** NMR yield (%)
1	1	CH_2Cl_2	25°C, 1h	1:0.31	76
2	1	CH_2Cl_2	25°C (30 min), reflux (1h)	1:0.26	79
3	1.5	CH_2Cl_2	RT (2.5 h)	1:0.38	72
4	1	toluene	RT (1 h)	1:0.41	71
5	1	THF	RT (1 h)	1:0.9	52
6	1	1,2-DCE	RT (1h)	1:0.21	82
7	1	1,2-DCE	50°C (1h)	1:0.22	81
8	1	1,2-DCE	50°C (1h), reflux (1h)	1:0.26	79
9	2	1,2-DCE	RT (1h)	1:0.25	74

B. Optimization of the sulfenamide **S1b** synthesis



Entry	NCS (equiv)	Solvent	Temperature (Reaction time)	**S1b/S2b** ratio	**S1b** NMR yield (%)
1	1	CH_2Cl_2	25°C, 1h	1:0.45	65
2	1	CH_2Cl_2	25°C (30 min), reflux (1h)	1:0.39	71
3	1.5	CH_2Cl_2	RT (2.5 h)	1:0.52	48
4	1	toluene	RT (1 h)	1:1.05	35
5	1	THF	RT (1 h)	1:0.91	38
6	1	1,2-DCE	RT (1h)	1:0.28	75
7	1	1,2-DCE	50°C (1h)	1:0.27	74
8	1	1,2-DCE	50°C (1h), reflux (1h)	1:0.31	69
9	2	1,2-DCE	RT (1h)	1:0.30	70

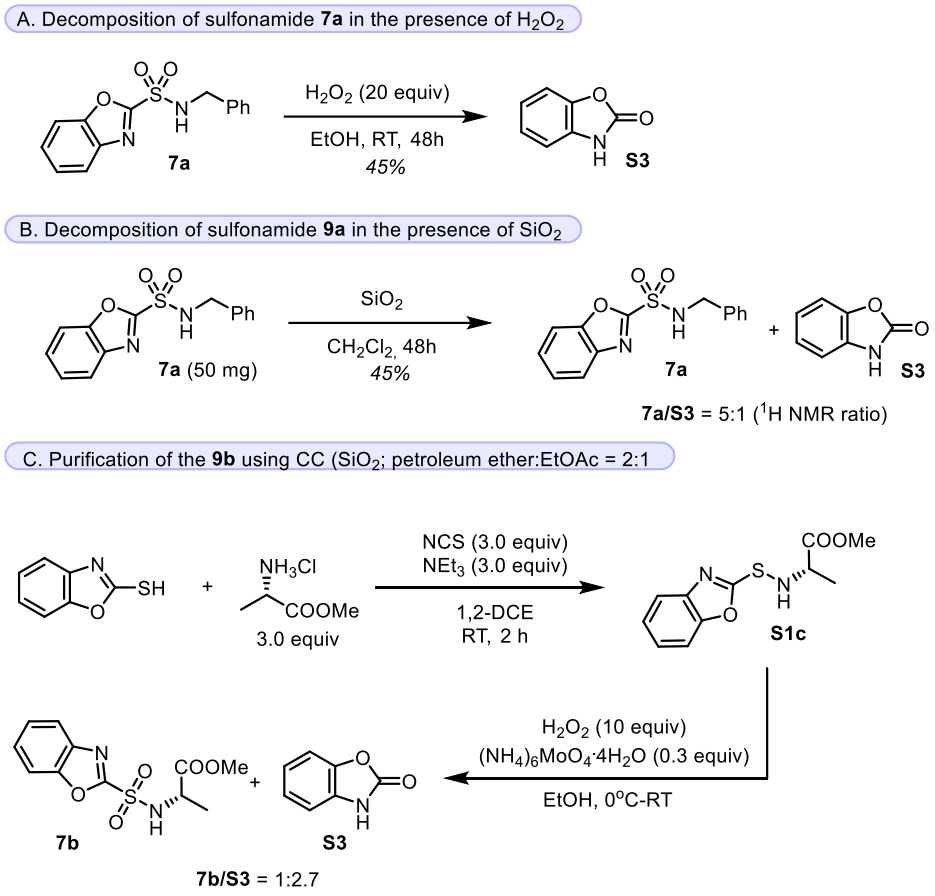
C. Sulfenamide **S1b** reaction mixture oxidation



Entry	Ox. reagent (equiv)	Solvent	Temperature (Reaction time)	**7a/S3** ratio	**7a** NMR yield (%)
1	*m*CPBA (5.0 equiv)	CH_2Cl_2	25°C, 1h	0:100	>5
2	*m*CPBA (2.2 equiv)	CH_2Cl_2	25°C (30 min), reflux (1h)	0:100	>5
3	$KMnO_4$ (10 equiv)	acetone	RT (18 h)	0:100	>5
4	H_2O_2 (20 equiv)	EtOH	RT (18 h)	0:100	>5
5	H_5IO_6 (3.0 equiv)/CrO_3 (0.3 equiv)	CH_3CN	0°C (6 h)	0:100	>5
6	H_2O_2 (20 equiv)/$(NH_4)_6MoO_4{\cdot}4H_2O$ (0.3 equiv)	EtOH	0°C (1h), RT (5h)	1:0.7	45
7	H_2O_2 (10 equiv)/$(NH_4)_6MoO_4{\cdot}4H_2O$ (0.3 equiv)	EtOH	0°C (1h), RT (18h)	1:0.6	55 (35)[a]

Figure S2. Selected examples of conditions evaluated to optimize the reaction yield of sulfenamides **S1**. (A) Optimization data for the synthesis of *N*-benzyl-S-(pyrimidin-2-yl)thiohydroxylamine (sulfenamide **S1a**) synthesis. (B) Optimization data for the synthesis of *N*-benzyl-S-(pyrimidin-2-yl)thiohydroxylamine (sulfenamide **S1a**) synthesis. (C) Optimization of the oxidation of the sulfenamide **S1b** reaction mixture. [a)] Isolated yield after recrystallization from 65% aq. EtOH. *All reactions were carried out on 1 mmol of heteroaryl thiol (A and B) or on the crude reaction mixture of sulfenamide **S1b** synthesis from Fig. S2B, entry 7. **S1a/S2a**, **S1b/S2b**, and **9a/S3** ratios are based on the ^{1}H NMR of the crude reaction mixture. NMR yield*

is based on the ^{1}H NMR spectra of the crude reaction mixture using dimethylsulfone as the internal standard.



Scheme S2. Side reactions of benzoxazole-based sulfonamides **7**. (A) Decomposition of **7a** to **S3** in the presence of H_2O_2. (B) Decomposition of sulfonamide **7a** on SiO_2. (C) Attempted synthesis of sulfonamide **7b** using the standard protocol that led to the formation of an inseparable mixture of **7b** and **S3**.

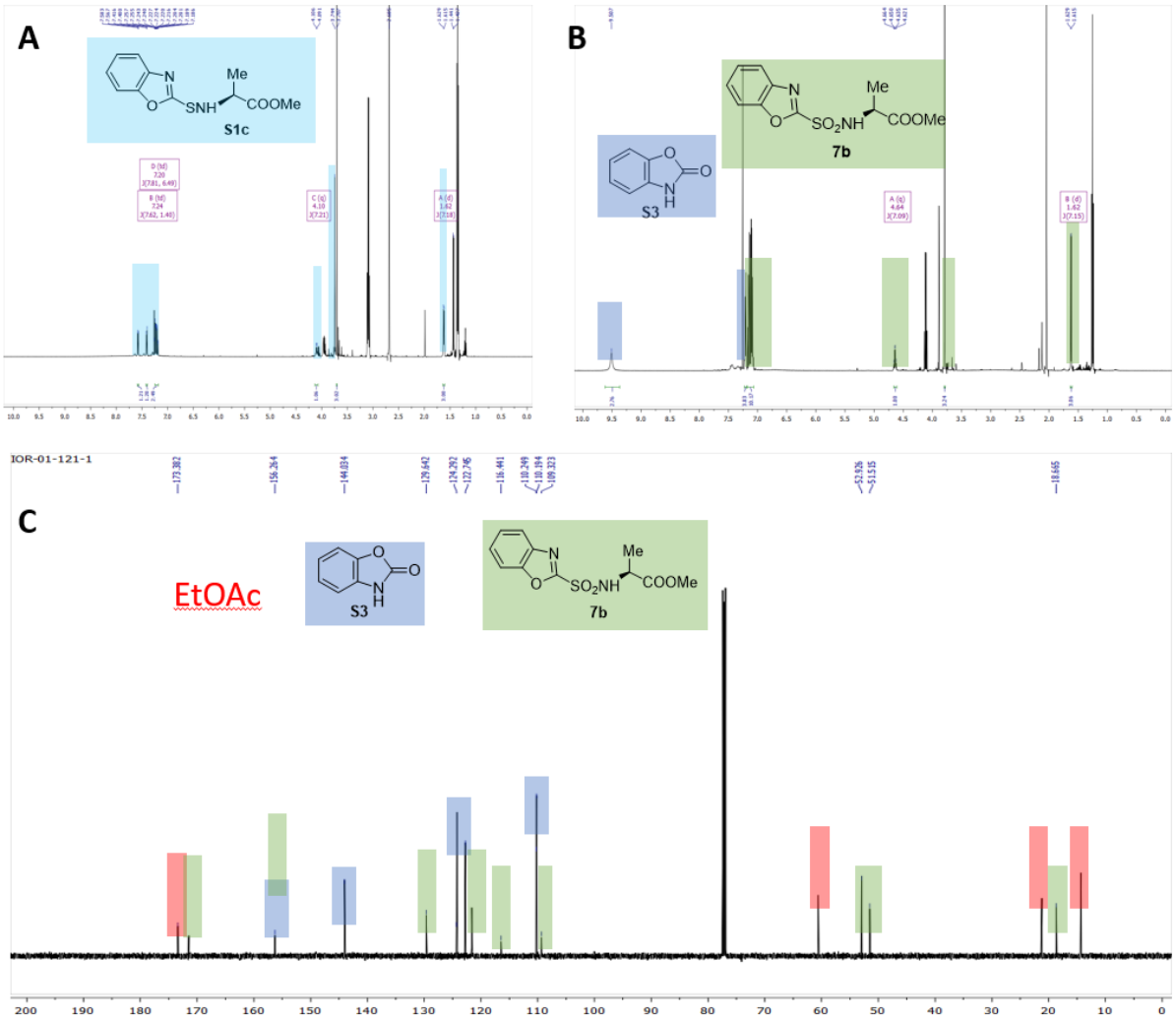


Figure S3. (A) ^{1}H NMR spectrum of the crude reaction mixture that yielded sulfenamide **S1c** (Scheme S2C; reaction recorded in $CDCl_3$, 500 MHz). Characteristic peaks of **S1c** highlighted in blue turquoise. (B) ^{1}H NMR spectrum of the crude reaction mixture of sulfenamide **S1c** oxidation to sulfonamide **7b** (Scheme S2C; reaction recorded in $CDCl_3$, 500 MHz). Characteristic peaks of the side product **S3** highlighted in blue and of sulfonamide **7b** in green. (C) $^{13}C\{^{1}H\}$ NMR spectrum of "purified" sulfonamide **7b** after column chromatography on silica gel (Scheme S2C; recorded in $CDCl_3$, 125 MHz). *Characteristic peaks of the side product **S3** highlighted in blue, of sulfonamide **7b** in green, and of EtOAc in red.*

Synthesis of sulfonamide 16

The synthesis of sulfonamide **16** starting with the corresponding 1-phenyl-1H-tetrazole-5-thiol proceeded well using the standard protocol (sulfenamide formation was not a problem (Figure S4A), the crude reaction mixture contained the desired product (Figure S4B)); however, product **16** proved to be unstable under all attempted purification techniques (Figure S4C). In addition, compound **16** also proved to be also bench unstable. The only pure compound that could be isolated was the product of **16** decompositions, phenyl tetrazole **S9** (Figure S4D).

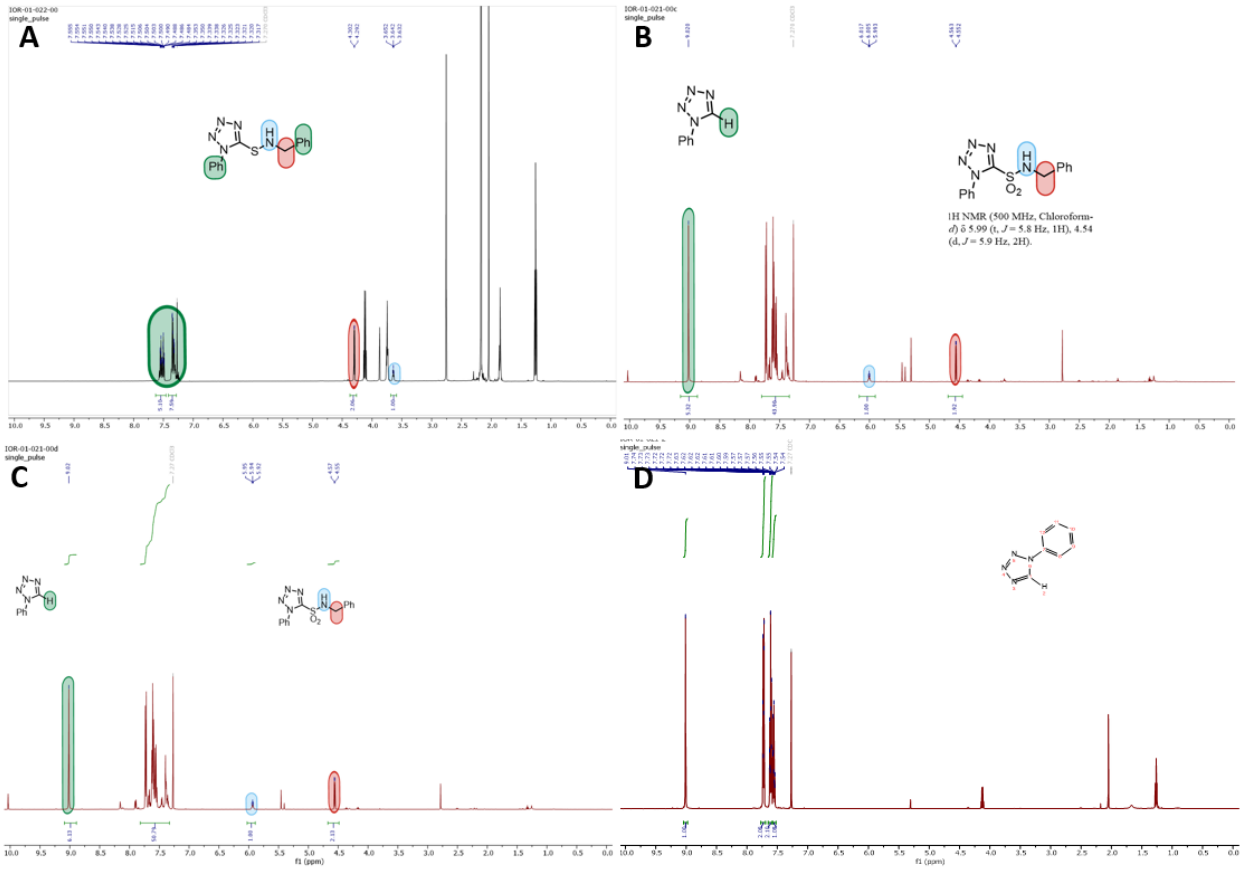
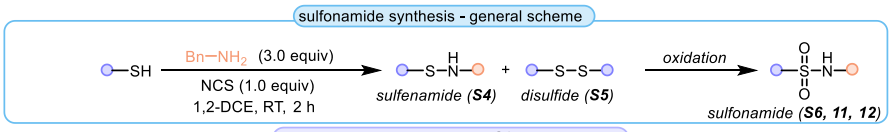


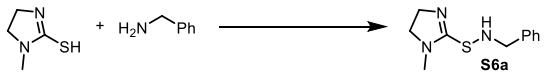
Figure S4. Sulfonamide **16** synthesis. (A) Crude ^{1}H NMR spectra of the reaction mixture after the formation of sulfenamide. Characteristic peaks of the product highlighted. (B) ^{1}H NMR spectra of the crude reaction mixture after the oxidation step. Characteristic peaks of sulfonamide **16** and side product **S9** are highlighted. Sulfonamide **16**: phenyl tetrazole **S9** = 1:5. (C) ^{1}H NMR spectra of the spot believed to correspond to pure sulfonamide **16** after purification by column chromatography on silica gel. Sulfonamide **16**: phenyl tetrazole **S9** = 1:6. (D) ^{1}H NMR spectra of pure isolated phenyl tetrazole side product **S9**.

Reactions of nonaromatic heterocycles

We were also interested in the synthesis of 4,5-dihydro imidazole-, oxazole- and thiazole-2-thiol-based sulfonamides. Therefore, the reaction conditions developed were applied to the corresponding dihydro thiols (Figure S5). In all cases, the formation of **S4** sulfenamide proceeded well and the desired compound could be generated smoothly along with small amounts of the corresponding disulfide (Figure S6). However, subsequent oxidation proved to be a problem, and, in most cases, a complex mixture of unidentifiable side products was formed. Only in two cases (Figure S5C, entry 4, and S5D, entry 1), a side product **S7** and **S8** were identified. The probable mechanism of **S7** and **S8** side product formation can be found in Scheme S3.

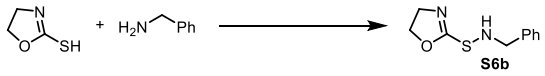


A. Attempted sulfonamide **S6a** synthesis



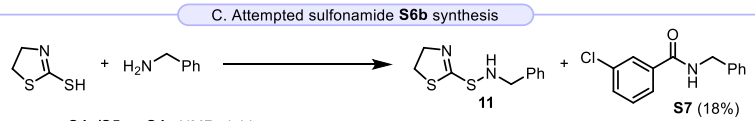
Entry	**S4a/S5a** ratio	**S4a** NMR yield (%)	*Oxidation conditions*	**S6a** NMR yield (%)	Note
1	1:0.28	68	30% aq. H_2O_2, cat. $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$ EtOH, 0°C to RT (2h)	>5	complex mixture
2	1:0.30	61	$KMnO_4$ (5 equiv), acetone, 0 °C, 24h	>5	complex mixture
3	1:0.31	59	H_5IO_6, CrO_3, MeCN, 0°C, 6h	>5	complex mixture
4	1:0.26	69	*m*CPBA (77%, 2.1 equiv), CH_2Cl_2, 0°C, 24h	>5	complex mixture

B. Attempted sulfonamide **S6b** synthesis



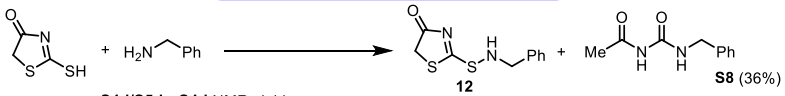
Entry	**S4b/S5b** ratio	**S4b** NMR yield (%)	*Oxidation conditions*	**S6b** NMR yield (%)	Note
1	1:0.35	51	30% aq. H_2O_2, cat. $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$ EtOH, 0°C to RT (2h)	>5	complex mixture
2	1:0.30	60	$KMnO_4$ (5 equiv), acetone, 0 °C, 24h	>5	complex mixture
3	1:0.28	61	H_5IO_6, CrO_3, MeCN, 0°C, 6h	>5	complex mixture
4	1:0.38	54	*m*CPBA (77%, 2.1 equiv), CH_2Cl_2, 0°C, 24h	>5	complex mixture

C. Attempted sulfonamide **S6b** synthesis



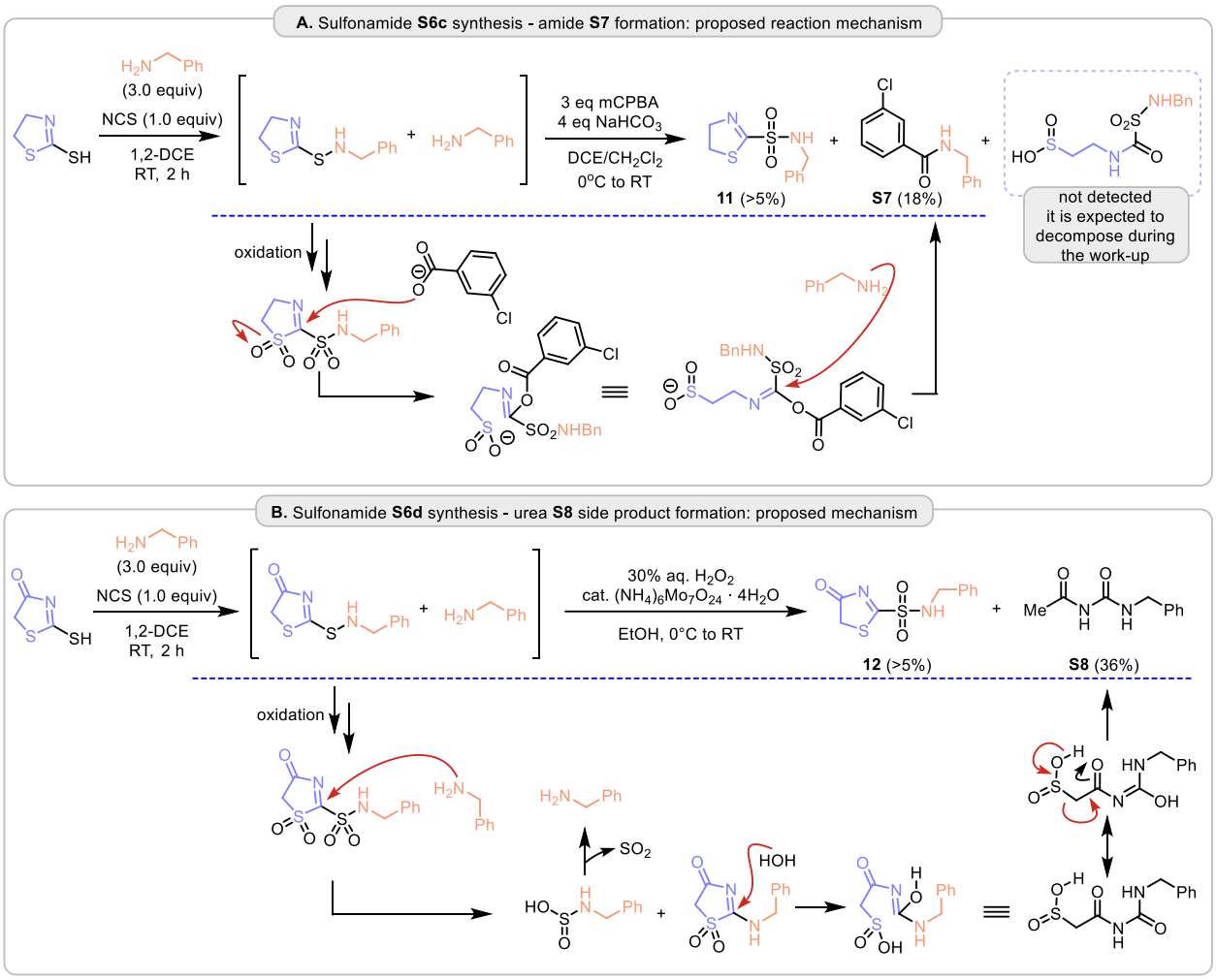
Entry	**S4c/S5c** ratio	**S4c** NMR yield (%)	*Oxidation conditions*	**11** NMR yield (%)	Note
1	1:0.11	68	30% aq. H_2O_2, cat. $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$ EtOH, 0°C to RT (2h)	>5	complex mixture
2	1:0.28	57	$KMnO_4$ (5 equiv), acetone, 0 °C, 24h	>5	complex mixture
3	1:0.29	59	H_5IO_6, CrO_3, MeCN, 0°C, 6h	>5	complex mixture
4	1:0.20	61	*m*CPBA (77%, 2.1 equiv), CH_2Cl_2, 0°C, 24h	>5	side product **S7** (18%)

C. Attempted sulfonamide **S6b** synthesis



Entry	**S4d/S5d** ratio	**S4d** NMR yield (%)	*Oxidation conditions*	**12** NMR yield (%)	Note
1	1:0.18	81	30% aq. H_2O_2, cat. $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$ EtOH, 0°C to RT (2h)	>5	side product **S8** (36%)
2	1:0.30	59	$KMnO_4$ (5 equiv), acetone, 0 °C, 24h	>5	complex mixture
3	1:0.27	63	H_5IO_6, CrO_3, MeCN, 0°C, 6h	>5	complex mixture
4	1:0.24	70	*m*CPBA (77%, 2.1 equiv), CH_2Cl_2, 0°C, 24h	>5	complex mixture

Figure S5. Selected reaction optimization results of attempted dihydro heteroaryl sulfonamide **S6**, **11** and **12** synthesis. All reactions were carried out on 5 mmol of dihydro heteroaryl-2-thiol. Ratios of **S4** and **S5** are based on the ^{1}H NMR spectra of crude reaction mixture. NMR yield is based on the ^{1}H NMR spectra of the crude reaction mixture using dimethylsulfone as an internal standard. The yields of side products **S7** and **S8** refer to the pure isolated compound.



Scheme S3. Proposed mechanism of the formation of the side product **S7** (Scheme S3A) and **S8** (Scheme S3B).

Taking into account the observed side products **S7** and **S8** and the proposed mechanism of their formation, we concluded that the targeted sulfonamides **S6** could be formed under the reaction conditions tested. However, we think that their decomposition occurred spontaneously as a result of the reaction conditions. Alternatively, decomposition might already occur from sulfinamide oxidative intermediates. In any case, we were unable to come up with any reaction conditions under which even traces of the desired sulfonamides would be formed.

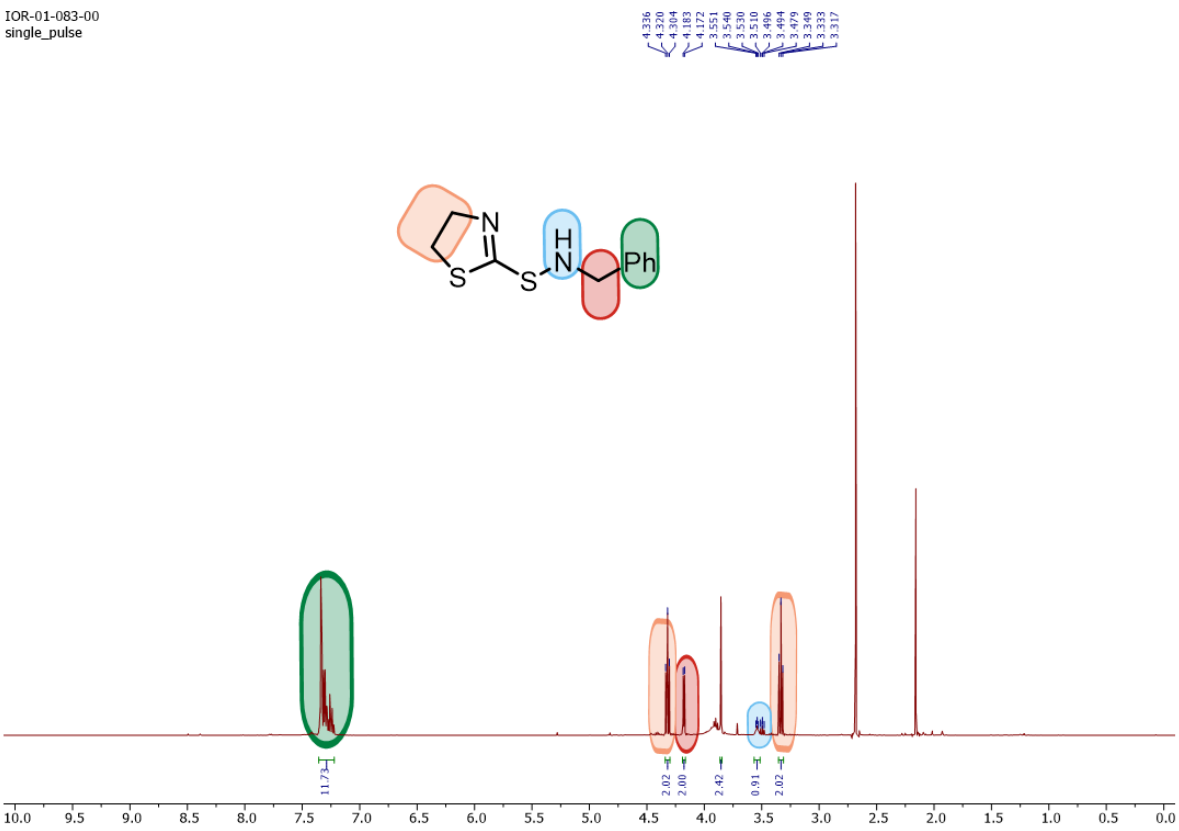


Figure S6. An example of the representative reaction mixture of the formation of sulfenamide **4** was shown for the formation of **S4c** (Figure S4C). Representative signals for **S4c** highlighted.

Microwave-assisted Fukuyama-Mitsunobu reaction

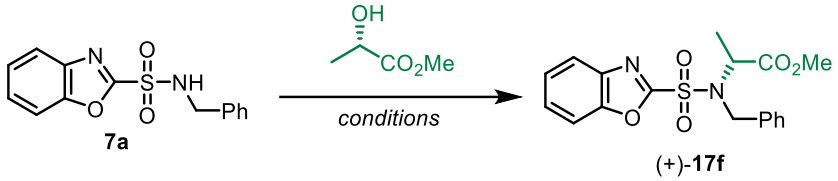
In our efforts to synthesize *N,N*-disubstituted sulfonamides by Fukuyama-Mitsunobu reaction (FMR), we focused directly on synthesis of sulfonamide (–)-**17f**. It was expected that this benzoxazole-based sulfonamide might be a troublemaker from both the stability and reactivity viewpoint. Our optimization efforts started with the reaction conditions we have recently developed[3] for benzothiazole sulfonamides (Table S4, entry 1). Unfortunately, it was very soon evident that such reaction conditions lead to the formation of the desired sulfonamide only in low isolated yields. Further variation in reagent and substrate equivalents did not bring much improvement (entries 2 to 4). In no case, the conversion of the starting sulfonamide **7a** was complete and therefore we attempted to extend the reactivity by adding additional amounts of reagents (entries 5 and 7) and reagents and starting alcohol (entries 6 and 8 – it was expected that starting alcohol can form olefin by elimination (competitive reaction upon alcohol activation)). Gratifyingly, under those reaction conditions (multiple repetition of sequence with fresh reagents and starting alcohol), full conversion of sulfonamide **7a** could be reached (entry 8). Unfortunately, in such cases, the crude reaction mixture contains a substantial amount of reduced form of DIAD, $OPPh_3$, and unreacted PPh_3 which makes the purification of the desired sulfonamide challenging. The low izolated yield (48%) should thus be attributed mainly to this limitation of the method.

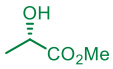
When optimized reaction conditions were performed without microwave irradiation (a preheated (53 °C) oil bath was used), no product formation was observed (entry 9). Similarly, when “standard” reaction

conditions for Mitsunobu reaction were used (various solvents, 0 °C or rt, various orders of addition of reagents), no product formation was observed (representative example can be found in entry 10).

Nevertheless, the described strategy was successfully used in the case of incomplete conversion of the starting sulfonamide and led in many cases to the formation of the targeted *N,N*-disubstituted sulfonamides in very good yields. It should also be noted that all evaluated reactions proved to be stereoselective.

Table S4. Selected examples of microwave-assisted Fukuyama-Mitsunobu alkylation optimization



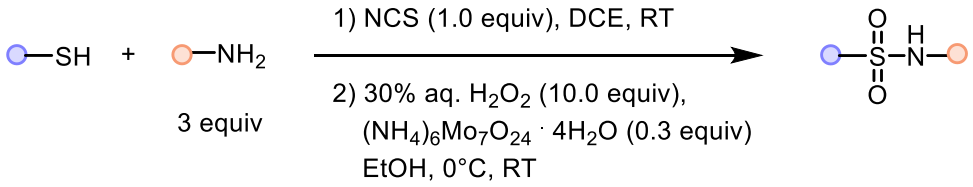
Entry	 (equiv)	Conditions	Yield (%)[a]	Conversion of **7a**[b]	Note
1	1.5	DIAD (1.5 equiv), Ph_3P (1.5 equiv), THF, μW = 100W, 50 °C, 10 min	10%	65%	
2	2.0	DIAD (1.5 equiv), Ph_3P (1.5 equiv), THF, μW = 100W, 50 °C, 10 min	11%	74%	
3	1.1	DIAD (1.5 equiv), Ph_3P (1.5 equiv), THF, μW = 100W, 50 °C, 10 min	8%	62%	
4	1.35	DIAD (1.5 equiv), Ph_3P (1.5 equiv), THF, μW = 100W, 50 °C, 10 min	13%	66%	
5	1.35	DIAD (1.5 equiv), Ph_3P (1.5 equiv), THF, μW = 100W, 50 °C, 10 min + 1 cycle more	16%	81%	DIAD (0.3 equiv) and Ph_3P (0.3 equiv) added, and the sequence was repeated
6	1.35	DIAD (1.5 equiv), Ph_3P (1.5 equiv), THF, μW = 100W, 50 °C, 10 min + 1 cycle more	25%	84%	Alcohol (0.25 equiv), DIAD (0.3 equiv) and Ph_3P (0.3 equiv) added, and the sequence was repeated
7	1.35	DIAD (1.5 equiv), Ph_3P (1.5 equiv), THF, μW = 100W, 50 °C, 10 min + 2 cycles more	18%	83%	DIAD (0.3 equiv) and Ph_3P (0.3 equiv) added, and the sequence was repeated
8	1.35	DIAD (1.5 equiv), Ph_3P (1.5 equiv), THF, μW = 100W, 50 °C, 10 min + 2 cycles more	48%	>95%	Alcohol (0.25 equiv), DIAD (0.3 equiv) and Ph_3P (0.3 equiv) added, and the sequence was repeated
9	1.35	DIAD (1.5 equiv), Ph_3P (1.5 equiv), THF, 50 °C, 10 min + 2 cycles more	<5%	~15%	Alcohol (0.25 equiv), DIAD (0.3 equiv) and Ph_3P (0.3 equiv) added, and the sequence was repeated
10	1.35	DIAD (1.5 equiv), Ph_3P (1.5 equiv), THF, r.t., 24h	<5%	~10%	Similar results were obtained when toluene and DCM were used as solvent

[a)] refers to isolated yield after the flash column chromatography. [b)] based on the ^1H NMR spectra of the crude reaction mixture.

Experimental part

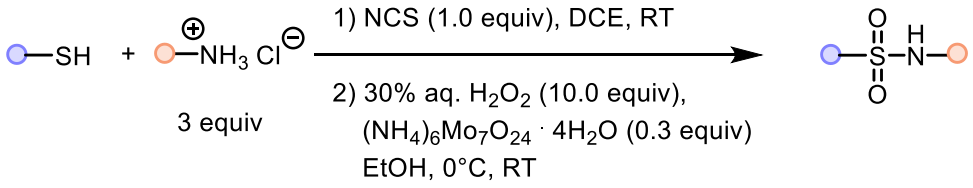
General protocol for sulfonamide synthesis

Method A



Heterocyclic thiol (1 mmol, 1.0 equiv) and amine (3 mmol, 3.0 equiv) were suspended in 1,2-DCE (5 mL, *CAUTION! CARE SHOULD BE TAKEN! 1,2-DCE is toxic and possibly carcinogenic*) at RT and the resulting mixture was stirred at RT for 10 min. NCS (1 mmol, 1.0 equiv) was added portion-wise for a period of 5 min and the whole mixture was stirred for an additional 2 h at RT. The whole slurry was filtered, the filter cake was washed with CH_2Cl_2 (2x5 mL), and the combined filtrates were evaporated in vacuo. The residue was dissolved in EtOH (5 mL), cooled to 0 °C and a premixed cold (0 °C) bright yellow solution of 30% aq. H_2O_2 (10 mmol, 10 equiv) and $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (0.3 mmol, 0.3 equiv) were added with the help of pipette Pasteur (*CAUTION: the use of metallic needle must be avoided!*). The resulting mixture was stirred at 0 °C for 30 min before being allowed to warm to RT (cooling bath removed) and stirred for an additional 8 h at RT. The whole mixture was cooled to 0 °C (ice/water) and sat. aq. Na_2SO_3 (10 mL) was added. The whole mixture was stirred at 0 °C for 10 min (*presence of peroxide was checked with iodide paper and if necessary additional 5 mL of Na_2SO_3 was added*) before filtered. The filter cake was washed with EtOH (2x10 mL) and the combined filtrates were concentrated under reduced pressure. The residue was diluted with water (10-15 mL) and the whole mixture was extracted with CH_2Cl_2 (3x10 mL). The combined organic layers were washed with H_2O (10 mL), brine (10 mL), dried over Na_2SO_4, and the volatiles were removed under reduced pressure. The crude product was washed with hexane (3x5 mL) and purified by recrystallization or by column chromatography.

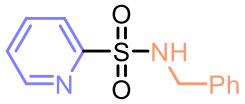
Method B



Heterocyclic thiol (1 mmol, 1.0 equiv), triethylamine (3.0 mmol, 3.0 equiv), and amine hydrochloride (3 mmol, 3.0 equiv) were suspended in 1,2-DCE (5 mL; *CAUTION! CARE SHOULD BE TAKEN! 1,2-DCE is toxic and possibly carcinogenic*) at RT and the resulting mixture was stirred at RT for 10 min. NCS (1 mmol, 1.0 equiv) was added portion-wise for a period of 5 min and the whole mixture was stirred for an additional 2 h at RT. The whole slurry was filtered, the filter cake was washed with CH_2Cl_2 (2x5 mL), and the combined filtrates were evaporated in vacuo. Residue was dissolved in EtOH (5 mL), cooled to 0 °C,and a premixed cold (0 °C) bright yellow solution of 30% aq. H_2O_2 (10 mmol, 10 equiv) and $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (0.3 mmol, 0.3 equiv) was added with the help of pipette Pasteur (*CAUTION: the use of metallic needle must be avoided!*). The resulting mixture was stirred at 0 °C for 30 min before being allowed to warm to RT (cooling

bath removed) and stirred for additional 8h at RT. The whole mixture was cooled to 0 °C (ice/water) and sat. aq. Na_2SO_3 (10 mL) was added. The whole mixture was stirred at 0 °C for 10 min (*presence of peroxide was checked with iodide paper and if necessary additional 5 mL of Na_2SO_3 was added*) before filtered. Filter cake was washed with EtOH (2x10 mL) and the combined filtrates were concentrated under reduced pressure. The residue was diluted with water (10-15 mL) and the whole mixture was extracted with CH_2Cl_2 (3x10 mL). Combined organic layers were washed with H_2O (10 mL), brine (10 mL), dried over Na_2SO_4, and the volatiles were removed under reduced pressure. The crude product was washed with hexane (3x5 mL) and purified by recrystallization or by column chromatography.

*N-benzylpyridine-2-sulfonamide (**2a**)*

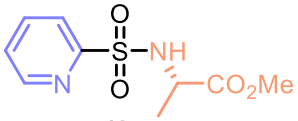


2a

Method A. Starting from pyridine-2-thiol (0.556 g, 5 mmol). **2a** was crystalized from the crude reaction mixture (50% aq. EtOH) in the form of colorless crystals (0.894 g, 56% yield).

mp = 96.8-98.4 °C (EtOH/H_2O), litt.[23] = 100-101 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.62 (ddd, *J* = 7.8, 1.7, 0.9 Hz, 1H), 7.97 (dt, *J* = 7.8, 1 Hz, 1H), 7.87 (td, *J* = 7.7, 1.7 Hz, 1H), 7.45 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H), 7.25-7.20 m (5H), 5.74 (broad t, *J* = 5.5 Hz, 1H, NH), 4.25 (d, *J* = 6.1 Hz, 2H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 157.6, 150.1, 138.3, 136.5, 128.8, 128.2, 128.0, 126.8, 122.5, 47.9 ppm; MS (ESI) *m/z* (%): 249 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{13}N_2O_2S$, 249.0692; found, 249.0691.

*Methyl (pyridin-2-ylsulfonyl)-L-alaninate ((–)-**2b**)*

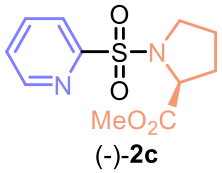


(-)-**2b**

Method B. Starting from pyridine-2-thiol (0.556 g, 5 mmol). (–)-**2b** was crystalized from the crude reaction mixture (33% aq. EtOH) in the form of colorless crystals (0.321 g, 53% yield).

$[\alpha]_D^{23.5}$ = –56.8° (*c* 1.01, MeOH); mp = 125.5-126.3 °C (EtOH/H_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.67 (d, *J* = 5.4 Hz, 1H), 7.98 (d, *J* = 7.9 Hz, 1H), 7.91 (td, *J* = 7.7, 1.7 Hz, 1H), 7.49 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H), 5.64 (broad d, *J* = 8.2 Hz, 1H), 4.38 (t, *J* = 8.0, 7.3 Hz, 1H), 3.64 (s, 3H), 1.45 (d, *J* = 7.2 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): 172.9, 158.1, 150.0, 138.3, 126.9, 121.9, 52.8, 52.6, 20.4 ppm; MS (ESI) *m/z* (%): 245 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_9H_{13}N_2O_4S$, 245.0591; found 245.0593.

*Methyl (pyrid-2-ylsulfonyl)-L-prolinate ((–)-**2c**)*

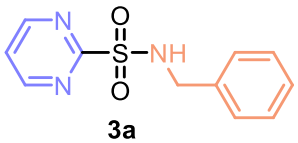


(-)-**2c**

Method B. Starting from pyridine-2-thiol (0.445 g, 4 mmol) and 3.5 equiv of Et_3N were used. The crude product was purified by CC (SiO_2; CH_2Cl_2:EtOAc = 17:3) and yielded the desired sulfonamide (–)-**2c** (0.541 g, 50%) as colorless crystals.

$[\alpha]_D^{24.1}$ = –163.0° (*c* 1.02, $CHCl_3$); mp = 73.4-74.0 °C (Petroleum ether/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.67 (d, *J* = 4.2 Hz, 1H), 7.95 (d, *J* = 7.8 Hz, 1H), 7.90 (td, *J* = 7.7, 1.7 Hz, 1H), 7.49 (ddd, *J* = 7.5, 4.7, 1.2 Hz, 2H), 4.68 (dd, *J* = 8.7, 3.6 Hz, 1H), 3.69 (s, 3H), 3.69 – 3.66 (m, 1H), 3.49 (dt, *J* = 9.7, 7.3 Hz, 1H), 2.31 – 2.12 (m, 1H), 2.09 – 1.92 (m, 2H), 1.91 – 1.77 (m, 1H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 172.7, 157.4, 150.0, 137.9, 126.7, 122.8, 61.5, 52.5, 49.3, 31.0, 24.9 ppm; MS (ESI) *m/z* (%): 271 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+K]^+$ calcd for $C_{11}H_{14}N_2O_4SK$, 309.0306; found 309.0311.

*N-benzylpyrimidine-2-sulfonamide (**3a**)*

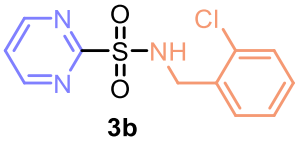


3a

Method A. Starting from pyrimidine-2-thiol (1.72 g, 15 mmol). **3a** was crystalized from the crude reaction mixture (50% aq. EtOH) in the form of colorless crystals (2.47 g, 66% yield).

mp = 114.6-115.4 °C (EtOH/H_2O); litt[24] = 117-118 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.85 (d, *J* = 4.9 Hz, 1H), 7.46 (t, *J* = 4.9 Hz, 1H), 7.32 – 7.22 (m, 5H), 5.40 (t, *J* = 6.0 Hz, 1H), 4.42 (d, *J* = 6.2 Hz, 2H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 166.1, 158.7, 136.5, 128.9, 128.2, 128.2, 123.3, 48.4 ppm; MS (ESI) *m/z* (%): 250 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{12}N_3O_2S$, 250.0645; found 250.0647.

*N-(2-chlorobenzyl)pyrimidine-2-sulfonamide (**3b**)*

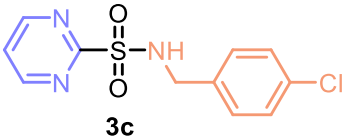


3b

Method A. Starting from pyrimidine-2-thiol (0.286 g, 2.5 mmol). **3b** was crystalized from the crude reaction mixture (50% aq. EtOH) in the form of colorless crystals (0.475 g, 67% yield).

mp = 122.1-123.1 °C (EtOH/H_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.81 (d, *J* = 4.9 Hz, 2H), 7.41 (t, *J* = 4.9 Hz, 1H), 7.35 (dd, *J* = 7.1, 1.9 Hz, 1H), 7.28 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.17 (td, *J* = 7.6, 2.0 Hz, 1H), 7.13 (td, *J* = 7.4, 1.5 Hz, 1H), 5.61 (t, *J* = 6.5 Hz, 1H), 4.53 (d, *J* = 6.6 Hz, 2H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 166.0, 158.5, 134.0, 133.8, 130.7, 129.6, 129.6, 127.3, 123.1, 46.3 ppm; MS (ESI) *m/z* (%): 284 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{11}N_3O_2SCl$, 284.0255, found 284.0255.

*N-(4-chlorobenzyl)pyrimidine-2-sulfonamide (**3c**)*

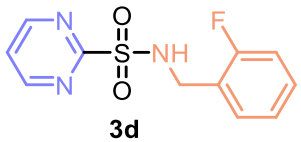


3c

Method A. Starting from pyrimidine-2-thiol (0.286 g, 2.5 mmol). **3c** was crystalized from the crude reaction mixture (50% aq. EtOH) in the form of colorless crystals (0.390 g, 55% yield).

mp = 141.8-142.9 °C (EtOH/H_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.85 (d, J = 4.9 Hz, 2H), 7.48 (d, J = 4.9 Hz, 1H), 7.24 (s, 4H), 5.68 (t, J = 6.3 Hz, 1H), 4.40 (d, J = 6.4 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 166.0, 158.7, 135.2, 134.0, 129.6, 129.0, 123.3, 47.6 ppm; MS (ESI) *m/z* (%): 284 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{11}N_3O_2SCl$, 284.0255; found 284.0259.

*N-(2-fluorobenzyl)pyrimidine-2-sulfonamide (**3d**)*

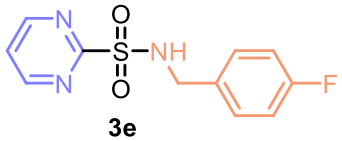


3d

Method A. Starting from pyrimidine-2-thiol (0.286 g, 2.5 mmol). **3d** was crystalized from the crude reaction mixture (50% aq. EtOH) in the form of colorless crystals (0.454 g, 68% yield).

mp = 141.1-141.4 °C (EtOH/H_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.82 (d, J = 4.9 Hz, 2H), 7.43 (t, J = 4.9 Hz, 1H), 7.30 (td, J = 7.6, 1.7 Hz, 1H), 7.21 (tdd, J = 7.3, 5.4, 1.7 Hz, 1H), 7.01 (td, J = 7.5, 1.1 Hz, 1H), 6.96 (ddd, J = 9.6, 8.3, 1.0 Hz, 1H), 5.50 (t, J = 6.2 Hz, 1H), 4.49 (d, J = 6.5 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 166.0, 161.0 (d, J = 246.6 Hz), 158.6, 130.5 (d, J = 4.1 Hz), 130.0 (d, J = 8.3 Hz), 124.5 (d, J = 3.7 Hz), 123.7 (d, J = 14.6 Hz), 123.2, 115.5 (d, J = 21.1 Hz), 42.4 (d, J = 3.9 Hz) ppm; $^{19}F\{^1H\}$ NMR (471 MHz, $CDCl_3$): δ -118.32 ppm; MS (ESI) *m/z* (%): 268 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{11}N_3O_2SF$, 268.0551; found 268.0556.

*N-(4-fluorobenzyl)pyrimidine-2-sulfonamide (**3e**)*

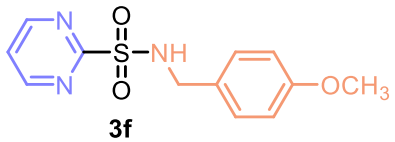


3e

Method A. Starting from pyrimidine-2-thiol (0.286 g, 2.5 mmol). **3e** was crystalized from the crude reaction mixture (50% aq. EtOH) in the form of colorless crystals (0.354 g, 53% yield).

mp = 154.1-155.5 °C (EtOH/H_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.87 (d, J = 4.9 Hz, 2H), 7.49 (t, J = 4.9 Hz, 1H), 7.28 (dd, J = 8.7, 5.3 Hz, 2H), 6.97 (t, J = 8.7 Hz, 2H), 5.49 (broad s, 1H), 4.40 (d, J = 6.3 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 166.1, 162.5 (d, J = 246.9 Hz), 158.7, 132.3 (d, J = 3.2 Hz), 130.1 (d, J = 8.3 Hz), 123.3, 115.7 (d, J = 21.6 Hz), 47.63 ppm; $^{19}F\{^1H\}$ NMR (471 MHz, $CDCl_3$): δ -113.9 ppm; MS (ESI) *m/z* (%): 268 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{11}N_3O_2SF$, 268.0551; found 268.0557.

*N-(4-methoxybenzyl)pyrimidine-2-sulfonamide (**3f**)*



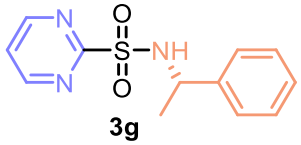
3f

Method A. Starting from pyrimidine-2-thiol (0.286 g, 2.5 mmol). **3f** was crystalized from the crude reaction mixture (50% aq. EtOH) in the form of colorless crystals (0.405 g, 58% yield).

mp = 127.7-127.9 °C (EtOH/H_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.86 (d, J = 4.8 Hz, 2H), 7.47 (t, J = 4.9 Hz, 1H), 7.20 (d, J = 8.6 Hz, 2H), 6.79 (d, J = 8.6 Hz, 2H), 5.44 (broad t, J = 5.9 Hz, 1H), 4.35 (d, J = 6.1 Hz, 2H),

3.77 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 166.1, 159.5, 158.6, 129.7, 128.6, 123.2, 114.2, 55.5, 47.8 ppm; MS (ESI) *m/z* (%): 318 $[M+K]^+$ (30); HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{12}H_{13}N_3O_3SNa$, 302.0570; found 302.0566.

*(S)-N-(1-phenylethyl)pyrimidine-2-sulfonamide (**3g**)*

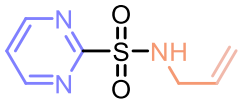


3g

Method A. Starting from pyrimidine-2-thiol (0.286 g, 2.5 mmol). **3g** was crystalized from the crude reaction mixture (50% aq. EtOH) in the form of colorless crystals (0.421 g, 64% yield).

$[\alpha]_D^{19.5}$ = +86.5° (*c* 1.01, $CHCl_3$); mp = 117.9-118.3 °C (EtOH/H_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.71 (d, *J* = 4.9 Hz, 2H), 7.34 (t, *J* = 4.8 Hz, 1H), 7.18 – 7.05 (m, 5H), 5.57 (broad d, *J* = 7.9 Hz, 1H), 4.77 (p, *J* = 7.0 Hz, 1H), 1.54 (d, *J* = 7.0 Hz, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 166.0, 158.3, 141.7, 128.7, 127.7, 126.4, 122.9, 54.7, 23.4 ppm; MS (ESI) *m/z* (%): 302 $[M+K]^+$ (8), 286.1 $[M+Na]^+$ (8); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{14}N_3O_2S$, 264.0801; found 264.0801.

*N-allylpyrimidine-2-sulfonamide (**3h**)*

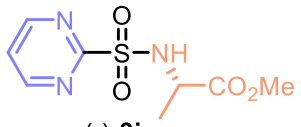


3h

Method A. Starting from pyrimidine-2-thiol (0.286 g, 2.5 mmol). The crude product was purified by CC (SiO_2; CH_2Cl_2:EtOAc = 4:1) and yielded the desired sulfonamide **3h** (0.209 g, 42%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.93 (d, *J* = 4.9 Hz, 2H), 7.53 (t, *J* = 4.9 Hz, 1H), 5.81 (ddt, *J* = 17.1, 10.2, 5.8 Hz, 1H), 5.36 (broad t, *J* = 6.0 Hz, 1H), 5.23 (dq, *J* = 17.1, 1.6 Hz, 1H), 5.10 (dq, *J* = 10.2, 1.3 Hz, 1H), 3.87 (tt, *J* = 6.1, 1.5 Hz, 2H) ppm; $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 166.0, 158.7, 133.4, 123.4, 117.9, 46.7 ppm; MS (ESI) *m/z* (%): 200 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_7H_{10}N_3O_2S$, 200.0488; found 200.0488.

*Methyl (pyrimidin-2-ylsulfonyl)-L-alaninate ((–)-**3i**)*

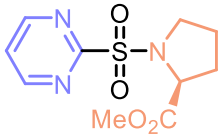


(-)-**3i**

Method B. Starting from pyrimidine-2-thiol (0.286 g, 2.5 mmol). (–)-**3i** was crystalized from the crude reaction mixture (50% aq. EtOH) in the form of colorless crystals (0.208 g, 34% yield).

$[\alpha]_D^{23.2}$ = –53.8° (*c* 1.00, $CHCl_3$); mp = 135.7-136.1 °C (EtOH/H_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.90 (d, *J* = 4.9 Hz, 2H), 7.51 (t, *J* = 4.8 Hz, 1H), 5.60 (broad d, *J* = 8.1 Hz, 1H), 4.47 (qd, *J* = 7.3, 6.5 Hz, 1H), 3.70 (s, 3H), 1.51 (d, *J* = 7.2 Hz, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 172. 9, 166.1, 158.6, 123.5, 52.9, 52.86, 20.4 ppm; MS (ESI) *m/z* (%): 246 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+K]^+$ calcd for $C_8H_{11}N_3O_4SK$, 284.0102; found 284.0102.

*Methyl (pyrimidin-2-ylsulfonyl)-L-prolinate ((–)-**3j**)*

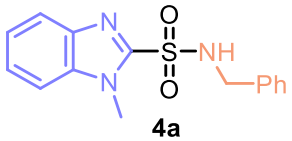


(-)-**3j**

Method B. Starting from pyrimidine-2-thiol (0.572 g, 5 mmol) and 3.5 equiv of Et_3N were used. The crude product was purified by CC (SiO_2; CH_2Cl_2:EtOAc = 17:3) and yielded the desired sulfonamide (–)-**3j** (0.680 g, 50%) as a colorless oil.

$[\alpha]_D^{23.4}$ = –154.0° (*c* 1.01, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 8.91 (d, *J* = 4.8 Hz, 2H), 7.52 (t, *J* = 4.9 Hz, 1H), 4.69 (dd, *J* = 8.7, 3.5 Hz, 1H), 3.88 – 3.77 (m, 1H), 3.67 (s, 3H), 3.66 – 3.60 (m, 1H), 2.31 (dtd, *J* = 12.5, 8.9, 7.4 Hz, 1H), 2.14 – 2.06 (m, 1H), 2.05 – 1.96 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 172.5, 165.7, 158.6, 123.4, 61.6, 52.6, 49.6, 31.2, 24.9 ppm; MS (ESI) *m/z* (%): 272 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{10}H_{14}N_3O_4S$, 272.0700; found 272.0699.

*N-benzyl-1-methyl-1H-benzimidazole-2-sulfonamide (**4a**)*

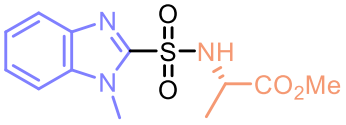


4a

Method A. Starting from 1-methyl-1H-benzo[d]imidazole-2-thiol (0.419 g, 2.5 mmol). **4a** was crystalized from the crude reaction mixture (50% aq. EtOH) in the form of slightly yellow crystals (0.407 g, 54% yield).

mp = 160.3-162 °C (EtOH/H_2O); ^1H NMR (500 MHz, $CDCl_3$): δ 7.82 (d, *J* = 8.2 Hz, 1H), 7.45 (ddd, *J* = 8.0, 6.9, 0.9 Hz, 1H), 7.42 – 7.36 (m, 2H), 7.34 (d, *J* = 7.3 Hz, 2H), 7.21 (dt, *J* = 12.7, 6.9 Hz, 3H), 6.98 (broad s, 1H), 4.51 (d, *J* = 6.2 Hz, 2H), 4.05 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 149.2, 139.9, 136.2, 135.9, 128.7, 128.3, 128.0, 125.8, 124.3, 121.2, 110.7, 48.5, 31.8 ppm; MS (ESI) *m/z* (%): 302 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+K]^+$ calcd for $C_{11}H_{13}N_3O_2SK$, 340.0517; found 340.0516.

*Methyl ((1-methyl-1H-benzimidazol-2-yl)sulfonyl)-L-alaninate ((+)-**4b**)*

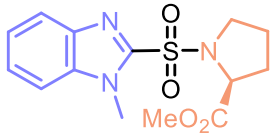


(+)-**4b**

Method B. Starting from 1-methyl-1H-benzo[d]imidazole-2-thiol (0.400 g, 2.4 mmol). (+)-**4b** was crystalized from the crude reaction mixture (40% aq. EtOH) in the form of colorless crystals (0.436 g, 61% yield).

$[\alpha]_D^{23.4}$ = +26.4° (*c* 1.00, MeOH); mp = 117.3-120.7 °C (EtOH/H_2O); ^1H NMR (500 MHz, $CDCl_3$): δ 7.79 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.45 (dd, *J* = 6.0, 1.1 Hz, 2H), 7.37 (ddd, *J* = 8.2, 6.0, 2.2 Hz, 1H), 6.13 (d, *J* = 7.1 Hz, 1H), 4.43 (p, *J* = 7.2 Hz, 1H), 4.08 (s, 3H), 3.68 (s, 3H), 1.54 (d, *J* = 7.2 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 172.8, 148.6, 139.9, 136.0, 125.9, 124.3, 121.3, 110.8, 53.1, 31.8, 19.9 ppm; MS (ESI) *m/z* (%): 298 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_8H_{14}N_3O_4S$, 298.0856; found 298.0863.

*Methyl ((1-methyl-1H-benzimidazol-2-yl)sulfonyl)-L-prolinate ((–)-**4c**)*

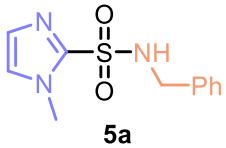


(-)-**4c**

Method B. Starting from 1-methyl-1H-benzo[d]imidazole-2-thiol (0.623 g, 3.6 mmol) and 3.5 equiv of Et_3N. The crude product was purified by CC (SiO_2; CH_2Cl_2:EtOAc = 2:1) and yielded the desired sulfonamide (–)-**4c** (0.536 g, 46%) as a colorless oil.

$[\alpha]_D^{24.2}$ = –171.0° (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.80 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.46 – 7.42 (m, 2H), 7.36 (ddd, *J* = 8.2, 4.9, 3.4 Hz, 1H), 4.74 (dd, *J* = 8.7, 3.4 Hz, 1H), 4.05 (s, 3H), 3.82 – 3.77 (m, 2H), 3.75 (s, 3H), 2.70 – 2.56 (m, 1H), 2.26 – 2.19 (m, 1H), 2.19 – 2.05 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 172.7, 147.9, 140.6, 136.0, 125.5, 123.8, 121.5, 110.6, 61.9, 52.7, 50.4, 31.6, 31.4, 25.1 ppm; MS (ESI) *m/z* (%): 324 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{17}N_3O_4SNa$, 346.0832; found 346.0832.

*N-benzyl-1-methyl-1H-imidazole-2-sulfonamide (**5a**)*

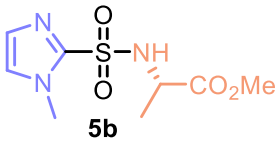


5a

Method A. Starting from 1-methyl-1H-imidazole-2-thiol (1.14 g, 10.0 mmol). **5a** was crystalized from the crude reaction mixture (50% aq. EtOH) in the form of slightly yellow crystals (1.86 g, 74% yield).

mp = 109.1-109.5 °C ($EtOH/H_2O$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.47 – 7.28 (m, 5H), 7.03 (s, 1H), 6.91 (s, 1H), 6.75 (s, 1H), 4.40 (d, *J* = 4.3 Hz, 2H), 3.88 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 143.8, 136.5, 128.8, 128.2, 128.0, 127.4, 124.8, 48.1, 35.3 ppm; MS (ESI) *m/z* (%): 252 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{11}H_{13}N_3O_2SNa$, 274.0620; found 274.0619.

*Methyl ((1-methyl-1H-imidazol-2-yl)sulfonyl)-L-alaninate ((–)-**5b**)*

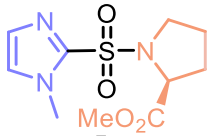


5b

Method B. Starting from 1-methyl-1H-imidazole-2-thiol (1.14 g, 10.0 mmol). **5b** was crystalized from the crude reaction mixture (33% aq. EtOH) in the form of colorless crystals (0.815 g, 33% yield).

$[\alpha]_D^{23.4}$ = –10.6° (*c* 1.00, MeOH); mp = 143.9-145.1 °C ($EtOH/H_2O$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.07 (s, 1H), 6.98 (s, 1H), 6.14 (broad s, 1H), 4.32 (p, *J* = 6.5 Hz, 1H), 3.94 (s, 3H), 3.71 (s, 3H), 1.50 (d, *J* = 7.2 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 173.0, 143.1, 128.0, 125.0, 53.1, 52.7, 35.3, 19.9 ppm; MS (ESI) *m/z* (%): 248 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_8H_{14}N_3O_4S$, 248.0700; found 248.0704.

*Methyl ((1-methyl-1H-imidazol-2-yl)sulfonyl)-L-prolinate ((–)-**5c**)*

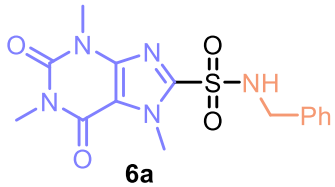


5c

Method B. Starting from 1-methyl-1H-imidazole-2-thiol (0.466 g, 4 mmol) and 3.5 equiv of Et_3N. The crude product was purified by CC (SiO_2; CH_2Cl_2:EtOAc:Et_3N = 9:1:0.1) and yielded the desired sulfonamide **5c** (0.524 g, 48%) as a colorless oil.

$[\alpha]_D^{24.2}$ = –188.8° (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.03 (d, *J* = 1.1 Hz, 1H), 6.96 (d, *J* = 1.1 Hz, 1H), 4.61 (dd, *J* = 8.9, 3.4 Hz, 1H), 3.91 (s, 3H), 3.74 (s, 3H), 3.72 (d, *J* = 6.9 Hz, 1H), 3.69 – 3.62 (m, 1H), 2.50 – 2.41 (m, 2H), 2.16 – 2.03 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 172.7, 142.5, 127.9, 124.7, 61.6, 52.6, 50.0, 35.0, 31.2, 24.9 ppm; MS (ESI) *m/z* (%): 274 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{10}H_{16}N_3O_4S$, 274.0856; found 274.0856.

*N-benzyl-1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purine-8-sulfonamide (**6a**)*

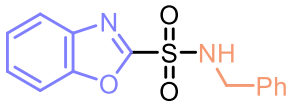


6a

Method A. Starting from caffeine-2-thiol (0.360 g, 1.54 mmol). **6a** was directly filtered off the reaction mixture, washed sequentially with H_2O (3x10 mL) and acetone (2x5 mL) and the resulting solid was dried under reduced pressure at 50 °C for 12 h. **6a** was obtained in the form of colorless crystals (0.47 g, 84% yield).

mp = 333.0-334.2 °C (EtOH); ^1H NMR (500 MHz, DMSO-d_6): δ 9.29 (s, 1H), 7.25 (d, *J* = 4.4 Hz, 4H), 7.17 (q, *J* = 4.5 Hz, 1H), 4.26 (s, 2H), 4.05 (s, 3H), 3.39 (s, 3H), 3.23 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ 154.9, 150.8, 146.5, 145.5, 136.9, 128.2, 127.6, 127.2, 108.7, 46.5, 33.7, 29.6, 27.9 ppm; MS (ESI) *m/z* (%): 364 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{18}N_5O_4S$, 364.1074; found 364.1079.

*N-benzylbenzoxazole-2-sulfonamide (**7a**)*



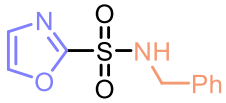
7a

Method A. Starting from benzo[d]oxazole-2-thiol (1.54 g, 10.0 mmol). **8a** was crystalized from the crude reaction mixture (65% aq. EtOH) in the form of slightly yellow crystals (1.066 g, 37% yield).

mp = 118.8-120.1 °C (EtOH); ^1H NMR (500 MHz, acetone-d_6): δ 8.14 (broad s, 1H), 7.87 (ddd, *J* = 8.0, 1.3, 0.7 Hz, 1H), 7.76 (ddd, *J* = 8.3, 7.4, 0.8 Hz, 1H), 7.61 (ddd, *J* = 8.3, 7.4, 1.3 Hz, 1H), 7.54 (ddd, *J* = 8.0, 7.4, 1.1 Hz, 1H), 7.40 – 7.36 (m, 2H), 7.26 (t, *J* = 7.4 Hz, 2H), 7.19 (t, *J* = 7.3 Hz, 1H), 4.52 (d, *J* = 4.3 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, acetone-d_6): δ 160.8, 151.6, 140.6, 137.9, 129.3, 128.9, 128.8, 128.5, 126.8, 122.5,

112.6, 48.2 ppm; MS (ESI) *m/z* (%): 289 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+K]^+$ calcd for $C_{14}H_{12}N_2O_3SK$, 327.0200; found 327.0200.

*N-benzyloxazole-2-sulfonamide (**8a**)*

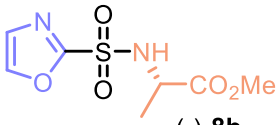


8a

Method A. Starting from oxazole-2-thiol (0.521 g, 5.0 mmol). **8a** was crystalized from the crude reaction mixture (50% aq. EtOH) in the form of slightly yellow crystals (0.415 g, 35% yield).

mp = 137.6-137.8 °C (EtOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (s, 1H), 7.39 – 7.28 (m, 5H), 7.23 (s, 1H), 5.73 (broad t, *J* = 5.3 Hz, 1H), 4.42 (d, *J* = 6.0 Hz, 2H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 158.6,* 141.6, 135.7, 129.0, 128.5, 128.5, 128.2, 48.0 ppm; MS (ESI) *m/z* (%): 239 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+K]^+$ calcd for $C_{10}H_{10}N_2O_3SK$, 277.0044; found 277.0046.

*Methyl (oxazol-2-ylsulfonyl)-L-alaninate ((–)-**8b**)*

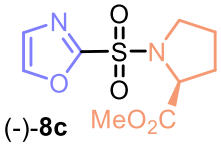


(-)-**8b**

Method B. Starting from oxazole-2-thiol (0.300 g, 2.97 mmol). (–)-**8b** was crystalized from the crude reaction mixture (33% aq. EtOH) in the form of colorless crystals (0.257 g, 37% yield).

$[\alpha]_D^{23.4}$ = –35.8° (*c* 1.01, MeOH); mp = 153.5-153.9 °C (EtOH/H_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1H NMR 7.80 (s, 1H), 7.30 (s, 1H), 5.90 (broad d, *J* = 7.9 Hz, 1H), 4.46 – 4.32 (m, 1H), 3.72 (s, 3H), 1.51 (d, *J* = 7.2 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 172.4, 156.6, 141.6, 128.7, 53.3, 52.5, 20.0 ppm; MS (ESI) *m/z* (%): 235 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+K]^+$ calcd for $C_7H_{10}N_2O_5SK$, 272.9942; found 272.9942.

*Methyl (oxazol-2-ylsulfonyl)-L-prolinate ((–)-**8c**)*



(-)-**8c**

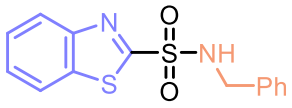
Method B. Starting from oxazole-2-thiol (0.275 g, 2.72 mmol) and 3.5 equiv of Et_3N. The crude product was purified by CC (SiO_2; Petroleum ether:EtOAc = 1:1) and yielded the desired sulfonamide (–)-**8c** (0.297 g, 42%) as colorless crystals.

$[\alpha]_D^{24.2}$ = –146.0° (*c* 1.00, $CHCl_3$); mp = 61.0-61.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (d, *J* = 0.6 Hz, 1H), 7.29 (s, 1H), 4.56 (dd, *J* = 8.6, 3.5 Hz, 1H), 3.75 (ddd, *J* = 9.6, 7.5, 4.7 Hz, 1H), 3.71 (s, 3H), 3.60 (dt, *J* = 9.6, 7.4 Hz, 1H), 2.33 – 2.24 (m, 1H), 2.14 – 2.07 (m, 1H), 2.07 – 1.93 (m, 2H) ppm; ^{13}C{^{1}H} NMR (126 MHz,

* The ^{13}C NMR signal was not observed during the ^{13}C NMR acquisition even when prolonged acquisition time and/or relaxation times was used, however is easy to be seen in HMBC spectrum (see page S81).

$CDCl_3$): δ 171.8, 157.6, 141.4, 128.4, 61.3, 52.9, 49.4, 31.1, 24.7 ppm; MS (ESI) *m/z* (%): 261 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_9H_{13}N_2O_5S$, 261.0540; found 261.0537.

*N-benzylbenzo[d]thiazole-2-sulfonamide (**9a**)*

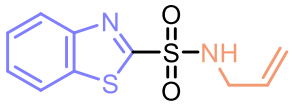


9a

Method A. Starting from benzo[d]thiazole-2-thiol (0.836 g, 5.0 mmol). The crude product was purified by flash column chromatography (SiO_2; hexane/EtOAc = 1:1) and **9a** was obtained as a slightly yellow solid (1.40 g, 92%).

mp = 108 – 112 °C; ^{1}H NMR (400 MHz, $CHCl_3$): δ 8.17 – 8.14 (m, 1H), 7.99 – 7.96 (m, 1H), 7.62 (ddd, *J* = 8.1, 7.2, 1.5 Hz, 1H), 7.57 (ddd, *J* = 7.8, 7.2, 1.4 Hz, 1H), 5.46 (t, *J* = 5.4 Hz, 1H), 4.44 (d, *J* = 6.1 Hz, 2H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CHCl_3$): δ 166.0, 152.4, 136.5, 135.7, 128.9, 128.3, 128.2, 127.8, 127.6, 125.2, 122.3, 48.2 ppm; MS (ESI) *m/z* (%) 305: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{14}H_{13}N_2O_2S_2$, 305.0413; found, 305.0412.

*N-allylbenzo[d]thiazole-2-sulfonamide (**9b**)*

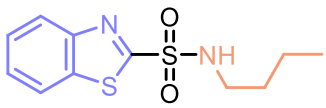


9b

Method A. Starting from benzo[d]thiazole-2-thiol (0.836 g, 5.0 mmol). The crude product was purified using flash column chromatography (SiO_2; hexane/EtOAc = 1:1) and **9b** was obtained as a slightly yellow solid (1.04 g, 82%).

mp = 107 – 110 °C; ^{1}H NMR (400 MHz, $CHCl_3$): δ 8.16 (ddd, *J* = 8.2, 1.3, 0.7 Hz, 1H), 7.96 (ddd, *J* = 7.8, 1.5, 0.7 Hz, 1H), 7.60 (ddd, *J* = 8.0, 7.2, 1.4 Hz, 1H), 7.55 (ddd, *J* = 8.1, 7.3, 1.5, 1H), 5.79 (ddt, *J* = 17.1, 10.2, 5.9 Hz, 1H), 5.46 (t, *J* = 6.2 Hz, 1H), 5.24 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.11 (dq, *J* = 10.2, 1.3 Hz, 1H), 3.88 (tt, *J* = 6.0, 1.5 Hz, 2H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CHCl_3$): δ 166.1, 152.4, 136.5, 132.5, 127.8, 127.6, 125.2, 122.3, 118.5, 46.5 ppm; MS (ESI) m/z (%) 255: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{10}H_{11}N_2O_2S_2$, 255.0256; found, 255.0257.

*N-butyl benzo[d]thiazole-2-sulfonamide (**9c**)*



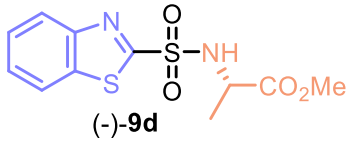
9c

Method A. Starting from benzo[d]thiazole-2-thiol (0.836 g, 5.0 mmol). The crude product was purified using flash column chromatography (SiO_2; hexane/EtOAc= 3:1) and **9c** was obtained as a colorless oil (1.05 g, 78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 – 8.16 (m, 1H), 7.99 – 7.96 (m, 1H), 7.56 (ddd, *J* = 8.1, 7.2, 1.4 Hz, 1H), 7.61 (ddd, *J* = 8.2, 7.2, 1.4 Hz, 1H), 5.18 (t, *J* = 6.0 Hz, 1H), 3.25 (td, *J* = 7.1, 6.1 Hz, 2H), 1.58 – 1.51 (m, 2H),

1.40 – 1.30 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): *δ* 166.2, 152.5, 136.6, 127.7, 127.6, 125.2, 122.3, 43.9, 31.9, 19.7, 13.6 ppm; MS (ESI) m/z (%) 271: $[M+H]^+$ (100); HRMS (ESI) *m/z:* $[M+H]^+$ calcd. for $C_{11}H_{15}N_2O_2S_2$, 271.0569; found, 271.0569.

*Methyl (benzo[d]thiazol-2-ylsulfonyl)-L-alaninate ((-)-**9d**)*

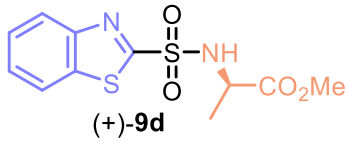


(-)-**9d**

Method B. Starting from benzo[d]thiazole-2-thiol (1.45 g, 8.7 mmol). The crude product was purified using flash column chromatography (SiO_2; hexane/EtOAc = 3:1) and (-)-**9d** was obtained as a colorless oil (2.01 g, 77%).

$[\alpha]_D^{20}$ = −18.2° (*c* 0.45, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 8.14 (dt, *J* = 7.5, 1.6 Hz, 1H), 7.97 (dt, *J* = 8.7, 1.3 Hz, 1H), 7.63 – 7.58 (m, 1H), 7.58 – 7.54 (m, 1H), 5.87 (d, *J* = 7.8 Hz, 1H), 4.52 – 4.43 (m, 1H), 3.60 (s, 3H), 1.51 (d, *J* = 7.1 Hz, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): *δ* 172.4, 165.9, 152.38, 136.4, 127.9, 127.7, 127.6, 125.2, 122.4, 53.0, 52.6, 20.1 ppm. MS (ESI) m/z (%): 301 $[M+H]^+$ (100); HRMS (ESI) m/z: $[M+K]^+$ calc. for $C_{11}H_{12}KN_2O_4S_2$, 338.9876; found, 338.9873.

*Methyl (benzo[d]thiazol-2-ylsulfonyl)-D-alaninate ((+)-**9d**)*

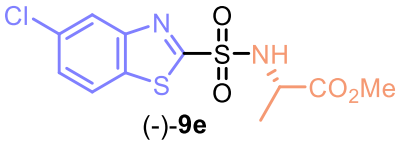


(+)-**9d**

Method B. Starting from benzo[d]thiazole-2-thiol (4.72 g, 28.2 mmol). The crude product was purified using flash column chromatography (SiO_2; hexane/EtOAc = 6:1->4:1) and (+)-**9d** was obtained as a colorless oil (7.45 g, 88%).

$[\alpha]_D^{20}$ = +18.6° (*c* 0.60, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 8.14 (dt, *J* = 7.5, 1.6 Hz, 1H), 7.97 (dt, *J* = 8.7, 1.3 Hz, 1H), 7.63 – 7.58 (m, 1H), 7.58 – 7.54 (m, 1H), 5.87 (d, *J* = 7.8 Hz, 1H), 4.52 – 4.43 (m, 1H), 3.60 (s, 3H), 1.51 (d, *J* = 7.1 Hz, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): *δ* 172.4, 165.9, 152.4, 136.4, 127.9, 127.7, 127.6, 125.2, 122.4, 53.0, 52.6, 20.1 ppm. MS (ESI) m/z (%): 301 $[M+H]^+$ (100); HRMS (ESI) m/z: $[M+K]^+$ calc. for $C_{11}H_{12}KN_2O_4S_2$, 338.9876; found, 338.9873.

*methyl ((6-chlorobenzo[d]thiazol-2-yl)sulfonyl)-L-alaninate ((–)-**9e**)*



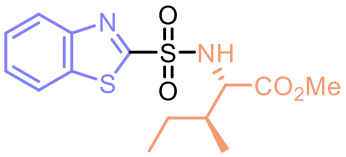
(-)-**9e**

Method B. Starting from 6-chlorobenzo[d]thiazole-2-thiol (0.330 g, 2.43 mmol). The crude product was purified using flash column chromatography (SiO_2; hexane/EtOAc = 4:1) and (–)-**9e** was obtained as a colorless oil (0.440 g, 54%).

$[\alpha]_D^{25}$= −36.8° (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 8.12 (d, *J* = 2.0 Hz, 1H), 7.90 (d, *J* = 8.7 Hz, 1H), 7.54 (dd, *J* = 8.6, 2.0 Hz, 1H), 5.86 (d, *J* = 8.1 Hz, 1H), 4.51 – 4.45 (m, 1H), 3.64 (s, 3H), 1.52 (d, *J* = 7.4 Hz, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): *δ* 172.4, 167.8, 153.2, 134.6, 133.9, 128.6, 124.8, 123.2, 53.1,

52.6, 20.2 ppm; MS (ESI) *m/z* (%): 334 $[M+H]^+$ (100); HRMS (ESI) *m/z:* $[M+H]^+$ calc. for $C_{11}H_{12}ClN_2O_4S_2$, 334.9922; found, 334.9929.

*Methyl (benzo[d]thiazol-2-ylsulfonyl)-L-isoleucinate ((+)-**9g**)*

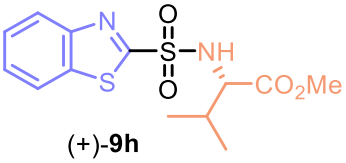


(+)-**9g**

Method B. Starting from benzo[d]thiazole-2-thiol (0.5 g, 2.96 mmol). The crude product was purified using flash column chromatography (SiO_2; hexane/EtOAc = 4:1) and yielded 0.37 g (37%) of sulfonamide (–)-**9g**.

$[\alpha]_D^{25}$= + 36.5° (*c* 1.0 $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 8.10 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.93 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.55 (dddd, *J* = 21.5, 8.4, 7.2, 1.3 Hz, 2H), 5.93 – 5.85 (m, 1H), 4.31 (dd, *J* = 9.7, 5.0 Hz, 1H), 3.47 (s, 3H), 1.97 – 1.83 (m, 1H), 1.48 – 1.34 (m, 1H), 1.23 – 1.11 (m, 1H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.87 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C $\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 171.6, 165.7, 152.4, 136.4, 127.8, 127.6, 125.1, 122.4, 61.5, 52.6, 38.6, 24.7, 15.6, 11.5 ppm; MS (ESI) *m/z* (%): 343 $[M+H]^+$ (100); HRMS (ESI) *m/z:* $[M+H]^+$ calc. for $C_{14}H_{19}N_2O_4S_2$, 343.0786; found, 343.0782.

*Methyl (benzo[d]thiazol-2-ylsulfonyl)-L-valinate ((+)-**9h**)*

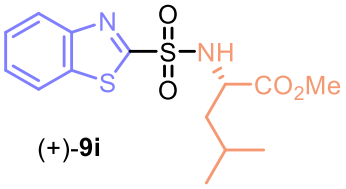


(+)-**9h**

Method B. Starting from benzo[d]thiazole-2-thiol (1.0 g, 5.98 mmol). (+)-**9h** was crystalized from the crude reaction mixture (40% aq. EtOH) in the form of colorless crystals (1.45 g, 74% yield).

$[\alpha]_D^{24}$ = +52.8° (*c* 1.0, $CHCl_3$); mp = 106-107 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 8.11 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.97 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.63 – 7.52 (m, 2H), 5.89 – 5.60 (m, 1H), 4.28 (dd, *J* = 9.9, 4.6 Hz, 1H), 3.50 (s, 3H), 2.17 (pd, *J* = 6.8, 4.7 Hz, 1H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.9 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 171.7, 165.7, 152.4, 136.4, 127.8, 127.6, 125.1, 122.4, 62.1, 52.7, 31.7, 19.1, 17.3 ppm; MS (ESI) *m/z* (%): 329 $[M+H]^+$ (100); HRMS (ESI) *m/z:* $[M+H]^+$ calc. for $C_{13}H_{17}N_2O_4S_2$, 329.0624; found, 329.0629.

*Methyl (benzo[d]thiazol-2-ylsulfonyl)-L-leucinate ((+)-**9i**)*



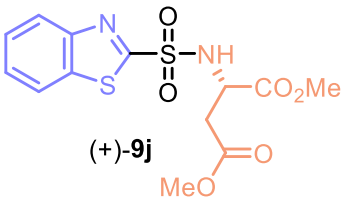
(+)-**9i**

Method B. Starting from benzo[d]thiazole-2-thiol (1.0 g, 5.98 mmol). (+)-**9h** was crystalized from the crude reaction mixture (40% aq. EtOH) in the form of colorless crystals (1.49 g, 73% yield).

$[\alpha]_D^{22}$ = + 27.8° (*c* 1.0, $CHCl_3$); mp = 110 – 112 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 8.17 – 8.09 (m, 1H), 8.01 – 7.93 (m, 1H), 7.62 – 7.54 (m, 2H), 5.50 (d, *J* = 10.6 Hz, 1H), 4.44 (td, *J* = 9.4, 5.5 Hz, 1H), 3.50 (s, 3H), 1.88

(dh, *J* = 8.3, 6.5 Hz, 1H), 1.63 – 1.55 (m, 2H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.94 (d, *J* = 6.7 Hz, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): *δ* 172.6, 165.7, 152.4, 136.5, 127.9, 127.6, 125.1, 122.4, 55.6, 52.8, 42.5, 24.5, 22.9, 21.5 ppm; MS (ESI) *m/z* (%) 343: $[M+H]^+$ (100); HRMS (ESI) *m/z:* $[M+H]^+$ calc. for $C_{14}H_{19}N_2O_4S_2$, 343.0781; found, 343.0773.

*Dimethyl (benzo[d]thiazol-2-ylsulfonyl)-L-aspartate ((+)-**9j**)*

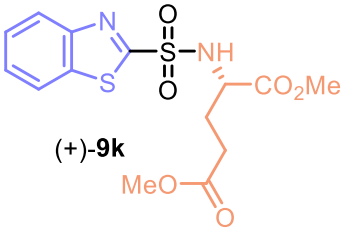


(+)-**9j**

Method B. Starting from benzo[d]thiazole-2-thiol (1.0 g, 5.98 mmol). (+)-**9j** was crystalized from the crude reaction mixture (40% aq. EtOH) in the form of colorless crystals (1.52 g, 71% yield).

$[\alpha]_D^{23}$ = +38° (*c* 1.0, $CHCl_3$); mp = 100 – 102 °C; ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 8.15 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.98 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.59 (dtd, *J* = 21.7, 7.3, 1.4 Hz, 2H), 6.19 (d, *J* = 8.4 Hz, 1H), 4.67 (dt, *J* = 8.5, 4.3 Hz, 1H), 3.67 (s, 3H), 3.55 (s, 3H), 3.15 – 3.01 (m, 2H) ppm; $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 171.0, 170.0, 165.7, 152.4, 136.5, 127.9, 127.6, 125.2, 122.4, 53.3, 53.1, 52.4, 37.6 ppm; MS (ESI) *m/z* (%): 358 $[M+H]^+$ (100); HRMS (ESI) *m/z:* $[M+H]^+$ calc. for $C_{13}H_{15}N_2O_6S_2$, 359.0366; found, 359.0359.

*Dimethyl (benzo[d]thiazol-2-ylsulfonyl)-L-glutamate ((+)-**9k**)*

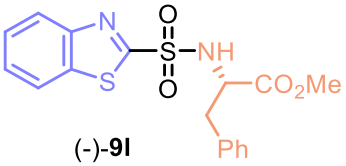


(+)-**9k**

Method B. Starting from benzo[d]thiazole-2-thiol (1.0 g, 5.98 mmol). (+)-**9k** was crystalized from the crude reaction mixture (40% aq. EtOH) in the form of colorless crystals (1.61 g, 72% yield).

$[\alpha]_D^{23}$ = + 38.1° (*c* 1.0, $CHCl_3$); mp = 106 – 108 °C; ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 8.11 (ddd, *J* = 8.2, 1.4, 0.7 Hz, 1H), 7.97 (ddd, *J* = 7.9, 1.4, 0.7 Hz, 1H), 7.62 – 7.54 (m, 2H), 5.83 (d, *J* = 8.8 Hz, 1H), 4.50 (td, *J* = 8.7, 4.6 Hz, 1H), 3.66 (s, 3H), 3.59 (s, 3H), 2.61 – 2.48 (m, 2H), 2.31 – 2.22 (m, 1H), 2.01 (dddd, *J* = 14.2, 8.8, 7.7, 6.4 Hz, 1H) ppm; $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): *δ* 173.1, 171.5, 165.6, 152.3, 136.4, 127.9, 127.6, 125.1, 122.38, 56.2, 53.1, 52.0, 29.7, 28.3 ppm; MS (ESI) *m/z* (%): 373 $[M+H]^+$ (100); HRMS (ESI) *m/z:* $[M+H]^+$ calc. for $C_{14}H_{17}N_2O_6S_2$, 373.0523; found, 373.0531.

*(–)-Methyl (benzo[d]thiazol-2-ylsulfonyl)-L-phenylalaninate ((–)-**9l**)*

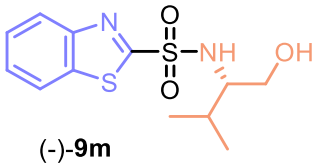


(-)-**9l**

Method B. Starting from benzo[d]thiazole-2-thiol (1.0 g, 5.98 mmol). The crude product was purified using flash column chromatography (SiO_2; hexane/EtOAc = 3:1) and yielded 1.79 g (80%) of sulfonamide (–)-**9l**.

$[\alpha]_D^{23}$ = –129° (*c* 0.51, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.12 (ddd, *J* = 7.9, 1.7, 0.6 Hz, 1H), 7.95 (ddd, *J* = 7.7, 1.5, 0.6 Hz, 1H), 7.60 (ddd, *J* = 8.2, 7.2, 1.5 Hz, 1H), 7.55 (ddd, *J* = 7.9, 7.2, 1.4 Hz, 1H), 7.26 – 7.14 (m, 3H), 7.11 – 7.09 (m, 2H), 5.58 (bs, 1H), 4.72 (t, *J* = 5.8 Hz, 1H), 3.55 (s, 3H), 3.19 (dd, *J* = 13.9, 5.7 Hz, 1H), 3.13 (dd, *J* = 13.9, 5.9 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): *δ* 170.9, 165.6, 152.4, 136.5, 134.7, 129.5, 128.7, 127.8, 127.5, 127.4, 125.2, 122.3, 57.6, 52.7, 39.5 ppm; MS (ESI) *m/z* (%): 377 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{17}H_{17}N_2O_4S_2$, 377.0624; found, 377.0627.

*(–)-(S)-N-(1-hydroxy-3-methylbutan-2-yl)benzo[d]thiazole-2-sulfonamide ((–)-**9m**).*

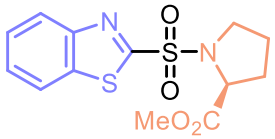


(-)-**9m**

Method B. Starting from benzo[d]thiazole-2-thiol (1.0 g, 5.98 mmol). The crude product was purified using flash column chromatography (SiO_2; hexane/EtOAc = 1:1) and yielded 1.24 g (69%) of sulfonamide (–)-**9m**.

$[\alpha]_D^{21}$ = –335° (*c* 0.2, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.11 (ddd, *J* = 7.4, 1.6, 0.5 Hz, 1H), 7.98 – 7.96 (m, 1H), 7.62 – 7.54 (m, 2H), 5.25 (d, *J* = 8.3 Hz, 1H), 3.74 – 3.65 (m, 2H), 3.58 – 3.52 (m, 1H), 3.10 (t, *J* = 5.9 Hz, 1H), 1.94 (oct, *J* = 6.8 Hz, 1H), 0.99 (d, *J* = 6.8 Hz, 6H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): *δ* 167.9, 151.5, 136.3, 127.8, 127.7, 124.9, 122.3, 62.9, 30.4, 19.3, 18.6 ppm; MS (ESI) *m/z* (%): 301 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{17}N_2O_3S_2$, 301.0675; found, 301.0677.

*Methyl (benzothiazol-2-ylsulfonyl)-L-prolinate ((–)-**9n**)*

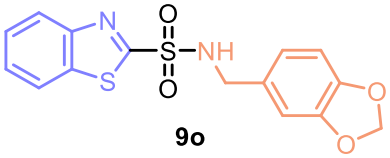


(-)-**9n**

Method B. Starting from benzo[d]thiazole-2-thiol (1.0 g, 5.98 mmol) and 3.5 equiv of Et_3N. The crude product was purified by CC (SiO_2; Petroleum ether:EtOAc = 3:2) and yielded the desired sulfonamide (–)-**9n** (1.27 g, 65%) as slightly yellowish crystals.

$[\alpha]_D^{23.5}$ = -214.8° (*c* 1.01, $CHCl_3$); mp = 74.6-74.7 °C (CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 8.18 (d, *J* = 8.2 Hz, 1H), 7.99 (d, *J* = 7.9 Hz, 1H), 7.65 – 7.59 (m, 1H), 7.57 (td, *J* = 7.7, 7.3, 1.2 Hz, 1H), 4.71 (dd, *J* = 8.6, 3.5 Hz, 1H), 3.85 – 3.77 (m, 1H), 3.74 (s, 3H), 3.64 (dt, *J* = 9.8, 7.4 Hz, 1H), 2.26 – 2.14 (m, 1H), 2.14 – 1.99 (m, 2H), 1.97 – 1.85 (m, 1H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): *δ* 172.0, 164.5, 152.6, 136.3, 127.7, 127.5, 125.3, 122.2, 61.4, 52.7, 49.5, 31.1, 24.8 ppm; MS (ESI) *m/z* (%): 327 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{13}H_{15}N_2O_4S_2$, 327.0468; found 327.0467.

*N-(benzo[d][1,3]dioxol-5-ylmethyl)benzo[d]thiazole-2-sulfonamide (**9o**)*

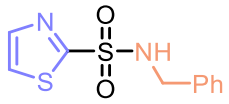


9o

Method B. Starting from benzo[d]thiazole-2-thiol (1.0 g, 5.98 mmol). The crude product was purified using flash column chromatography (SiO_2; hexane/EtOAc = 4:3) and yielded 1.23 g (59%) of sulfonamide **9o**.

mp = 140 – 141 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, J = 8.1 Hz, 1H), 7.97 (d, J = 8.3 Hz, 1H), 7.61 (dt, J = 7.2, 1.1 Hz), 7.56 (dt, J = 8.1, 1.4 Hz, 1H), 7.59 - 7.54 (m, 1H), 6.76 (s, 1H), 6.72 (d, J = 8.6 Hz, 1H), 6.65 (d, J = 8.6 Hz, 1H), 5.84 (s, 2H), 5.76 – 5.60 (broad s, 1H), 4.32 (d, J = 5.5 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 166.3, 152.4, 148.1, 147.6, 136.5, 129.5, 127.7, 127.6, 125.2, 122.3, 121.9, 108.8, 108.4, 101.3, 48.0 ppm; MS (ESI) *m/z* (%) 349: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{13}N_2O_4S_2$, 349.0311; found, 349.0307.

*N-benzylthiazole-2-sulfonamide (**10a**)*

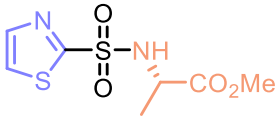


10a

Method A. Starting from thiazol-2-thiol (0.604 g, 5.0 mmol). **10a** was crystalized from the crude reaction mixture (50% aq. EtOH) in the form of slightly yellow crystals (0.928 g, 73% yield).

mp = 90.6-94.8 °C (EtOH/H_2O), litt.[24] 98-99 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (d, J = 3.0 Hz, 1H), 7.59 (d, J = 3.1 Hz, 1H), 7.35 – 7.22 (m, 5H), 5.90 (t, J = 5.7 Hz, 1H), 4.36 (d, J = 6.1 Hz, 2H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 165.9, 144.5, 136.0, 128.9, 128.3, 128.2, 124.8, 48.0 ppm; MS (ESI) *m/z* (%): 255 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{10}H_{11}N_2O_2S_2$, 255.0256; found, 255.0261.

*Methyl (thiazol-2-ylsulfonyl)-L-alaninate ((–)-**10b**)*

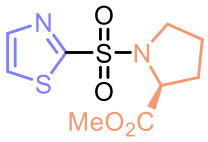


(-)-**10b**

Method B. Starting from thiazol-2-thiol (0.604 g, 5.0 mmol). (–)-**10b** was crystalized from the crude reaction mixture (33% aq. EtOH) in the form of colorless crystals (0.637 g, 51% yield).

$[\alpha]_D^{23.7}$ = –52.2° (*c* 1.0, MeOH); mp = 119.6-120.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 – 7.91 (m, 1H), 7.64 (d, J = 2.6 Hz, 1H), 5.88 (d, J = 8.0 Hz, 1H), 4.40 (dq, J = 8.0, 7.2 Hz, 1H), 3.68 (s, 3H), 1.49 (d, J = 7.2 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 172.5, 165.7, 144.5, 124.9, 53.1, 52.5, 20.1 ppm; MS (ESI) *m/z* (%): 251 $[M+H]^+$ (100); HRMS (ESI) *m/z:* $[M+H]^+$ calc. for $C_7H_{11}N_2O_4S_2$, 251.0155; found, 251.0161.

*Methyl (thiazol-2-ylsulfonyl)-L-prolinate ((–)-**10c**)*

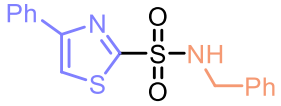


(-)-**10c**

Method B. Starting from thiazol-2-thiol (0.604 g, 5.0 mmol) and 3.5 equiv of Et_3N. The oxidation step was stopped after 2.5 h at RT. The crude product was purified by CC (SiO_2; Petroleum ether:EtOAc = 1:1) and yielded the desired sulfonamide (–)-**10c** (0.677 g, 59%) as a colorless oil.

$[\alpha]_D^{23.5}$ = -211.0° (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, *J* = 3.1 Hz, 1H), 7.64 (d, *J* = 3.2 Hz, 1H), 4.61 (dd, *J* = 8.6, 3.7 Hz, 1H), 3.74 (s, 3H), 3.76 – 3.70 (m, 1H), 3.54 (dt, *J* = 9.9, 7.4 Hz, 1H), 2.19 – 2.11 (m, 1H), 2.10 – 1.96 (m, 2H), 1.90 – 1.80 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 172.2, 164.3, 144.7, 124.6, 61.4, 52.8, 49.5, 31.1, 24.8 ppm; MS (ESI) *m/z* (%): 277 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_9H_{13}N_2O_4S_2$, 277.0311; found 277.0307.

*N-benzyl-4 phenylthiazole-2-sulfonamide (**10d**)*

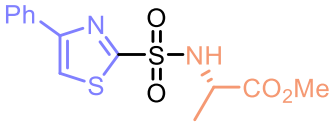


10d

Method A. Starting from 4-phenylthiazol-2-thiol (0.986 g, 5.0 mmol). **10d** was crystalized from the crude reaction mixture (55% aq. EtOH) in the form of slightly pink crystals (0.693 g, 42% yield).

mp = 139.1-142.3 °C (EtOH/H_2O); ^1H NMR (500 MHz, $CDCl_3$): δ 7.89 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.70 (s, 1H), 7.48 (d, *J* = 7.1 Hz, 2H), 7.41 (t, *J* = 7.3 Hz, 1H), 7.33 – 7.19 (m, 5H), 5.37 (t, *J* = 6.1 Hz, 1H), 4.43 (d, *J* = 6.1 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 165.0, 157.2, 135.6, 132.9, 129.1, 128.9, 128.7, 128.1, 128.0, 126.6, 117.7, 48.0 ppm; MS (ESI) *m/z* (%): 331 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{16}H_{14}N_2O_2S_2Na$, 353.0389; found 353.0387.

*Methyl ((4-phenylthiazol-2-yl)sulfonyl)-L-alaninate ((–)-**10e**)*



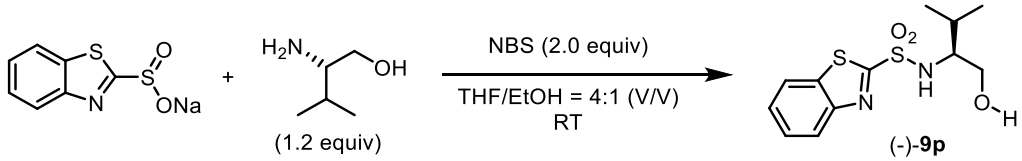
(-)-**10e**

Method B. Starting from 4-phenylthiazol-2-thiol (0.986 g, 5.0 mmol). The crude product was purified by CC (SiO_2; Petroleum ether:EtOAc = 3:1) and yielded the desired sulfonamide (–)-**10e** (0.962 g, 59%) as a yellowish oil.

$[\alpha]_D^{23.8}$ = –90.6° (*c* 1.0, MeOH); ^1H NMR (500 MHz, $CDCl_3$): δ 7.88 (dd, *J* = 8.3, 1.4 Hz, 3H), 7.72 (s, 1H), 7.45 (t, *J* = 7.3 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 1H), 5.72 (d, *J* = 8.3 Hz, 1H), 4.54 (dq, *J* = 8.2, 7.2 Hz, 1H), 3.56 (s, 3H), 1.53 (d, *J* = 7.2 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 172.7, 165.1, 157.2, 133.1, 129.4, 129.1, 126.7, 117.8, 53.0, 52.7, 20.5 ppm; MS (ESI) *m/z* (%): 327 $[M+H]^+$ (100); HRMS (ESI) *m/z:* $[M+H]^+$ calc. for $C_{13}H_{15}N_2O_4S_2$, 327.0468; found, 327.0463.

Sulfonamides 9p and q synthesis

*(–)-(S)-N-(1-hydroxy-3-methylbutan-2-yl)benzo[d]thiazole-2-sulfonamide ((–)-**9p**)*

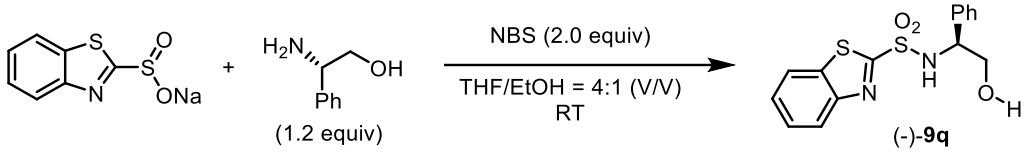


Sulfinic salt (0.5 g, 2.22 mmol, 1 equiv) and amine (2.71 mmol, 1.2 equiv) were added to the solvent mixture of THF/EtOH = 4:1 (V/V) (25 mL) at RT. The resulting mixture was stirred at RT for 5 min and NBS (0.800 g, 4.52 mmol, 2 equiv) was added portion-wise over a period of 5 min. The reaction mixture turned color to orange upon the NBS

addition. After an additional 10 min at RT, the reaction mixture was divided between CH_2Cl_2 (25 mL) and water (25 mL). The resulting layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). Combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, and filtered, and the solvents were evaporated under reduced pressure to provide the crude product. The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:1) and obtained in the form of colorless oil (0.426 g, 64%).

$[\alpha]_D^{21} = -335°$ (*c* 0.2, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (ddd, *J* = 7.4, 1.6, 0.5 Hz, 1H), 7.98 – 7.96 (m, 1H), 7.62 – 7.54 (m, 2H), 5.25 (d, *J* = 8.3 Hz, 1H), 3.74 – 3.65 (m, 2H), 3.58 – 3.52 (m, 1H), 3.10 (t, *J* = 5.9 Hz, 1H), 1.94 (oct, *J* = 6.8 Hz, 1H), 0.99 (d, *J* = 6.8 Hz, 6H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 167.9, 151.5, 136.3, 127.8, 127.7, 124.9, 122.3, 62.9, 30.4, 19.3, 18.6 ppm; MS (ESI) *m/z* (%) 301: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{17}N_2O_3S_2$, 301.0675; found, 301.0677.

*(–)-N-(2-hydroxy-1-phenylethyl)benzo[d]thiazole-2-sulfonamide ((–)-**9q**)*

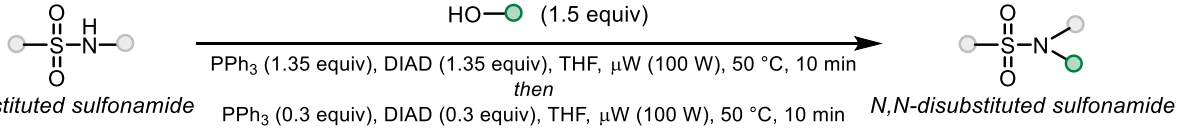


Sulfinic salt (0.5 g, 2.22 mmol, 1 equiv) and amine (2.71 mmol, 1.2 equiv) were added to the solvent mixture of THF/EtOH = 4:1 (V/V) (25 mL) at RT. The resulting mixture was stirred at RT for 5 min and NBS (0.800 g, 4.52 mmol, 2 equiv) was added portion-wise over a period of 5 min. The reaction mixture turned orange upon the addition of NBS. After an additional 10 min at RT, the reaction mixture was partitioned between CH_2Cl_2 (25 mL) and water (25 mL). Resulting layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). Combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, and filtered, and the solvents were evaporated under reduced pressure to provide the crude product. The crude product was purified using flash column chromatography (SiO_2; hexane/EtOAc = 2:1->1:1) and obtained as a white solid (0.416 g, 56%).

$[\alpha]_D^{23} = -144°$ (c 0.25, CH_2Cl_2); mp = 118–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (ddd, *J* = 7.9, 1.5, 0.5 Hz, 1H), 7.90 (ddd, *J* = 7.5, 1.5, 0.6 Hz, 1H), 7.60 – 7.51 (m, 2H), 7.27 – 7.25 (m, 2H), 7.22 – 7.13 (m, 3H), 4.84 (dd, *J* = 6.3, 4.3 Hz, 1H), 3.94 (dd, *J* = 11.7, 4.3 Hz, 1H), 3.86 (dd, *J* = 11.7, 6.4 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 167.0, 151.8, 137.6, 136.5, 128.8, 128.3, 127.8, 127.6, 127.0, 125.0, 122.2, 66.1, 60.5 ppm; MS (ESI) *m/z* (%) 335: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{15}N_2O_3S_2$, 335.0519; found, 335.0516.

General protocol for *N*-alkylation of *N*-monosubstituted sulfonamides

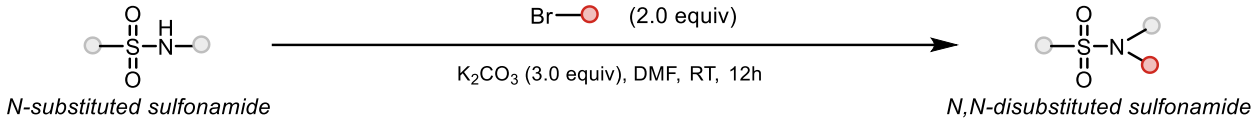
Fukuyama-Mitsunobu reaction protocol (FMR protocol)



Sulfonamide (0.9 mmol, 1.0 equiv) and PPh_3 (0.319 g, 1.22 mmol, 1.35 equiv) in dry THF (18 mL, 0.05M) were placed to μW vial at RT, and alcohol (1.35 mmol, 1.5 eq) followed by DIAD (0.265 mL, 1.22 mmol, 1.35 equiv) were added. The vial was closed with a Teflon tap and the entire mixture was heated to 50 °C for 10 min in the microwave reactor (100 W). After being cooled to RT, organic solvents were removed under reduced pressure and the conversion of sulfonamide was analyzed with help of the ^{1}H NMR experiments. In case of incomplete conversion, the whole mixture was redissolved in dry THF (18 mL), additional PPh_3 (0.3 equiv) and DIAD (0.3 equiv) were added, and the entire procedure was repeated. In case of missing signals of the starting alcohol, an additional 0.3 equiv of the corresponding alcohol was

also added. When the starting sulfonamide was consumed, the crude product was purified by flash column chromatography on silica gel.

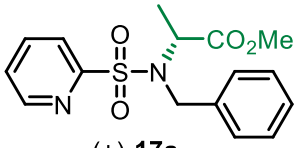
Alkylation protocol



N-substituted sulfonamide *N,N-disubstituted sulfonamide*

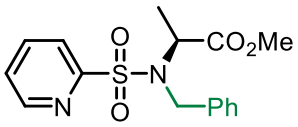
Sulfonamide (3.0 mmol, 1 equiv) was dissolved in DMF (30 mL, 0.1 M) and K_2CO_3 (3.74 g, 9.0 mmol, 3.0 equiv) was added. The resulting mixture was stirred at RT for 5 min, and benzyl bromide (1.43 mL, 6.0 mmol, 2 equiv) was added dropwise over a period of 5 min. The whole mixture was stirred at RT for 16 h, before diluted with H_2O (50 mL). The entire mixture was extracted with EtOAc (3 x 75 mL), and the combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure.

*Methyl N-benzyl-N-(pyridin-2-ylsulfonyl)-D-alaninate ((+)-**17a**) & methyl N-benzyl-N-(pyridin-2-ylsulfonyl)-L-alaninate ((–)-**17a**)*



(+)-**17a**

FMR protocol: Prepared from sulfonamide **2a** (0.223 g, 0.9 mmol) and methyl L-lactate (0.129 mL, 1.35 mmol). An additional cycle was carried out. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 1:1) and yielded the desired product (+)-**17a** (0.298 g, 99%, *e.r.* = 96:4) as a colorless oil.



(-)-**17a**

FMR protocol: Prepared from sulfonamide (–)-**2b** (0.220 g, 0.9 mmol) and benzyl alcohol (0.140 mL, 1.35 mmol). One additional cycle was carried out. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 1:1) and yielded the desired product (–)-**17a** (0.286 g, 95%, *e.r.* = 97:3) as a colorless oil.

Alkylation protocol: Prepared from sulfonamide (–)-**2b** (0.220 g, 0.9 mmol) and benzyl bromide (0.214 mL, 1.8 mmol). The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 1:1) and yielded the desired product (–)-**17a** (0.285 g, 95%) as a colorless oil.

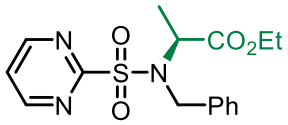
(+)-**17a**: $[\alpha]_D^{21.1}$ = +32.8° (*c* 1.0, $CHCl_3$)

(–)-**17a**: $[\alpha]_D^{20.6}$ = –33.0° (*c* 1.02, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.81 – 8.66 (m, 1H), 7.91 – 7.87 (m, 1H), 7.86 (dq, *J* = 7.8, 1.5 Hz, 1H), 7.48 (ddt, *J* = 7.6, 4.7, 1.5 Hz, 1H), 7.40 – 7.36 (m, 2H), 7.31 – 7.27 (m, 3H), 7.24 (dddd, *J* = 8.6, 5.8, 2.8, 1.5 Hz,

1H), 4.90 – 4.82 (m, 1H), 4.79 (d, *J* = 16.4 Hz, 1H), 4.55 (d, *J* = 16.4 Hz, 1H), 3.43 (t, *J* = 1.5 Hz, 3H), 1.32 (dd, *J* = 7.3, 1.4 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): *δ* 171.8, 158.2, 150.0, 137.9, 137.5, 128.5, 128.3, 127.6, 126.7, 122.4, 55.9, 52.3, 50.0, 16.7 ppm; MS (ESI) *m/z* (%) 335: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{19}N_2O_4S$, 335.1060; found, 335.1059. HPLC (Chiral ART Amylose-SA, hexan/EtOAc = 90/10 to 10/90, flow rate = 0.5 mL/min) t_R = 14.96 min ((+)**17a**), 15.85 min ((–)**17a**).

*Ethyl N-benzyl-N-(pyrimidin-2-ylsulfonyl)-L-alaninate ((–)-**17b**)*

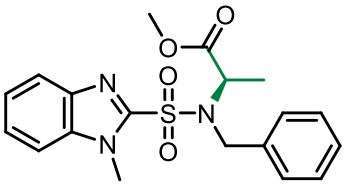


(-)-**17b**

FMR protocol: Prepared from sulfonamide **3a** (0.225 g, 0.9 mmol) and ethyl D-lactate (0.155 mL, 1.35 mmol). An additional cycle was carried out. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 1:1) and yielded the desired product (–)-**17b** (0.290 g, 96%, *e.r.* = 91:9) as a colorless oil.

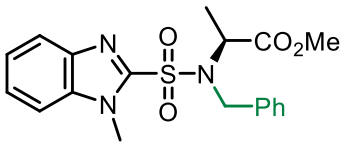
$[\alpha]_D^{19.8}$ = –34.7° (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): *δ* 8.91 (d, *J* = 4.9 Hz, 1H), 7.50 (t, *J* = 4.9 Hz, 1H), 7.43 (d, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 1H), 5.06 (d, *J* = 16.5 Hz, 1H), 4.86 (q, *J* = 7.4 Hz, 1H), 4.45 (d, *J* = 16.5 Hz, 1H), 1.32 (d, *J* = 7.4 Hz, 3H), 1.12 (t, *J* = 7.2 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): *δ* 171.2, 166.0, 158.4, 137.7, 128.5, 128.1, 127.7, 123.3, 61.5, 56.6, 50.6, 17.2, 14.2 ppm; MS (ESI) *m/z* (%) 350: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+K]^+$ calcd. for $C_{16}H_{19}N_3O_4SK$, 388.0728; found, 388.0731; HPLC (Chiral ART Amylose-SA, hexan/EtOAc = 90/10 to 10/90, flow rate = 0.5 mL/min) t_R = 16.80 min (major), 17.57 min (minor).

*Methyl N-benzyl-N-((1-methyl-1H-benzimidazol-2-yl)sulfonyl)-D-alaninate ((+)-**17c**) & methyl N-benzyl-N-((1-methyl-1H-benzimidazol-2-yl)sulfonyl)-L-alaninate ((–)-**17c**)*



(+)-**17c**

FMR protocol: Prepared from sulfonamide **4a** (0.271 g, 0.9 mmol) and methyl L-lactate (0.139 mL, 1.35 mmol). An additional cycle was carried out. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 7:2) and further by semiprep HPLC (SiO_2-C18, MeOH-H_2O) to give the desired product (+)-**17c** (0.282 g, 81%, *e.r.* = 96:4) as a colorless oil.



(-)-**17c**

FMR protocol: Prepared from sulfonamide (+)-**4b** (0.268 g, 0.9 mmol) and benzyl alcohol (0.140 mL, 1.35 mmol). An additional cycle was carried out. The residue was purified by column chromatography (SiO_2;

petroleum ether:EtOAc = 4:1) and further by semiprep HPLC (SiO_2-C18, MeOH-H_2O) to give the desired product (–)-**17c** (0.307 g, 88%, *e.r.* = 97:3) as a colorless oil.

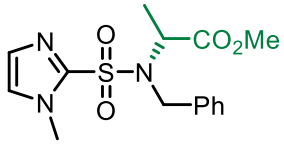
Alkylation protocol: Prepared from sulfonamide (+)-**4b** (0.268 g, 0.9 mmol) and benzyl bromide (0.214 mL, 1.8 mmol). The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 10:1->4:1) and yielded the desired product (–)-**17c** (0.275 g, 79%) as a colorless oil.

(+)-**17c**: $[\alpha]_D^{24.2}$ = +64.4° (c 1.0, $CHCl_3$)

(–)-**17c**: $[\alpha]_D^{21.7}$ = –64.1° (*c* 0.99, $CHCl_3$)

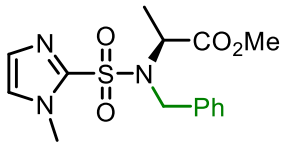
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.49 – 7.37 (m, 4H), 7.37 (ddd, *J* = 8.2, 6.5, 1.8 Hz, 1H), 7.30 (t, *J* = 7.2 Hz, 2H), 7.25 (t, *J* = 7.3 Hz, 1H), 4.86 (d, *J* = 16.3 Hz, 1H), 4.81 (q, *J* = 7.4 Hz, 1H), 4.72 (d, *J* = 16.3 Hz, 1H), 4.04 (s, 3H), 3.35 (s, 3H), 1.48 (d, *J* = 7.3 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 171.5, 148.7, 140.8, 136.8, 136.1, 128.6, 128.4, 127.9, 125.6, 123.9, 121.6, 110.6, 56.1, 52.4, 50.4, 31.8, 16.0 ppm; MS (ESI) *m/z* (%) 388: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{19}H_{21}N_3O_4S$, 388.1326; found, 388.1325; HPLC (Chiral ART Amylose-SA, hexan/EtOAc = 90/10 to 10/90, flow rate = 0.5 mL/min) t_R = 15.42 min ((+)-**17c**), 18.97 min ((–)-**17c**).

*Methyl N-benzyl-N-((1-methyl-1H-imidazol-2-yl)sulfonyl)-D-alaninate (+)-**17d** & methyl N-benzyl-N-((1-methyl-1H-imidazol-2-yl)sulfonyl)-L-alaninate (–)-**17d***



(+)-**17d**

FMR protocol: Prepared from sulfonamide **5a** (0.226 g, 0.9 mmol) and methyl L-lactate (0.139 mL, 1.35 mmol). An additional cycle was carried out. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc:Et_3N = 1:1:0.01) to give the desired product (+)-**17d** (0.291 g, 96%, *e.r.* = 94:6) as a colorless oil.



(-)-**17d**

FMR protocol: Prepared from sulfonamide (+)-**5b** (0.223 g, 0.9 mmol) and benzyl alcohol (0.140 mL, 1.35 mmol). An additional cycle was carried out. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc:Et_3N = 1:1:0.01) to give the desired product (–)-**17d** (0.285 g, 94%, *e.r.* = 97:3) as a colorless oil.

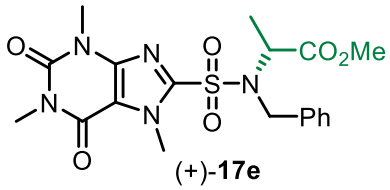
Alkylation protocol: Prepared from sulfonamide (+)-**5b** (0.223 g, 0.9 mmol) and benzyl bromide (0.214 mL, 1.8 mmol). The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc:Et_3N = 1:1:0.01) to give the desired product (–)-**17d** (0.267 g, 88%) as a colorless oil.

(+)-**17d**: $[\alpha]_D^{24.2}$ = +66.4° (c 1.0, $CHCl_3$)

(–)-**17d**: $[\alpha]_D^{21.7}$ = –66.2° (*c* 1.0, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 – 7.38 (m, 2H), 7.36 – 7.27 (m, 2H), 7.31 – 7.21 (m, 1H), 7.09 (d, J = 1.1 Hz, 1H), 6.95 (d, J = 1.0 Hz, 1H), 4.79 (d, J = 16.5 Hz, 1H), 4.75 (q, J = 7.3 Hz, 1H), 4.62 (d, J = 16.3 Hz, 1H), 3.88 (s, 3H), 3.47 (s, 3H), 1.41 (d, J = 7.3 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 171.6, 143.3, 137.0, 128.6, 128.5, 128.2, 127.7, 124.9, 55.8, 52.5, 50.0, 35.2, 16.0 ppm; MS (ESI) *m/z* (%) 338: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{20}N_3O_4S$, 338.1169; found, 338.1169; HPLC (Chiral ART Amylose-SA, hexan/EtOAc = 90/10 to 10/90, flow rate = 0.5 mL/min) t_R = 14.23 min ((–)-**17d**), 14.75 min ((+)-**17d**).

*Methyl N-benzyl-N-(benzoxazol-2-ylsulfonyl)-D-alaninate (+)-**17e***

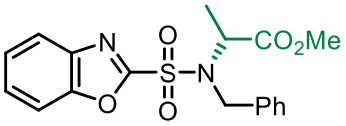


(+)-**17e**

FMR protocol: Prepared from sulfonamide **6a** (0.327 g, 0.9 mmol) and methyl L-lactate (0.139 mL, 1.35 mmol). Two additional cycles were carried out, and in the second cycle additional methyl lactate (0.3 equiv) was added. The residue was purified using the following protocol to remove the excess of Ph_3PO (has the same R_f as the product). A solution of $ZnCl_2$ (440 mg, 2.16 mmol) in EtOH was added to the crude mixture at 40 °C and the resulting mixture was stirred overnight at 40 °C. Solvents were evaporated under reduced pressure and EtOAc (30 mL) was added. The precipitate was filtered, and the filter cake was washed with EtOAc (2x15 mL). Solvents were combined and concentrated under reduced pressure. The residue was purified by semiprep HPLC (SiO_2-C18, MeOH/H_2O) and yielded the desired sulfonamide (+)-**17e** (0.174 g, 43%, *e.r.* = 97:3) as colorless crystals.

$[\alpha]_D^{21.4}$ = +24.8° (c 1.0, $CHCl_3$); mp = 135.7-136.1 °C (CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (d, J = 7.1 Hz, 2H), 7.33 (dt, J = 6.7, 1.6 Hz, 2H), 7.32 – 7.28 (m, 1H), 4.80 (d, J = 16.3 Hz, 1H), 4.77 (t, J = 7.3 Hz, 1H), 4.60 (d, J = 16.1 Hz, 1H), 4.20 (s, 3H), 3.58 (s, 3H), 3.53 (s, 3H), 3.43 (s, 3H), 1.48 (d, J = 7.3 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 171.3, 155.6, 151.5, 147.1, 146.3, 136.1, 128.7, 128.5, 128.2, 109.2, 56.4, 52.7, 50.5, 34.3, 30.1, 28.5, 16.4 ppm; MS (ESI) *m/z* (%) 450: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+K]^+$ calcd. for $C_{19}H_{23}N_5O_6SK$, 488.1001; found, 488.0999; HPLC (Chiral ART Amylose-SA, hexan/EtOAc = 90/10 to 10/90, flow rate = 0.5 mL/min) t_R = 16.58 min (minor), 19.75 min (major).

*Methyl N-benzyl-N-(benzoxazol-2-ylsulfonyl)-D-alaninate (+)-**17f***



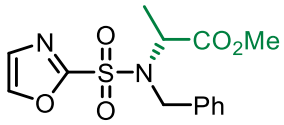
(+)-**17f**

FMR protocol: Prepared from sulfonamide **7a** (0.260 g, 0.9 mmol) and methyl L-lactate (0.139 mL, 1.35 mmol). Three additional cycles were carried out and, in each cycle, additional methyl L-lactate (0.3 equiv) was added. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 3:1) and semiprep HPLC (SiO_2-C18, MeOH/H_2O) to obtain the desired product (+)-**17f** (0.162 g, 48%, *e.r.* = 99:1) as a colorless oil.

$[\alpha]_D^{20.7}$ = +39.0° (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 8.2 Hz, 1H), 7.58 – 7.53 (m, 1H), 7.49 (td, J = 7.7, 1.1 Hz, 1H), 7.43 (d, J = 7.3 Hz, 2H), 7.34 (t, J = 7.3 Hz, 2H), 7.29 (d, J = 7.3 Hz, 1H), 4.99 (d, J = 16.5 Hz, 1H), 4.86 (q, J = 7.4 Hz, 1H), 4.47 (d, J = 16.4 Hz, 1H), 3.31 (s, 3H), 1.37 (d,

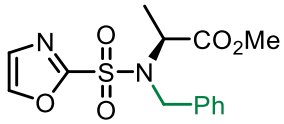
J = 7.4 Hz, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): *δ* 170.9, 158.7, 150.9, 139.8, 136.5, 128.7, 128.1, 128.1, 128.0, 126.1, 122.1, 111.8, 56.6, 52.6, 50.5, 16.8 ppm; MS (ESI) *m/z* (%) 375: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+K]^+$ calcd. for $C_{18}H_{12}N_2O_5SK$, 413.0568; found, 413.0566; HPLC (Chiral ART Amylose-SA, hexan/EtOAc = 90/10 to 10/90, flow rate = 0.5 mL/min) t_R = 12.10 min (minor), 15.22 min (major).

*Methyl N-benzyl-N-(oxazol-2-ylsulfonyl)-D-alaninate (+)-**17g** & methyl N-benzyl-N-(oxazol-2-ylsulfonyl)-L-alaninate (–)-**17g***



(+)-**17g**

FMR protocol: Prepared from sulfonamide **8a** (0.214 g, 0.9 mmol) and methyl L-lactate (0.139 mL, 1.35 mmol). Two additional cycles were carried out and, in each cycle, additional methyl L-lactate (0.3 equiv) was added. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 3:2) and semiprep HPLC (SiO_2-C18, MeOH/H_2O) to give the desired product (+)-**17g** (0.260 g, 89%, *e.r.* = 99:1) as a colorless oil.



(-)-**17g**

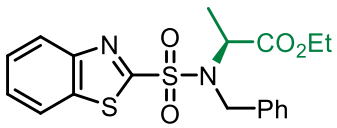
FMR protocol: PreparedPrepared starting from sulfonamide (–)-**8b** (0.211 g, 0.9 mmol) and benzyl alcohol (0.140 mL, 1.35 mmol). Two additional cycles were carried out and, in each cycle, additional benzyl alcohol (0.3 equiv) was added. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 3:2) and semiprep HPLC (SiO_2-C18, MeOH/H_2O) to give the desired product (–)-**17g** (0.274 g, 94%, *e.r.* = 99:1) as a colorless oil.

(+)-**17g**: $[\alpha]_D^{24.2}$ = +57.5° (c 1.0, $CHCl_3$)

(–)-**17g**: $[\alpha]_D^{21.7}$ = –57.8° (c 1.0, $CHCl_3$)

$[\alpha]_D^{20.5}$ = +57.5° (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): *δ* 7.81 (d, *J* = 0.8 Hz, 1H), 7.43 – 7.38 (m, 2H), 7.43 – 7.29 (m, 2H), 7.32 (d, *J* = 0.8 Hz, 1H), 7.33 – 7.25 (m, 1H), 4.89 (d, *J* = 16.4 Hz, 1H), 4.78 (q, *J* = 7.4 Hz, 1H), 4.43 (d, *J* = 16.4 Hz, 1H), 3.51 (s, 3H), 1.34 (d, *J* = 7.4 Hz, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): *δ* 171.0, 158.0, 141.3, 136.6, 128.7, 128.7, 128.0, 128.0, 56.4, 52.7, 50.3, 16.7 ppm; MS (ESI) *m/z* (%) 325: $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{14}H_{17}N_2O_5S$, 325.0853; found, 325.0849; HPLC (Chiral ART Amylose-SA, hexan/EtOAc = 90/10 to 10/90, flow rate = 0.5 mL/min) t_R = 14.31 min ((–)-**17g**), 15.07 min ((+)-**17g**).

*Ethyl N-(benzo[d]thiazol-2-ylsulfonyl)-N-benzyl-L-alaninate (–)-**17h***

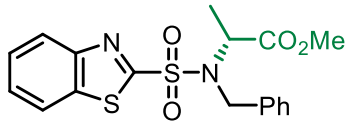


(-)-**17h**

FMR protocol: Prepared from sulfonamide **9a** (0.274 g, 0.9 mmol) and ethyl D-lactate (0.155 mL, 1.35 mmol). An additional cycle was carried out. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 10:1->4:1) and yielded the desired product (–)-**17h** (0.335 g, 92%, *e.r.* = 99:1) as a yellowish oil.

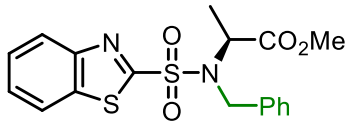
$[\alpha]_D^{19.8}$ = –440° (c 0.25, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 – 8.15 (m, 1H), 8.00 – 7.95 (m, 1H), 7.61 (ddd, *J* = 8.3, 7.2, 1.4 Hz, 1H), 7.56 (ddd, *J* = 8.5, 7.2, 1.4 Hz, 1H), 7.44 – 7.41 (m, 2H), 7.34 – 7.25 (m, 3H), 4.93 (d, *J* = 16.4 Hz, 1H), 4.86 (q, *J* = 7.3 Hz, 1H), 4.54 (d, *J* = 16.4 Hz, 1H), 3.86 – 3.72 (m, 2H), 1.34 (d, *J* = 7.4 Hz, 3H), 0.96 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.7, 165.6, 152.7, 137.0, 136.5, 128.6, 128.2, 127.9, 127.7, 127.5, 125.3, 122.2, 61.6, 56.4, 50.3, 16.9, 13.8 ppm; MS (ESI) *m/z* (%): 405 $[M^+H]^+$ (100); HRMS (ESI) *m/z:* $[M^+H]^+$ calcd. for $C_{19}H_{21}N_2O_4S_2$, 405.0937; found, 405.0938; HPLC (Chiral ART Amylose-SA, hexan/EtOAc = 90/10 to 10/90, flow rate = 0.5 mL/min) t_R = 14.18 min (*major*), 15.67 min (*minor*).

*Methyl N-(benzo[d]thiazol-2-ylsulfonyl)-N-benzyl-L-alaninate (–)-**17i** & methyl N-(benzo[d]thiazol-2-ylsulfonyl)-N-benzyl-D-alaninate (+)-**17i***



(+)-**17i**

FMR protocol: Prepared from sulfonamide **9a** (0.274 g, 0.9 mmol) and methyl L-lactate (0.155 mL, 1.35 mmol). An additional cycle was carried out. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 4:1) and yielded the desired product (+)-**17i** (0.306 g, 87%, *e.r.* = 99:1) as yellow oil.



(-)-**17i**

FMR protocol: Prepared from sulfonamide (–)-**9d** (0.270 g, 0.9 mmol) and benzyl alcohol (0.140 mL, 1.35 mmol). An additional cycle was carried out. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 4:1) and yielded the desired product (–)-**17i** (0.323 g, 92%, *e.r.* = 99:1) as yellow oil.

Alkylation protocol: Prepared from sulfonamide (–)-**9d** (0.270 g, 0.9 mmol) and benzyl bromide (0.214 mL, 1.8 mmol). The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 4:1->2:1->1:1) to give the desired product (–)-**17i** (0.193 g, 80%) as a colorless oil.

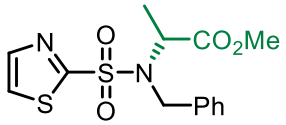
(–)-**17i**: $[\alpha]_D^{23}$ = –29.1° (*c* 1.0, $CHCl_3$)

(+)-**17i**: $[\alpha]_D^{22.7}$ = +29.5° (*c* 1.01, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (ddd, *J* = 8.1, 1.4, 0.6 Hz, 1H), 8.03 – 7.93 (m, 1H), 7.62 (ddd, *J* = 8.3, 7.2, 1.4 Hz, 1H), 7.56 (ddd, *J* = 8.0, 7.2, 1.4 Hz, 1H), 7.45 – 7.40 (m, 2H), 7.36 – 7.26 (m, 3H), 4.92 – 4.83 (m, 2H), 4.60 (d, *J* = 16.3 Hz, 1H), 3.34 (s, 3H), 1.36 (d, *J* = 7.3 Hz, 3H) ppm; ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$): δ 171.1, 165.6, 152.7, 136.8, 136.5, 128.6, 128.3, 127.9, 127.7, 127.5, 125.3, 122.3, 56.18, 5.4, 50.3, 16.6 ppm; MS

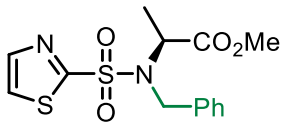
(ESI) *m/z* (%) 391: $[M+H]^+$ (100); HRMS (ESI) *m/z:* $[M+H]^+$ calc. for $C_{18}H_{19}N_2O_4S_2$, 391.0786; found, 391.0784; HPLC (Chiral ART Amylose-SA, hexan/EtOAc = 90/10 to 10/90, flow rate = 0.5 mL/min) t_R = 14.27 min ((–)-**17i**), 15.20 min ((+)-**17i**).

*Methyl N-benzyl-N-(thiazol-2-ylsulfonyl)-D-alaninate (+)-**17j** & methyl N-benzyl-N-(thiazol-2-ylsulfonyl)-L-alaninate (–)-**17j***



(+)-**17j**

FMR protocol: Prepared from sulfonamide **10a** (0.229 g, 0.9 mmol) and methyl L-lactate (0.155 mL, 1.35 mmol). Two additional cycles were carried out. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 3:2) and semiprep HPLC (SiO_2-C18, MeOH/H_2O) to give the desired product (+)-**17j** (0.251 g, 82%, *e.r.* = 99:1) as a colorless oil.



(-)-**17j**

FMR protocol: Prepared from sulfonamide (–)-**10b** (0.306 g, 0.9 mmol) and benzyl alcohol (0.140 mL, 1.35 mmol). Two additional cycles were carried out. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 3:2) and semiprep HPLC (SiO_2-C18, MeOH/H_2O) to give the desired product (–)-**17j** (0.275 g, 90%, *e.r.* = 99:1) as a colorless oil.

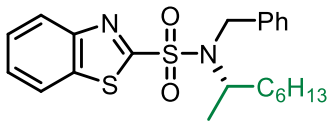
Alkylation protocol: Prepared from sulfonamide (–)-**10b** (0.306 g, 0.9 mmol) and benzyl bromide (0.214 mL, 1.8 mmol). The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 4:1->2:1->1:1) to give the desired product (–)-**17j** (0.230 g, 75%) as a colorless oil.

(–)-**17j**: $[\alpha]_D^{22.7}$ = –39.0° (*c* 1.01, $CHCl_3$)

(+)-**17j**: $[\alpha]_D^{20.1}$ = +38.8° (*c* 1.01, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 (d, *J* = 3.1 Hz, 1H), 7.63 (d, *J* = 3.1 Hz, 1H), 7.39 (d, *J* = 7.4 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.27 (t, *J* = 7.0 Hz, 1H), 4.82 (q, *J* = 7.4 Hz, 1H), 4.81 (d, *J* = 16.3 Hz, 1H), 4.54 (d, *J* = 16.3 Hz, 1H), 3.46 (s, 3H), 1.34 (d, *J* = 7.3 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 171.3, 165.4, 144.6, 136.9, 128.6, 128.2, 127.9, 124.7, 56.1, 52.5, 50.1, 16.6 ppm; MS (ESI) *m/z* (%): 341 $[M+H]^+$ (100); HRMS (ESI) *m/z:* $[M+H]^+$ calc. for $C_{14}H_{17}N_2O_4S_2$, 341.0624; found, 341.0624; HPLC (Chiral ART Amylose-SA, hexan/EtOAc = 90/10 to 10/90, flow rate = 0.5 mL/min) t_R = 13.15 min ((–)-**17j**), 14.42 min ((+)-**17j**).

*(S)-N-benzyl-N-(octan-2-yl)benzo[d]thiazole-2-sulfonamide ((–)-**17k**)*

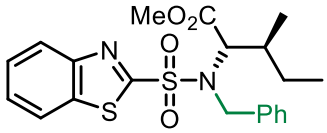


(-)-**17k**

FMR protocol: Prepared from sulfonamide **9a** (0.274 g, 0.9 mmol) and (*R*)-octan-2-ol (0.147 mL, 1.35 mmol). An additional cycle was carried out and additional (*R*)-octan-2-ol (0.3 equiv) was added. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 8:1) and yielded the desired product (–)-**17k** (0.367 g, 98%, *e.r.* = 99:1) as a colorless oil.

$[\alpha]_D^{22}$ = −183° (*c* 0.31, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.18 – 8.16 (m, 1H), 7.96 (ddd, *J* = 7.9, 1.3, 0.6 Hz, 1H), 7.60 (ddd, *J* = 8.2, 7.3, 1.4 Hz, 1H), 7.54 (ddd, *J* = 8.4, 7.3, 1.3 Hz, 1H), 7.46 – 7.45 (m, 2H), 7.33 – 7.24 (m, 3H), 4.64 (d, *J* = 15.9 Hz, 1H), 4.51 (d, *J* = 15.9 Hz, 1H), 4.12 (hept, *J* = 6.8 Hz, 1H), 1.39 – 1.30 (m, 1H), 1.26 – 1.18 (m, 1H), 1.12 – 1.05 (m, 4H), 1.03 (d, *J* = 6.8 Hz, 3H), 1.02 – 0.93 (m, 4H), 0.76 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): *δ* 166.9, 152.7, 137.8, 136.5, 128.6, 128.5, 127.8, 127.5, 127.4, 125.2, 122.2, 56.2, 48.3, 35.6, 31.7, 29.0, 26.5, 22.6, 19.6, 14.2 ppm; MS (ESI) *m/z* (%): 417 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{19}H_{21}N_2O_4S_2$, 417.1665; found, 417.1667; HPLC (Chiralpak IA3, CO_2/MeOH = 93/7, flow rate = 2.2 mL/min, I = 272 nm) tR = 4.21 min (minor), 4.51 min (major).

*Methyl N-(benzo[d]thiazol-2-ylsulfonyl)-N-benzyl-L-isoleucinate (–)-**17l***



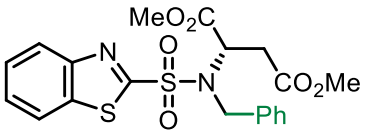
(-)-**17l**

FMR protocol: Prepared from sulfonamide (+)-**9g** (0.306 g, 0.9 mmol) and benzyl alcohol (0.140 mL, 1.35 mmol). An additional cycle was carried out. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 10:1->4:1->2:1) to give the desired product (–)-**17l** (0.331 g, 85%, *d.r.* = >99:1) as a colorless oil.

Alkylation protocol: Prepared from sulfonamide (+)-**9g** (0.365 g, 1.06 mmol) and benzyl bromide (0.250 mL, 2.11 mmol). The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 4:1) to give the desired product (–)-**17l** (0.376 g, 82%, *d.r.* = >99:1) as a colorless oil.

$[\alpha]_D^{23}$ = − 32.7° (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 8.17 (ddd, *J* = 8.2, 1.3, 0.7 Hz, 1H), 7.98 (ddd, *J* = 8.0, 1.4, 0.7 Hz, 1H), 7.63 – 7.52 (m, 4H), 7.35 – 7.31 (m, 2H), 7.30 – 7.26 (m, 1H), 5.09 (d, *J* = 16.1 Hz, 1H), 4.73 (d, *J* = 16.1 Hz, 1H), 4.35 (d, *J* = 10.7 Hz, 1H), 3.26 (s, 3H), 1.70 – 1.61 (m, 1H), 1.47 (dtd, *J* = 15.1, 7.5, 2.4 Hz, 1H), 0.90 – 0.82 (m, 1H), 0.74 (d, *J* = 6.6 Hz, 3H), 0.38 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): *δ* 170.4, 165.7, 152.5, 137.0, 136.5, 129.1, 128.5, 127.9, 127.7, 127.6, 125.2, 122.2, 65.8, 51.7, 50.2, 34.7, 25.6, 15.7, 10.4 ppm; MS (ESI) *m/z* (%) 433: $[M+H]^+$ (100); HRMS (ESI) *m/z:* $[M+K]^+$ calc. for $C_{21}H_{24}KN_2O_4S_2$, 471.0809; found, 471.0811.

*Dimethyl N-(benzo[d]thiazol-2-ylsulfonyl)-N-benzyl-L-aspartate (–)-**17m***



(-)-**17m**

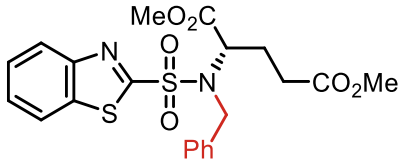
FMR protocol: Prepared from sulfonamide (+)-**9j** (0.323 g, 0.9 mmol) and benzyl alcohol (0.140 mL, 1.35 mmol). An additional cycle was carried out. The residue was purified by column chromatography (SiO_2;

petroleum ether:EtOAc = 20:1 –> 15:1 –> 10:1 –> 5:1) to give the desired product (–)-**17m** (0.355 g, 88%) as a white solid.

Alkylation protocol: Prepared from sulfonamide (+)-**9j** (0.323 g, 0.9 mmol) and benzyl bromide (0.214 mL, 1.8 mmol). The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 20:1 –> 15:1 –> 10:1 –> 5:1) to give the desired product (–)-**17m** (0.319 g, 79%) as a white solid.

$[\alpha]_D^{22}$ = –50.6° (*c* 1.0, $CHCl_3$); mp = 110-112 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.20 – 8.17 (m, 1H), 8.01 – 7.98 (m, 1H), 7.63 (ddt, *J* = 8.1, 7.0, 1.1 Hz, 1H), 7.58 (ddt, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.43 (dd, *J* = 7.9, 1.6 Hz, 2H), 7.35 – 7.29 (m, 3H), 5.02 (dd, *J* = 8.4, 5.8 Hz, 1H), 4.89 (d, *J* = 15.7 Hz, 1H), 4.51 (d, *J* = 15.7 Hz, 1H), 3.53 (s, 3H), 3.34 (s, 3H), 2.99 (dd, *J* = 17.0, 8.4 Hz, 1H), 2.76 (dd, *J* = 17.0, 5.7 Hz, 1H) ppm; ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 170.6, 169.5, 165.7, 152.6, 136.5, 135.5, 128.9, 128.7, 128.4, 127.8, 127.6, 125.3, 122.3, 56.9, 52.7, 52.1, 52.0, 35.4 ppm; MS (ESI) *m/z* (%): 449 $[M^+H]^+$ (100); HRMS (ESI) *m/z:* $[M^+H]^+$ calcd. for $C_{20}H_{21}N_2O_6S_2$, 449.0836; found, 449.0829.

*Dimethyl N-(benzo[d]thiazol-2-ylsulfonyl)-N-benzyl-L-glutamate (–)-**17n***

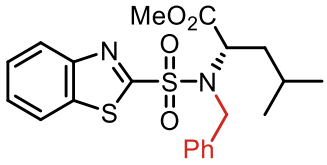


(-)-**17n**

Alkylation protocol: Prepared from sulfonamide (+)-**9k** (1.0 g, 2.69 mmol) and benzyl bromide (0.650 mL, 5.37 mmol). The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 20:1 –> 15:1 –> 10:1 –> 5:1) to give the desired product (–)-**17n** (1.1 g, 89%) as a white solid.

$[\alpha]_D^{23}$= –26.3° (*c* 0.4, $CHCl_3$); mp = 58 – 60 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18 (ddd, *J* = 8.2, 1.4, 0.7 Hz, 1H), 7.99 (ddd, *J* = 8.1, 1.4, 0.7 Hz, 1H), 7.62 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 7.59 – 7.55 (m, 1H), 7.48 – 7.45 (m, 2H), 7.34 – 7.27 (m, 3H), 5.00 (d, *J* = 15.9 Hz, 1H), 4.74 (dd, *J* = 9.9, 4.9 Hz, 1H), 4.45 (d, *J* = 15.9 Hz, 1H), 3.57 (s, 3H), 3.30 (s, 3H), 2.36 – 2.23 (m, 1H), 2.25 – 2.09 (m, 2H), 1.88 – 1.77 (m, 1H) ppm; ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 172.8, 170.1, 165.3, 152.6, 136.5, 136.2, 128.9, 128.7, 128.2, 127.8, 127.6, 125.2, 122.3, 60.1, 52.4, 51.8, 51.0, 29.9, 25.1 ppm; MS (ESI) *m/z* (%): 463 $[M^+H]^+$ (100); HRMS (ESI) *m/z:* $[M^+H]^+$ calcd. for $C_{21}H_{23}N_2O_6S_2$, 463.0992; found, 463.1001.

*Methyl N-(benzo[d]thiazol-2-ylsulfonyl)-N-benzyl-L-leucinate (–)-**17o***



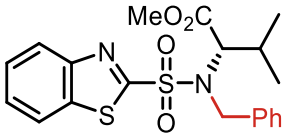
(-)-**17o**

Alkylation protocol: Prepared from sulfonamide (+)-**9i** (1.0 g, 2.92 mmol) and benzyl bromide (0.71 mL, 5.84 mmol). The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 15:1 –> 10:1 –> 5:1) to give the desired product (–)-**17o** (1.94 g, 87%) as a white solid.

$[\alpha]_D^{23}$= –66.8° (*c* 1.2, $CHCl_3$); mp = 100-102 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 – 8.16 (m, 1H), 7.99 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.62 (ddd, *J* = 8.3, 7.2, 1.4 Hz, 1H), 7.57 (ddt, *J* = 8.0, 7.1, 1.6 Hz, 1H), 7.50 – 7.46 (m, 2H),

7.33 (td, *J* = 6.9, 1.2 Hz, 2H), 7.30 – 7.27 (m, 1H), 5.02 (d, *J* = 16.3 Hz, 1H), 4.80 (dd, *J* = 8.3, 6.4 Hz, 1H), 4.51 (d, *J* = 16.4 Hz, 1H), 3.29 (s, 3H), 1.54 – 1.49 (m, 2H), 1.44 (dt, *J* = 13.1, 6.5 Hz, 1H), 0.86 (d, *J* = 6.3 Hz, 3H), 0.49 (d, *J* = 6.5 Hz, 3H) ppm; ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): *δ* 171.2, 165.4, 152.7, 137.1, 136.5, 128.6, 128.6, 127.9, 127.7, 127.6, 125.2, 122.3, 59.3, 52.3, 50.6, 39.1, 24.4, 22.4, 21.4 ppm; MS (ESI) *m/z* (%): 433 $[M^+H]^+$ (100); HRMS (ESI) *m/z:* $[M^+H]^+$ calcd. for $C_{21}H_{25}N_2O_4S_2$, 433.1250; found, 433.1263.

*Methyl N-(benzo[d]thiazol-2-ylsulfonyl)-N-benzyl-L-valinate (–)-**17p***

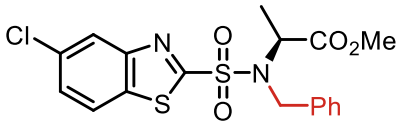


(-)-**17p**

Alkylation protocol: Prepared from sulfonamide (+)-**9h** (1.0 g, 3.04 mmol) and benzyl bromide (0.74 mL, 6.1 mmol). The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 15:1 –> 10:1 –> 5:1) to give the desired product (–)-**17p** (1.06 g, 83%) as a white solid.

$[\alpha]_D^{23}$= –40.7° (*c* 1, $CHCl_3$); mp = 110–112°C; ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 8.17 (ddd, *J* = 8.4, 1.2, 0.7 Hz, 1H), 7.98 (ddd, *J* = 8.1, 1.3, 0.7 Hz, 1H), 7.61 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 7.56 (ddd, *J* = 8.3, 7.1, 1.3 Hz, 1H), 7.54 – 7.50 (m, 2H), 7.34 – 7.26 (m, 3H), 5.02 (d, *J* = 15.9 Hz, 1H), 4.69 (d, *J* = 15.9 Hz, 1H), 4.27 (d, *J* = 10.7 Hz, 1H), 3.24 (s, 3H), 2.04 – 1.94 (m, 1H), 0.81 (d, *J* = 6.6 Hz, 3H), 0.73 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): *δ* 170.2, 165.8, 152.5, 136.8, 136.5, 129.3, 128.5, 128.00, 127.7, 127.5, 125.1, 122.2, 67.1, 51.8, 50.4, 28.7, 19.7, 19.5 ppm; MS (ESI) *m/z* (%): 419 $[M^+H]^+$ (100); HRMS (ESI) *m/z:* $[M^+H]^+$ calcd. for $C_{20}H_{23}N_2O_4S_2$, 433.1094; found, 419.1110.

*methyl N-benzyl-N-((5-chlorobenzo[d]thiazol-2-yl)sulfonyl)-L-alaninate (–)-**17q***



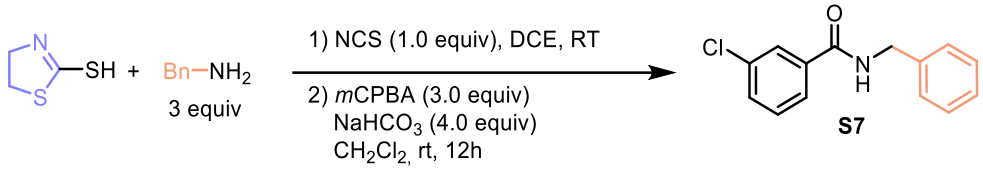
(-)-**17q**

Alkylation protocol: Prepared from sulfonamide (–)-**9e** (0.39 g, 1.16 mmol) and benzyl bromide (0.28 mL, 2.33 mmol). The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 10:1 –> 5:1) to give the desired product (–)-**17q** (0.36 g, 72%) as a slightly yellow oil.

$[\alpha]_D^{23}$ = –24.9° (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 8.17 (dd, *J* = 2.1, 0.5 Hz, 1H), 7.90 (dd, *J* = 8.6, 0.5 Hz, 1H), 7.54 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.42 – 7.39 (m, 2H), 7.34 – 7.30 (m, 2H), 7.29 – 7.25 (m, 1H), 4.91 – 4.82 (m, 2H), 4.56 (d, *J* = 16.3 Hz, 1H), 3.38 (s, 3H), 1.36 (d, *J* = 7.3 Hz, 3H) ppm; ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): *δ* 171.1, 167.6, 153.4, 136.6, 134.7, 133.8, 128.7, 128.7, 128.4, 128.2, 128.0, 127.1, 124.9, 123.1, 56.3, 52.5, 50.3, 32.0, 16.7, 14.3 ppm; MS (ESI) *m/z* (%): 424 $[M+H]^+$ (100); HRMS (ESI) *m/z:* $[M+H]^+$ calc. for $C_{18}H_{18}ClN_2O_4S_2$, 425.0391; found, 425.0394.

Formation of side products S7, S8, and S9

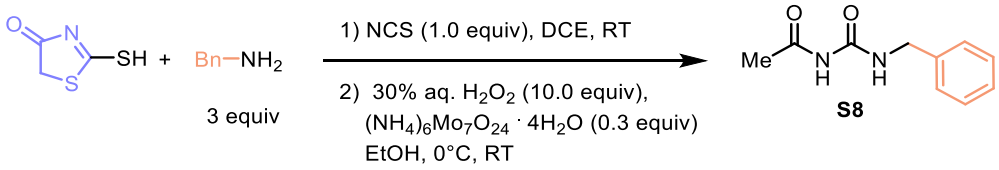
N-benzyl-3-chlorobenzamide (S7)



Thiazoline-2-thiol (0.608 g, 5.0 mmol, 1.0 equiv) and benzylamine (1.61 g, 15 mmol, 3.0 equiv) were suspended in 1,2-DCE (25 mL; *CAUTION! CARE SHOULD BE TAKEN! 1,2-DCE is toxic, and possibly carcinogenic*) at RT and the resulting mixture was stirred at RT for 10 min. NCS (0.663 g, 5 mmol, 1.0 equiv) was added portion-wise for a period of 5 min and the whole mixture was stirred for an additional 2 h at RT. The whole slurry was filtered, the filter cake was washed with CH_2Cl_2 (2x5 mL), and the combined filtrates were evaporated in vacuo. The generated crude sulfenamide was dissolved in CH_2Cl_2 (25 mL) at 0 °C and $NaHCO_3$ (1.68 g, 20 mmol, 4 equiv) followed by *m*CPBA (3.36 g, 3 mmol, 3 equiv; 77% purity) were added sequentially in portion for 5 minutes. The reaction mixture was allowed to warm to RT and stirred for 12 h at RT. Water (10 mL) and sat. aq. Na_2SO_3 (10 mL) were added and the resulting mixture was stirred at RT for 20 min. Resulting layers were separated and the organic phase was washed with sat. $NaHCO_3$ (20 mL), brine (30 mL), dried over Na_2SO_4, and solvents were removed under reduced pressure. The residue was dispersed in hexane/Et_2O = 10:1 (V/V) and sonicated for 10 min. The solid was decanted and the organic layer was dried over Na_2SO_4, filtered, and the organic solvents were removed under reduced pressure. The residue was purified by chromatography (SiO_2, petroleum ether:EtOAc = 3:1) and yielded side product **S7** (0.221 g, 18%). The The characteristic data corresponded to the literature.[25]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (t, J = 1.8 Hz, 1H), 7.66 (ddd, J = 7.8, 1.7, 1.1 Hz, 1H), 7.48 (ddd, J = 8.0, 2.1, 1.1 Hz, 1H), 7.41 – 7.34 (m, 5H), 7.34 – 7.29 (m, 1H), 6.49 (broad s, 1H), 4.63 (d, J = 5.7 Hz, 2H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 166.1, 137.9, 136.2, 134.9, 131.7, 130.0, 128.9, 128.1, 127.9, 127.4, 125.2, 44.4 ppm; MS (ESI) *m/z* (%): 246 $[M+H]^+$ (100).

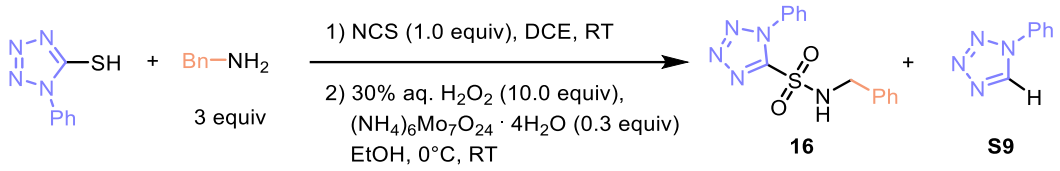
N-(benzylcarbamoyl)acetamide (S8)



Method A. Starting from 2-mercaptothiazol-4(5H)-one (0.673 g, 5.0 mmol). **S8** was crystalized from the crude reaction mixture (50% aq. EtOH) in the form of slightly pink crystals (0.346 g, 36% yield). Obtained characteristic data corresponded to the literature.[26]

mp = 116.7-117.8 °C (EtOH/H_2O), litt.[26] mp = 130 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.73 (s, 1H), 8.86 (s, 1H), 7.41 – 7.28 (m, 5H), 4.49 (d, J = 6.0 Hz, 2H), 2.11 (s, 3H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 172.5, 154.8, 138.1, 128.8, 127.6, 127.6, 43.7, 24.1 ppm; MS (ESI) *m/z* (%): 215 $[M+Na]^+$ (30), 193 $[M+H]^+$ (50); HRMS (ESI) *m/z:* $[M+Na]^+$ calc. for $C_{10}H_{10}N_2O_2Na$, 215.0791; found 215.0785.

Phenyl tetrazole (S9)



Method A. Starting from 4-phenylthiazol-2-thiol (0.540 g, 3.0 mmol). Sulfonamide **16** detected in the crude reaction mixture, but all attempts to isolate failed. Instead, only phenyl tetrazole **S9** isolated was the only product of the reaction.

The crude product was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 3:2) and yielded 1-phenyltetrazole **S9** (0.485 g, 37%). Spectral data of **S9** correspond to the literature.[27]

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.01 (s, 1H), 7.75 – 7.70 (m, 2H), 7.66 – 7.58 (m, 2H), 7.58 – 7.53 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 140.7, 134.0, 130.4, 130.3, 121.4 ppm.

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