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Unified Approach to Benzo[*d*]thiazol-2-yl-Sulfonamides

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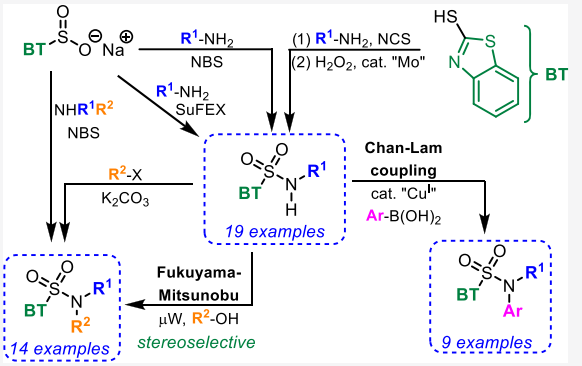
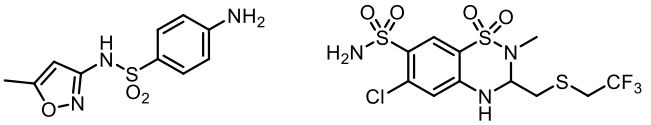
ABSTRACT: In this paper, we report a unified approach to *N*-substituted and *N,N*-disubstituted benzothiazole (BT) sulfonamides. Our approach to BT-sulfonamides starts from simple commercially available building blocks (benzo[*d*]thiazole-2-thiol and primary and secondary amines) that are connected via (a) a S oxidation/S−N coupling approach, (b) a S−N coupling/S-oxidation sequence, or via (c) a S-oxidation/S−F bond formation/SuFEx approach. The labile N−H bond in *N*-monoalkylated BT-sulfonamides (pK_a ($BTSO_2N(\mathbf{H})Bn$) = 3.34 ± 0.05) further allowed us to develop a simple weak base-promoted N-alkylation method and a stereoselective microwave-promoted Fukuyama−Mitsunobu reaction. *N*-Alkyl-*N*-aryl BT-sulfonamides were accessed with the help of the Chan−Lam coupling reaction. Developed methods were further used in stereo and chemoselective transformations of podophyllotoxin and several amino alcohols.



INTRODUCTION

Sulfonamide-containing natural products[1−4] occupy a privileged place in the group of biologically active compounds. The biological activity of such compounds varies from antibacterial,[5] antiviral,[6] antiretroviral,[7] and diuretic,[8] to anticonvulsant[9] (Figure 1). Such a broad spectrum of biological activities



Sulfamethoxazole (antibiotic) **Polythiazide** (diuretic)

Figure 1. Two examples of sulfonamides containing antibiotic (sulfamethoxazole) and diuretic[8] (polythiazide) drugs.

triggered the interest of the synthetic community and led to the development of several interesting ways for sulfonamide moiety synthesis (Scheme 1). The most commonly used approach is based on the reaction of amines and sulfonyl chlorides,[10−12] that are in their turn obtained via chlorosulfonylation of (hetero)aryl compounds,[13,14] via sulfochlorination of hydrocarbons,[15] or via thiol oxidation[16]/chlorination[17] sequence (Scheme 1A). The main drawbacks of these methods are (a) low thermal stability of (heteroaryl) sulfonyl chlorides and (b) rather limited functional group tolerance.

These limitations led scientists to develop an alternative synthetic route based on the use of sulfinic salts (Scheme 1B). In this approach, sulfinic salts are smoothly prepared via sulfinic ester hydrolysis,[18] or by sulfonylation (using DABSO reagent)[19,20] or trans-sulfonylation (using SMOPS reagent)[21] of alkyl halides. Generated sulfinic salts are usually thermally and moisture insensitive solids that can be readily transformed into the desired sulfonamides using various oxidative protocols. In such cases, sulfinic salts are reacted with in situ generated electrophilic brominating or iodinating species (in situ generation of the corresponding sulfonyl halides) in the presence of an excess of amine.[22−26] Alternatively, sulfinic salts can also be oxidized in the presence of amines to sulfonamides with the help of electrochemistry.[27] Finally, sulfinic salts can be readily converted to sulfonamides using the SuFEx chemistry approach.[28,29] The last approach, which is only scarcely used, is based on the transformation of thiols into sulfenamides, which are further oxidized to sulfonamides (Scheme 1C).[30−32] The main drawback of this approach is the oxidation step that yielded the desired sulfonamides in low yields.

All three described methods are working well in the case of alkyl or aryl sulfonamide synthesis. However, in the case of heteroaryl sulfonamides (Scheme 2), generated reaction intermediates are either unstable,[33] prepared under harsh reaction conditions (use of $Cl_2(g)$),[34,35] obtained in low reaction yields, or unsuitable for *N,N*-arylalkyl sulfonamide synthesis.[26,34−36] In our contribution, we wish to report a unified approach to *N*-monoalkyl, *N,N*-dialkyl-, and *N,N*-

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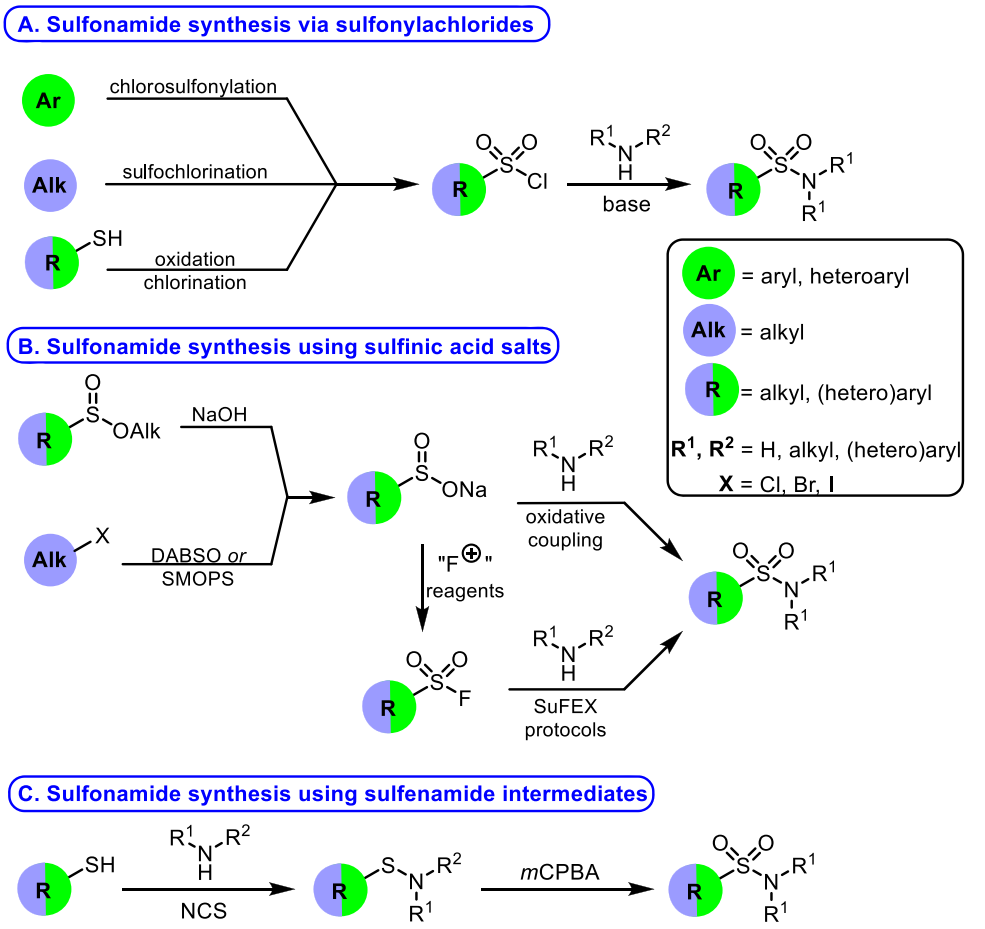
Scheme 1. Current Methods of Sulfonamide Synthesis—General Overview



alkylaryl benzothiazole sulfonamides. Several approaches to target *N*-substituted and *N,N*-disubstituted benzothiazole sulfonamides are (mechanistically) investigated, and scope and limitations are established.

RESULTS AND DISCUSSION

Approaches Based on S Oxidation and S−N Bond Formation Sequences. At the onset of our project was the desire to extend our research interest from benzothiazoylsulfones[37−39] ($BTSO_2R$) to the corresponding amides ($BTSO_2NR_2$). To do so, a short, practical, and convenient way of BT-sulfonamides was searched. Unfortunately, most of the common synthetic paths to such heteroaryl sulfonamides proved to be either unpractical (e.g., use of $Cl_2(g)$)[33,35] or failed in our hands (for selected examples, see Table 1, entries 1−3).[34,36] Thus, the readily available BT-sulfinic acid salt **2** was used as a starting material for the sulfonamide synthesis. In this regard, the conditions of Yan and co-workers[22] proved to be suitable and generated the desired sulfonamide **2a** in 77% yield (Table 1, entry 7). The protocol, however, lacks the atom economy. Fortunately, the reaction mechanism evaluation identified bromine cations as the key reagent of transformation[40] and a simplified version of the protocol based on the use of Br_2 (suitable for small-scale reactions) and NBS (safer bromine cation source), respectively, (Table 1, entries 8 and 9) was developed.[41] Under such conditions, the reaction was fast and yielded the desired sulfonamide **3a** in excellent isolated yields (86% and 91%, respectively) even on a 10 mmol scale (Table 1, entry 10).

Even though we had a short and efficient way to **3a** starting from sulfinic salt **2**, an alternative way starting from sulfide **1** was searched. As demonstrated in Tables 1A and 1B, all previously tested methods employ the same sequence, S^{-II}/S^{IV}-oxidation followed by the S−N bond formation. Interestingly, the S−N[32] bond formation followed by the S^{-II}/S^{IV}-oxidation approach is scarcely used in the literature when heterocyclic sulfonamides are targeted.[42−44] The main drawback of such an approach is the low-yielding oxidation step. After the careful reaction optimization, the combination of Brownbridge's[32] sulfenamide formation and Mo-promoted[37−39] H_2O_2-based oxidation sequence was found to be the most suitable (Table 1, entry 5). The reaction was again readily scalable up to a 10 mmol scale (Table 1, entry 6).

Having found suitable and robust reaction conditions for sulfonamide **3a** synthesis, the scope and limitations of both methods were established (Table 2). In general, both methods yielded the desired *N*-substituted sulfonamides **3** in good to very good yields if unfunctionalized primary α-unbranched amines were used as the starting material (**3a−c**). The methods became supplementary if heteroaryl substituted amine (**3d**), aryl-substituted amines (**3f, 3g, 3m**), and ester or carbamoyl group bearing amines were used ((−)-**3j−l**). Both methods tolerate the free hydroxy groups ((−)-**3h,i**). If a diamino-substituted substrate was used, both amino groups were transformed into the corresponding sulfonamides, albeit in low reaction yield ((+)-**3n**). When homochiral amines with α-stereogenic centers were used as a starting material

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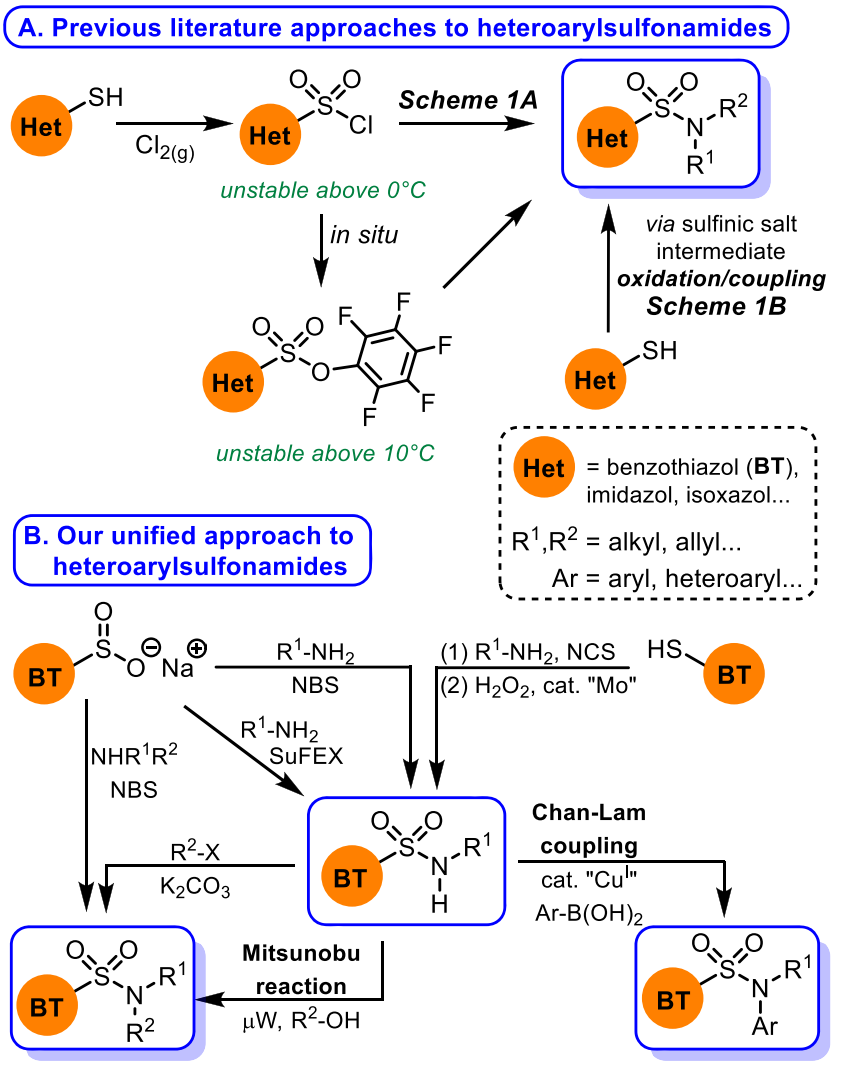
Scheme 2. (A) Previous Approaches to Various Heteroarylsulfones,[34−36] and (B) our Unified Approach to Such Structures



((−)-**3h−l**, (+)-**3n**), no breach in stereo integrity was observed.

The reactivity of secondary amines proved to be problematic, and the corresponding sulfonamides **4** were obtained in reasonable yields only in the case of piperidine derivatives **4a** and **b**. The only exception was sulfonamide **4c** that was prepared in 34% yield.[40] Aromatic amines and simple amine sources such as NH_4Cl (to generate ammonia in situ) and NH_2CN failed to generate the desired products. In both cases, we speculate that the stability or inability to generate the key intermediates, sulfonyl bromide (Method A) and sulfenyl chloride (Method B), respectively, is responsible for the observed nonreactivity.[40]

***N*-Alkylation of *N*-Monosubstituted Sulfonamides.** Having easy access to *N*-monosubstituted sulfonamides, *N*-alkylation of the prepared sulfonamides **3** seemed to use as the best synthetic path to *N,N*-disubstituted sulfonamides. To evaluate the feasibility of this approach, the pK_a value of **3a** was determined.[45] The low pK_a value of sulfonamide N−H hydrogen (pK_a(**3a**) = 3.34 ± 5) suggested that two different approaches to *N,N*-disubstituted sulfonamide **4** can be considered (Table 3). The first approach relied on the reaction with alkyl halides in the presence of K_2CO_3, and the second explored sulfonamides **3** as *N*-nucleophiles in the microwave irradiation-promoted[40,46] Fukuyama−Mitsunobu alkylation reaction.[47] Scope and limitations of these transformations are highlighted in Table 3.

It was observed that both primary and secondary alkyl halides react with *N*-monosubstituted **3a−c** smoothly and yielded the desired *N,N*-disubstituted sulfonamides **4d−i** in good to excellent yields (Table 3A). In addition, microwave-promoted Fukuyama−Mitsunobu alkylation (FMA) reaction of sulfonamides **3a−c** with primary, allylic, and even secondary alcohols resulted in the formation of *N,N*-disubstituted sulfonamides **4d−o** in good to excellent yields (Table 3A). In all evaluated examples, microwave conditions tolerated a wide range of functional groups (alkenes and alkynes (**4e,f,i**), epoxide (**4k**), esters ((−)-**4l−n**), or lactone ((−)-**4o**)), and the transformation proceeded with complete stereoinversion of the hydroxy group bearing the carbon center ((−)-**4l,m,o**). If several stereogenic centers were present, no influence of the substrate on the FMA selectivity was observed. Using such an approach, a meso sulfonamide *meso*-**4n** was prepared starting from N-monosubstituted sulfonamide (−)-**3l** and methyl lactate, and the C4-hydroxy group in podophyllotoxin was transformed into BT-sulfonamide (−)-**4o**. No competitive elimination was observed.

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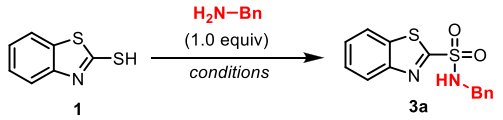
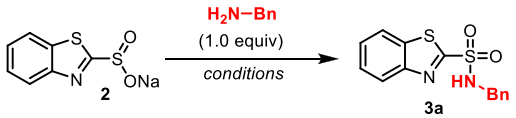
Table 1. Selected Examples of *N*-Benzylbenzo[d]thiazole-2-sulfonamide 3a Synthesis Optimization



1 3a

Entry	Conditions	Yield [%][a]
1[35]	(1) **1** (5.0 equiv), HCl, NaClO, 0°C, CH_2Cl_2, 1h (2) **BnNH$_2$**, CH_2Cl_2, -10°C, 4h	15%
2[33]	(1) **1** (5.0 equiv), HCl, NaClO, 0°C, CH_2Cl_2, 1h, then -30°C, C_6F_5OH (3.0 equiv), Et_3N (5.0 equiv), CH_2Cl_2, 5h (2) **BnNH$_2$**, CH_2Cl_2, -30°C to 0°C, 1h	48%
3[36]	**1** (1.0 equiv), $ZrCl_4$ (1 equiv), H_2O_2 (4 equiv), pyr, rt, 1h	n.d.
4[44]	(1) **1** (1.0 equiv), NCS (1.2 equiv), -40°C, CH_2Cl_2, 1h *then* **BnNH$_2$** (2.0 equiv), -40°C to rt, 24h (2) $KMnO_4/CuSO_4$, CH_3CN, rt	<5%
5	**1** (1.0 equiv), **BnNH$_2$** (3.0 equiv), NCS (1.0 equiv), rt, CH_2Cl_2, 30 min *then* H_2O_2 (10 equiv), $(NH_4)_6MoO_4•4H_2O$ (0.2 equiv), EtOH, 0°C to rt, 5h	92%
6[b]	**1** (1.0 equiv), **BnNH$_2$** (3.0 equiv), NCS (1.0 equiv), rt, CH_2Cl_2, 30 min *then* H_2O_2 (10 equiv), $(NH_4)_6MoO_4•4H_2O$ (0.2 equiv), EtOH, 0°C to rt, 5h	94%



2 3a

7[22]	**2** (1.0 equiv), DIPEA (1.5 equiv), TBAB (1.5 equiv), *m*CPBA (3 equiv), THF:EtOH (30:1), rt, 4h	77 %
8	**2** (1.0 equiv), DIPEA (1.5 equiv), Br_2 (2 equiv) THF:EtOH (1:1), rt, 5 min	86%
9	**2** (1.0 equiv), NBS (1.5 equiv) THF:EtOH (4:1), rt, 5 min	91%
10[b]	**2** (1.0 equiv), NBS (1.25 equiv) THF:EtOH (4:1), rt, 10 min	90%

[a]Refers to the isolated yield. [b]Performed on a 10 mmol scale of **2**. DIPEA, diisopropylethylamine; TBAB, tetrabutylammonium bromide; *m*CPBA, *m*-chloroperbenzoic acid; NBS, *N*-bromosuccinimide; and NCS, *N*-chlorosuccinimide.

FMA substitution can also be successfully applied in an intramolecular fashion (Table 3B). Combination of the primary BT-sulfonamide coupling with FMA step yields in a two-pot inter/intramolecular approach to cyclic *N,N*-disubstituted sulfonamide **5** in 59% overall yield.

Buchwald−Hartwig Amination. Having secured the synthesis of *N,N*-dialkyl-substituted sulfonamides **4** and **5**, our attention turned to *N,N*-alkylaryl sulfonamides **6**. Based on the literature analogy with phenylsulfonamides, we expected that either Buchwald−Hartwig amination[48,49] or Chan−Lam coupling[50,51] would smoothly accomplish such transformation. Unfortunately, in our hands, Buchwald−Hartwig amination failed to generate any traces of the desired arylated sulfonamide **6a** (Scheme 3A).[41] In most cases, only the product of compound **3a** formal SO_2 extrusion, compound **7a**, was isolated (Scheme 3B, eq 1). In analogy with Ni^0-promoted SO_2 extrusion observed in the case of sulfonamides,[52] the same mechanism of compound **7a** formation was expected. Much to our surprise, no product **7a** was formed if Pd^0-mediated SO_2 extrusion was attempted (Scheme 3B, eqs 2 and 3). Thus, the role of phenyl iodide under the reaction conditions was questioned (Scheme 3B, eq 4). It was observed that if 0.2 equiv of phenyl iodide is used, SO_2-free compound **7a** is obtained in 11% yield. This observation suggested that Pd^{II} that is generated via oxidative addition of Pd^0 to phenyl iodide is the real reaction promoter. To validate this hypothesis, the reaction was carried out in the presence of a catalytic amount of $(PPh_3)_2PdCl_2$ (Scheme 3B, eq 5). Expected product **7** was obtained in 6% isolated yield. When the transformation was attempted in the presence of a base (Scheme 3B, eq 6), compound **7a** was isolated in 76% yield. The last two observations led us to propose a tentative reaction mechanism shown in Scheme 3B below. It is expected that Pd^{II} interacts with **3a** to yield intermediate **A**. The interaction with strong Lewis acid increases the acidity of the sulfonamide-placed hydrogen atom that might be readily removed with an external base to yield intermediate **B**. A newly generated 5-membered ring in **B** further undergoes intramolecular rearrangement via intermediate **C** to anion **D**. The loss of SO_2 followed by the resulting amide anion reprotonation leads to the Pd^{II} release and the formation of final product **7a**.

Chan−Lam Coupling. Having failed to generate the desired C−N bond in sulfonamides with Pd-mediated coupling, our attention turned to copper-promoted Chan−Lam coupling (Scheme 4).[50,51] Being aware that the use of heteroarylsulfonamides as substrates in Chan−Lam coupling might be problematic,[53] intensive reaction condition screening was carried out.[40] Based on the obtained data, we concluded that the reaction has to be carried out starting from the copper(I) precatalyst with a non-nucleophilic counter ion, under an atmosphere of oxygen (1 atm), in the presence of a bidentate diamine ligand and that DCE is an optimal solvent. Using such reaction conditions, the scopes and limitations of the transformation were established (Scheme 4A). Consequently, a tentative reaction mechanism of sulfonamide-based Chan−Lam coupling that is based on our experimental results and previously published Chan−Lam coupling mechanistic studies[51,53,54] was proposed (Scheme 4B). The key observations are listed below:

- Copper: No reaction was observed when copper(II) precatalysts were used to promote the reaction.[51]
- Anion: The nature of the copper(I) anion proved to be essential for the reaction yields. In agreement with the previously published observations, it was observed that if strongly binding anions such as Cl^-, Br^-, I^-, CN^-, or AcO^- were present in the copper(I) precatalyst, weakly nucleophilic BT-sulfonamides **3** were slow to replace them. Consequently, low BT-sulfonamide **3** conversion was observed.
- Ligand: The use of tetramethylenediamine (TMEDA) as a ligand proved to be crucial to promote the coupling

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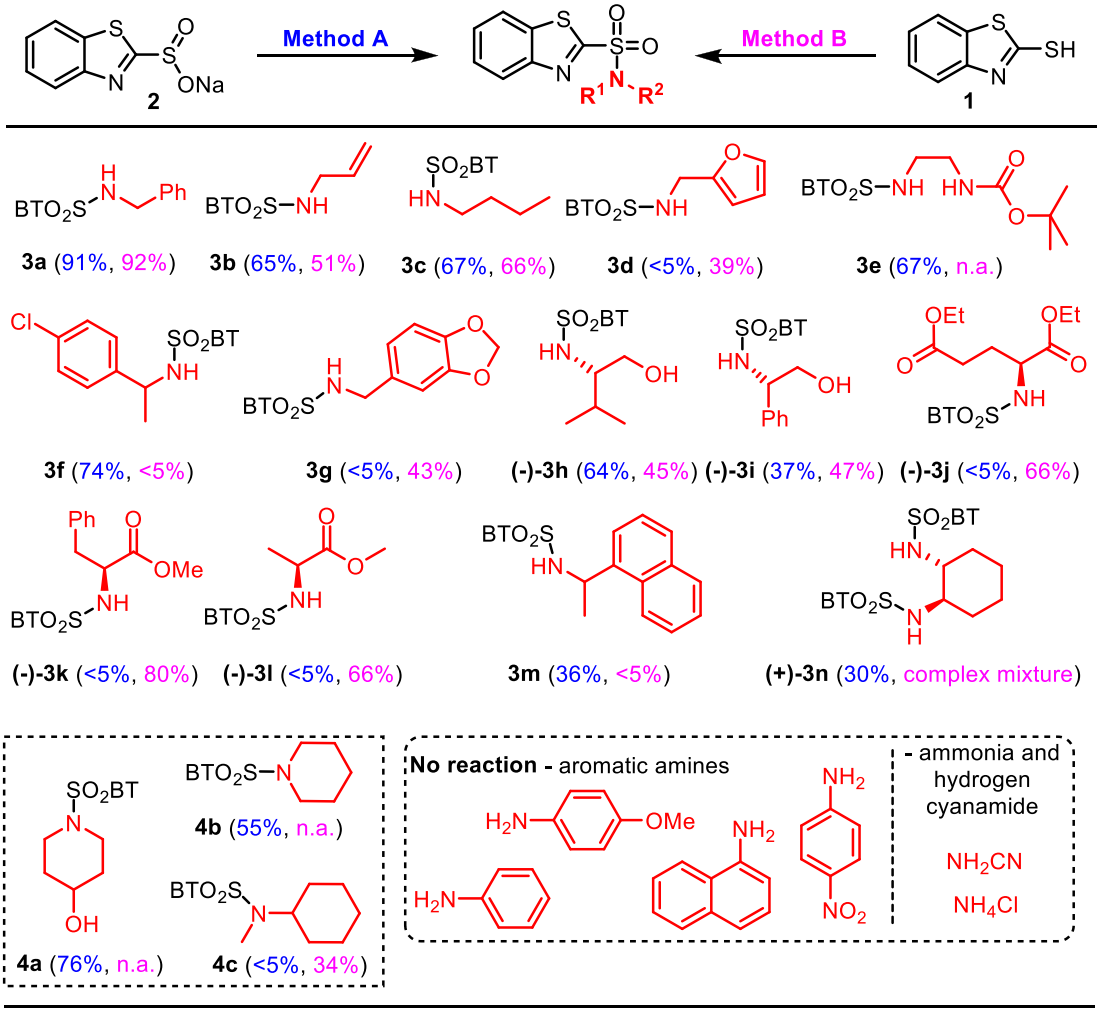
Table 2. Scope and Limitations of Sulfonamide 3 and 4 Synthesis[a]



[a]The reactions were performed with 2 mmol of substrate **2** (Method A) and 1 mmol of substrate **1** (Method B); Yields refer to pure isolated compounds; Conditions. Method A: Substrate **2** (1 equiv), RNH_2 (1.2 equiv), NBS (2 equiv), THF/EtOH, rt, 10 mins. Method B: Substrate **1** (1 equiv), NCS (1 equiv), RNH_2 (3 equiv), CH_2Cl_2, rt, 30 min, then $(NH_4)_6MoO_4{\cdot}4H_2O$ (0.3 equiv), H_2O_2 (20 equiv), EtOH, 0 °C to rt, 5 h. NBS-, *N*-bromosuccinimide; NCS, *N*-chlorosuccinimide.

reaction. Based on the literature,[51] the presence of TMEDA is increasing the electron density on copper(I) intermediate and facilitates its oxidation to copper(II). In addition, the bidentate character of TMEDA[55] seems to be also beneficial in regard to transmetalation of intermediate **F** to **G**, and possibly also during the selective C−N disproportionation reaction[55] (**G** to **H**) that generates product **6** and regenerates the copper(I) complex. The amount of the TMEDA ligand proved in our case also has a dramatic impact on the reaction yield. It was observed that 4 equiv of TMEDA were the optimal loading. If lower TMEDA loading was used, the conversion of sulfonamide **3** dropped rapidly. Higher loading of TMEDA increased the formation of biphenyl side products.

Based on these findings, we speculate that the biphenyl formation can be traced to the intermediate **G** (Scheme 4B). The presence of the excess of TMEDA (bidentate ligand) around copper(II) intermediate **G** is presumably increasing the lability of the sulfonamide ligand. Aryl boronic acid presented in excess in the reaction mixture can further occupy the free coordination place on copper (and protonate sulfonamide anion) and yield intermediate **I**. Intermediate **I** can further undergo intramolecular migration to yield complex **J** so that upon oxidation (Cu^{II} to Cu^{III}; intermediate **K**) and reductive elimination, biphenyl and regenerated copper(I) complex are observed.[56] It should be noted that the products of homocoupling reaction of boronic acids were commonly present in the reaction mixture during all our experiments since boronic acid was used in large excess.[56]

Unfortunately, even under the optimized reaction conditions, the scope of the Chan−Lam coupling proved to be limited (Scheme 4A). Evaluated sulfonamides **3a−c** reacted under such conditions only with phenylboronic acid (yielding sulfonamides **6a−c**), 4-biphenyl (**6h,i**), 3-methoxyphenyl (**6d**), and 3-fluoro and 4-halogen-substituted phenylboronic acids (**6i−k**). When heteroaryl substituted (expected products **6m−o**), 4-carboxylic acid or ester-substituted phenyl (**6s,t**), 4-methoxyphenyl (**6j**), styryl (**6p,q**), all tested 2-substituted phenyl (**6k,u,v**), or cyclopentyl boronic acid (**6r**) were reacted, no conversion of sulfonamide **3a** was observed. The only detected products in the reaction mixture were the

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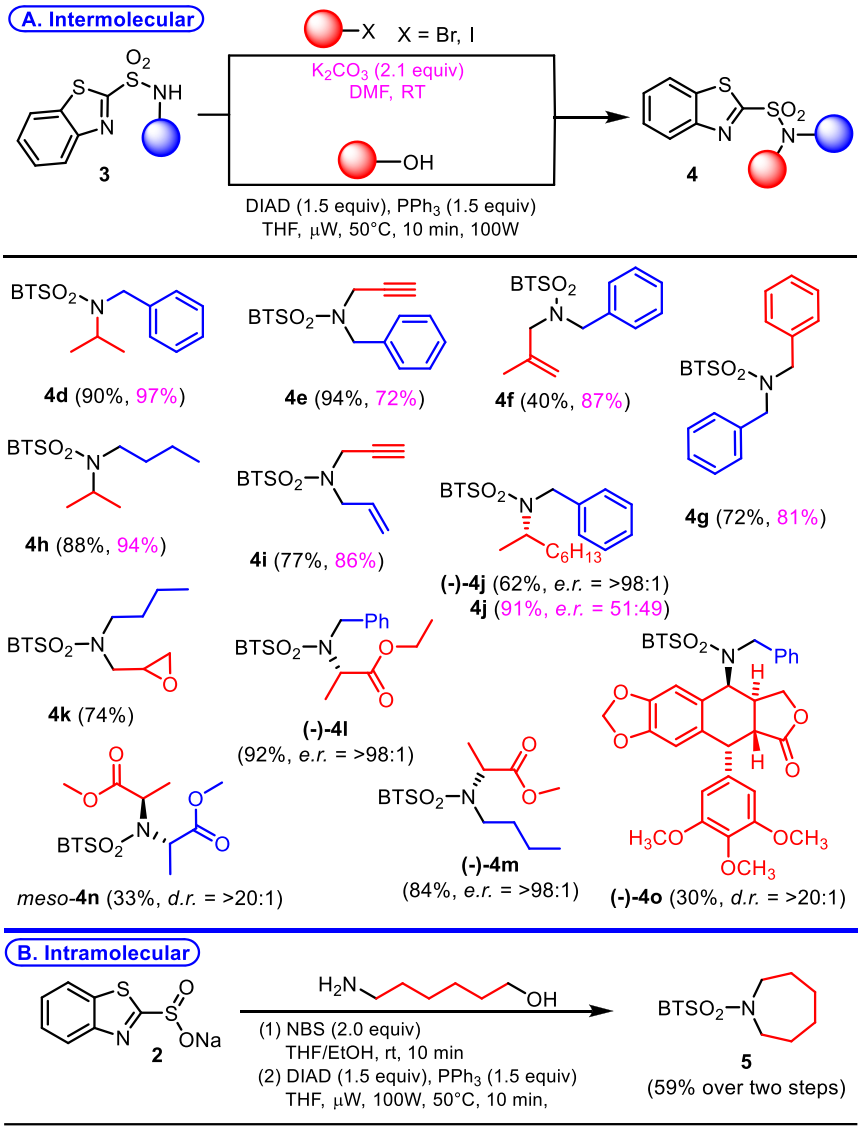
Table 3. Synthesis of *N,N*-Disubstituted Sulfonamides 4 and 5[a]



[a]Reactions were performed with 1 mmol of **3**; yields refer to pure isolated compounds. DIAD, diethyl azodicarboxylate; NBS, *N*-bromosuccinimide; and μW, microwave irradiation.

homocoupling products generated from the boronic acid employed.[40]

Benzothiazoyl Sulfonyl Fluoride. Facing the problems in *N,N*-alkylaryl BT-sulfonamide synthesis related to either high reactivity of phenylamines toward NBS (Table 2, Method A), low phenylamine nucleophilicity (Table 2, Method B), or low nucleophilicity of *N*-alkylsulfonamides **3** in Chan−Lam coupling (Scheme 4), our attention turned to benzothiazoyl sulfonyl fluoride **8** (Scheme 5).[57] We expected that $BTSO_2F$ (**8**) could be a shelf-stable but still very reactive $BTSO_2Cl$ equivalent. Sulfonyl fluoride **8** was readily prepared by the reaction of sulfinic salt **2** with Selectfluor in 73% yield (Scheme 5A). Thus, its reactivity toward a wide range of alkyl and aryl amines could be readily evaluated (Scheme 5B).

It was observed that primary and α-unbranched alkyl amines react smoothly and yield the desired sulfonamides **3a−c,n** in moderate to good yields. Unfortunately, a competitive attack of butylamine (sulfonamide **3c** synthesis) to the C-electrophilic center in the benzothiazole ring of **8** that yielded the undesired side product **7c** was observed even in the case of such sterically undemanding amine (Scheme 5B). The observed phenomena were even more pronounced when α-branched primary amines (compounds **3q** and **3n**) and secondary amines (**4b,c**) were reacted with **8**. When cyclohexane-1,2-diamine was used as a reaction partner, a mixture of bis-sulfonamide **3n**, mono-sulfonamide BT-amine **7f**, and mono BT-amine **7g** was formed in a 1:3:5 ratio (based on ^{1}H NMR analysis). In the case of tested anilines, only traces of the desired products were detected. Nonreactivity of anilines toward sulfonyl fluoride **8** was again attributed to their weak nucleophilicity since no traces of possible side product **7** were detected. Control experiments showed that the side product **7c** is not generated from sulfonamide **3c** (Scheme 5C).

Applications. Having assessed short and robust methods for BT-sulfonamide synthesis, we wished to demonstrate their synthetic utility. First, three representative sulfonamide syntheses were carried out on a 10 mmol scale without any significant erosion in the reaction yields (Scheme 6A). Next,

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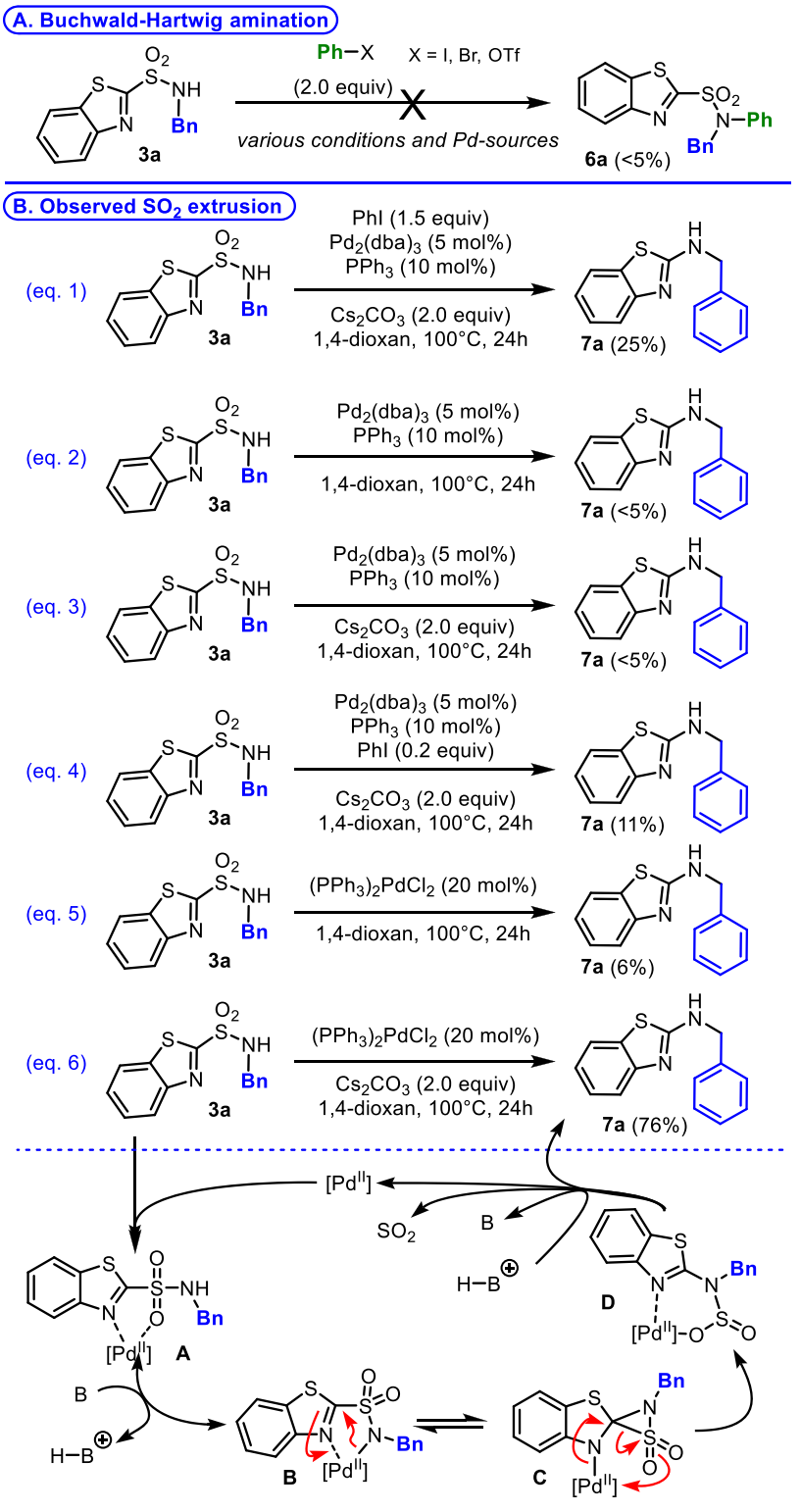
Scheme 3. Buchwald−Hartwig Amination of Sulfonamide 3a[a]



[a](A) Attempted amination reactions. (B) Evaluation of the side product formation.

one-pot synthesis of orthogonally protected amino alcohols **9a** and **b** was carried out with excellent *N*- and *O*-chemoselectivity. Targeted products **10a** and **b** were isolated in very good overall yields (Scheme 6B). Finally, the BT-sulfonyl group removal was achieved using either a thiolate anion or $NaBH_4$ (Scheme 6C).[38]

CONCLUSIONS

In short, we have developed a unified approach to *N*-monosubstituted and *N,N*-disubstituted BT-sulfonamides that relies on several independent synthetic pathways. First, targeted BT-sulfonamides are prepared from simple and commercially available starting compounds, benzothiazole,

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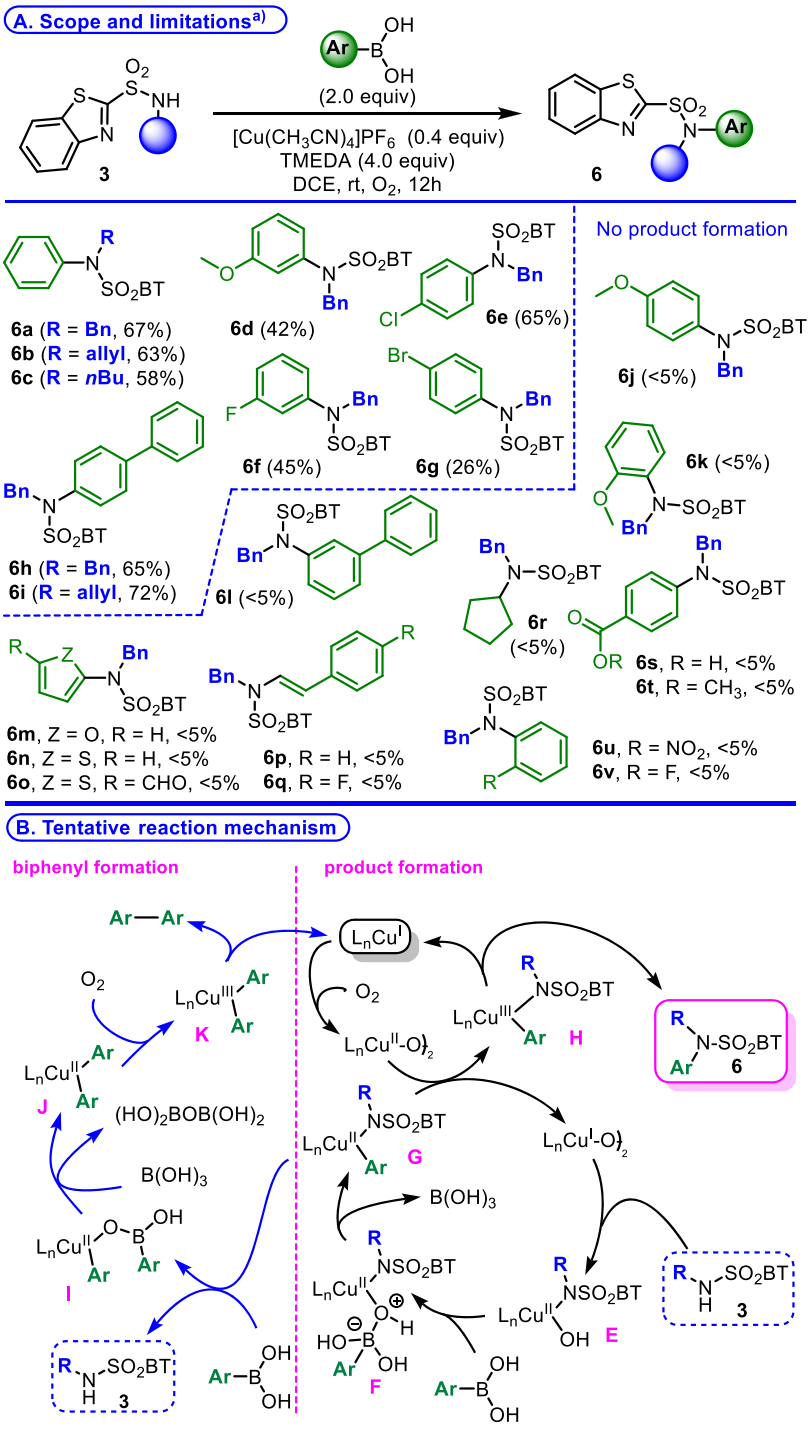
Scheme 4. Chan–Lam Coupling of Sulfonamides 3[a,b]



[a](A) Scope and limitations. (B) Proposed reaction mechanism of copper-catalyzed Chan–Lam coupling of sulfonamides 3. [b]Reactions were performed on 1 mmol of 3; yields refer to pure isolated compounds. TMEDA, tetramethylethylenediamine; DCE, dichloroethane; and Bn, benzyl.

and primary and secondary amines, using three approaches that differ in their elemental steps. The first approach is based on the sulfur oxidation/S–N bond formation sequence, the second on the S–N bond formation/sulfur oxidation process, and the third one is based on the sulfur oxidation/S–F formation/SuFEx coupling process. These approaches allowed us to access *N*-monoalkyl BT-sulfonamides that were further used as a starting building block for additional *N,N*-disubstituted BT-sulfonamide synthesis. The alkylation processes were achieved under mild reaction conditions using weak base-promoted alkylation with alkyl halides, stereospecific microwave-assisted Fukuyama–Mitsunobu alkylation using alcohols, and aryl substituents were installed with the help of Chan–Lam coupling reaction. The key coupling reaction sequences proved to be readily scalable (10 mmol scale), chemoselective (*N*-sulfonylation in the presence of, e.g., free hydroxy group), and it was shown that BT groups can be readily removed using either $NaBH_4$ or thiolate anions.

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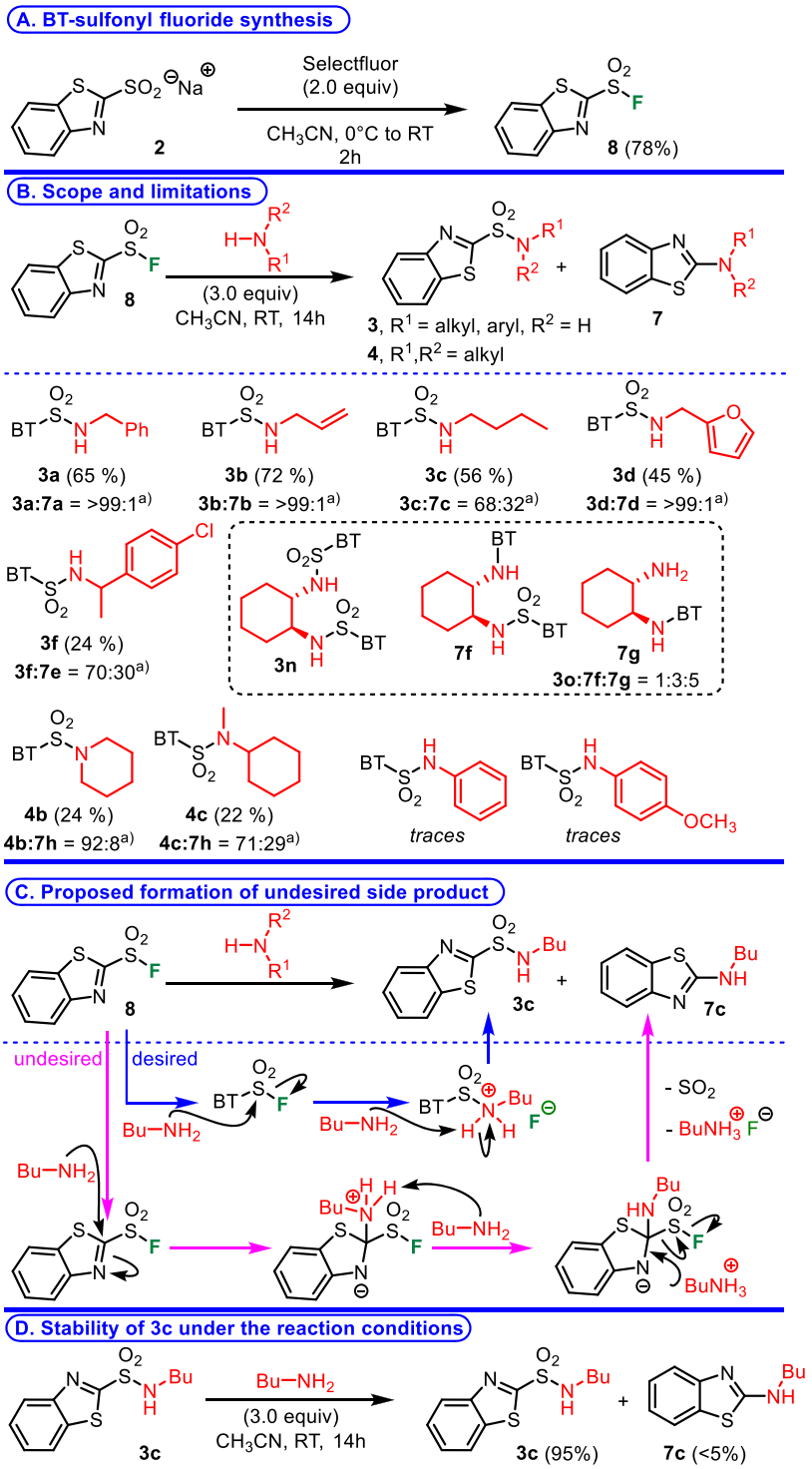
Scheme 5. SuFEx Approach to BT-Sulfonamides 3 and 4[a]



[a](A) BT-sulfonyl fluoride synthesis. (B) SuFEx approach-based scope and limitations. (C) Formation of the desired sulfonamide **3c** and side product **7c**—Proposed mechanism. (D) Evaluation of the BT-sulfonamide **3c** stability under the reaction conditions.

EXPERIMENTAL PART

General Information. All reactions were performed in round-bottom flasks fitted with rubber septa using standard laboratory techniques. Reactions sensitive to air and/or moisture were performed under a positive pressure of argon. Reactions run at elevated temperatures were carried out in the oil bath, and the indicated temperature refers to the oil bath temperature. All starting materials were purchased from commercial suppliers and used without further purification unless otherwise stated. Progress of the reactions was monitored by thin-layer chromatography (TLC)—aluminum plates precoated with silica gel (silica gel 60 F254). Column chromatography was performed on silica gel 60 (40−63 μm). Determination of melting points was performed on a Büchi melting point apparatus and was uncorrected. ^{1}H NMR, ^{19}F {^{1}H} NMR, and ^{13}C {^{1}H} NMR spectra were measured on a Jeol ECA400II (400 MHz, 376 MHz, and 100 MHz, respectively) or Jeol 500 ECA (500 and 126 MHz) in $CDCl_3$ or DMSO. Chemical shifts are reported in ppm and their

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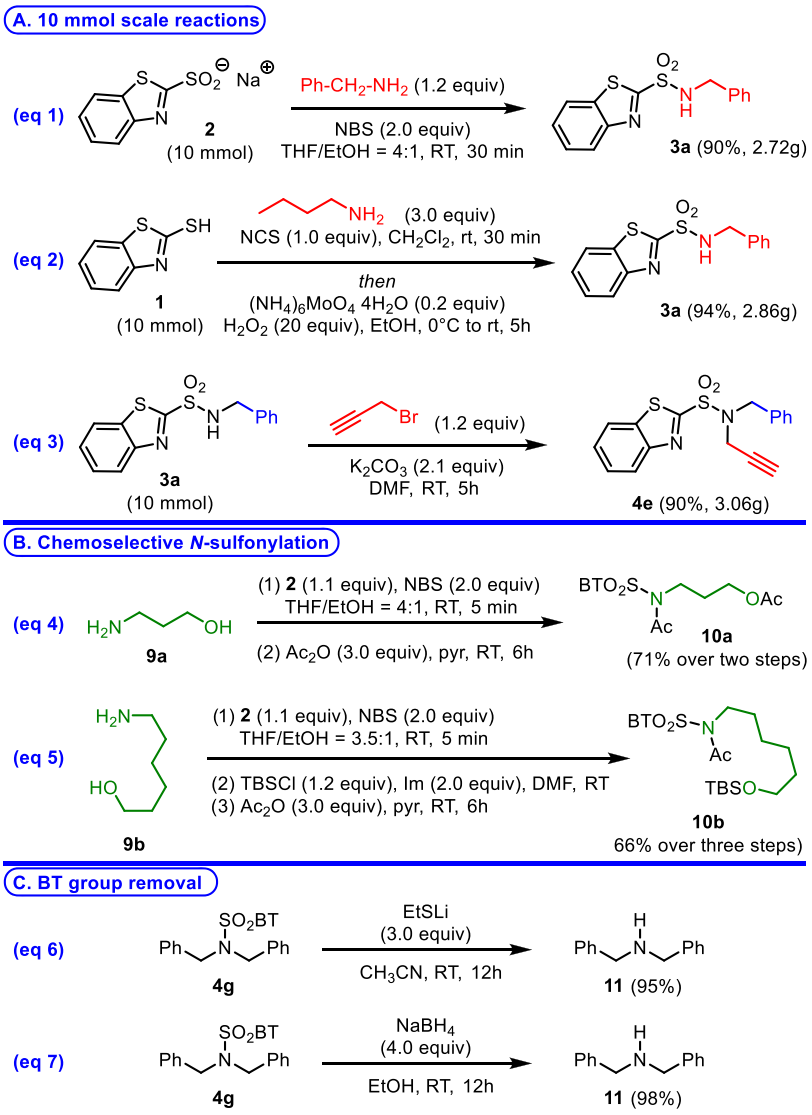
Scheme 6. Demonstration of the Synthetic Utility of BT-Sulfonamides[a]



[a](A) Three key sulfonamide preparations were carried out on a 10 mmol scale, (B) nitrogen atom selective chemoprotection, (C) BT-sulfonyl group removal.

calibration was performed (a) in the case of ^{1}H NMR experiments on the residual peak of nondeuterated solvent δ ($CHCl_3$) = 7.26 ppm; δ (DMSO) = 2.50 ppm, and (b) in the case of ^{13}C NMR experiments on the middle peak of the ^{13}C signal in deuterated solvent δ ($CDCl_3$) = 77.2 ppm; δ (DMSO-d_6) = 39.5 ppm. Proton coupling patterns are represented as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), triplet of triplet (tt), and multiplet (m). HRMS analyses were performed on a Thermo Exactive Plus high-resolution mass spectrometer with electrospray ionization (ESI) and an Orbitrap analyzer operating at a positive or negative full scan mode in the range of 60−800 m/z or on Agilent 6230 high-resolution mass spectrometer with electrospray ionization (ESI) and a time-of-flight analyzer operating at a positive or negative full scan mode in the range of 100−1700 m/z. SFC chiral analyses 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), and Chiralpak IE3 (4.6 mm × 100 mm, 3 μm particle size). The chromatographic runs were performed at a flow rate of 2.2 mL/min, column temperature of 38 °C, and ABPR 2000 psi. Microwave irradiation experiments were carried out in 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 mL glass vials sealed with a silicone/PTFE Vial cap top, 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 vessel was cooled to ambient temperature by gas jet cooling. Purification using semiprep HPLC was carried out on Agilent 1200 series using the C18 reverse-phase column (YMC Pack ODS-A, 20 mm ×100 mm, 5 mm particles). The gradient was formed from 10 mM aqueous ammonium acetate (buffer) and CH_3CN with a flow rate of 15 mL/min. Potentiometric titration for the determination of a dissociation constant was carried out using a benchtop meter pH 50+ DHS (Instruments XS, Italy) equipped with an ATC glass electrode. Before each measurement, a pH meter was calibrated with pH 4.01 and 7.00 buffer solutions. The titration was performed using Titronic basic piston burette (Schott Instruments, Germany). A 0.01 M basic solution was prepared by dissolving an appropriate amount of 50% (w/v) aqueous sodium hydroxide solution purchased from Sigma-Aldrich in deionized water (Merck Millipore, USA). The titrant was added in 0.02 mL

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increments. Dissociation constants were calculated from titration curves.

Sodium Benzo[*d*]thiazole-2-sulfinate (2) Synthesis.[18] Disulfide (2.0 g, 6.0 mmol, 1 equiv) was dissolved in dry CH_2Cl_2 (25 mL) and MeOH (25 mL). NBS (5.36 g, 30 mmol, 5 equiv) was added portionwise within 5 min and the reaction progress was followed by TLC. After disulfide consumption, the reaction was quenched with sat. aq. $NaHCO_3$ (25 mL) and the whole mixture was extracted with CH_2Cl_2 (3 × 30 mL). Combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, and the solvents were evaporated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, EtOAc/petroleum ether = 1:3) and the concentration of relevant fractions yielded the desired product as a yellowish amorphous solid (0.83 g, 65%). ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.54 (ddd, J = 8.0, 7.2, 1.3 Hz, 1H), 7.60 (ddd, J = 8.3, 7.2, 1.4 Hz, 1H), 8.01 (ddd, J = 7.9, 1.4, 0.7 Hz, 1H), 8.18 (ddd, J = 8.2, 1.4, 0.7 Hz, 1H), 3.74 (s, 3H); ^{13}C {^{1}H} NMR (101 MHz, chloroform-*d*): δ 175.0, 153.8, 136.2, 127.3, 127.3, 125.1, 122.5, 51.5; MS (ESI) m/z (%) 214: $[M + H]^+$ (78); HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_8H_8NO_2S_2$, 213.9991; found 213.9994.

Methyl sulfinate (1.3 g, 6 mmol, 1 equiv) was dissolved in THF (3 mL), and H_2O (3 mL) was added. Sodium hydroxide (0.243 g, 6 mmol, 1 equiv; powder) was added to the suspension at RT. The whole mixture became clear within 1 min, and the conversion of starting methyl ester was monitored by TLC. After the reaction completion, the organic solvents were evaporated under reduced pressure and the remaining water was removed with the help of a freeze-dry technique to yield compound **2** as a white powder (1.02 g, 93%). (*Attention*: all water content must be carefully removed to avoid lousy reactivity of **2** in subsequent reactions). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.39 (ddd, J = 8.1, 7.3, 1.3 Hz, 2H), 7.46 (ddd, J = 8.2, 7.3, 1.3 Hz, 2H), 7.92 (ddd, J = 8.1, 1.1, 0.6 Hz, 2H), 8.05 (ddd, J = 7.9, 1.2, 0.6 Hz, 2H); ^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6): δ 194.8, 153.9, 134.9, 125.6, 124.9, 122.9, 122.6.

Preparation of Benzo[*d*]thiazole-2-sulfonyl Fluoride (8). Sulfinic salt **2** (0.5 g, 2.26 mmol, 1 equiv) was suspended in CH_2Cl_2 (23 mL), and the resulting suspension was cooled to 0 °C (ice/water). After 5 min at 0 °C, a Selectfluor (1.60 g, 4.52 mmol, 2 equiv) was added in ten portions. After 5 min at 0 °C, the mixture was allowed to warm to RT (cooling bath removed), and the resulting mixture was stirred for an additional 30 min at RT. Water (25 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (3 × 50 mL). Combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure to yield a white crystalline product (0.383 g, 78%). Mp = 94−96 °C (litt.[57b] mp = 95−96 °C); ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.36−8.31 (m, 1H), 8.09−8.04 (m, 1H), 7.75−7.68 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 156.3 (d, J = 38.2 Hz), 152.1, 137.2, 129.5, 128.6, 126.5, 122.4; ^{19}F{^{1}H} NMR (376 MHz, chloroform-d): δ 64.2; MS (ESI) m/z (%) 218: $[M + H]^+$ (100); HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_7H_5FNO_2S_2$, 217.9746; found, 217.9755.

Sulfonamide 3, 4, and 10 Preparation. *Method A (Table 2, Method A).* Sulfinic salt **2** (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 portionwise over a period of 5 min. The reaction mixture turned the color to orange upon the NBS addition. After an additional 10 min at RT, the reaction mixture was partitioned 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 × 25 mL). The 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.

Method B (Table 2, Method B). Benzo[*d*]thiazole-2-thiol (0.167 g, 1 mmol, 1.0 equiv) and amine (3 mmol, 3.0 equiv) were dissolved in CH_2Cl_2 (5 mL) at RT, and NCS (0.133 g, 1 mmol, 1.0 equiv) was added portionwise over a period of 5 min. The resulting mixture was stirred at RT for 30 min before the solvent was removed under reduced pressure. The residue was suspended in EtOH (5 mL) and $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (0.37 g, 0.3 equiv) was added at once. The resulting mixture was cooled to 0 °C (ice/water bath), and a solution of H_2O_2 in water (2 mL, 20 equiv; 30% in water) was added dropwise (AVOID metallic needle). After 30 min at 0 °C, the cooling bath was removed, and the reaction mixture was allowed to warm to RT. The progress was monitored by TLC. The resulting mixture was repartitioned between CH_2Cl_2 (25 mL) and H_2O (25 mL). The resulting layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). Combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure to yield the crude product.

Method C (Scheme 5B). Sulfonyl fluoride **8** (0.050 g, 0.23 mmol, 1 equiv) was dissolved in CH_3CN (2.3 mL), and amine (0.69 mmol, 3 equiv) was added at RT. The reaction mixture was stirred overnight at RT. Aq. sat. NH_4Cl (10 mL) was added, and the resulting layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), and the organic layers were combined, washed with brine (10 mL), dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure to yield the crude product.

*N-Benzylbenzo[d]thiazole-2-sulfonamide (**3a**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:4) and obtained as a white solid.

Method A. Starting from 0.050 g (0.22 mmol) of **2**, yielded 0.061 g (91%); starting from 2.13 g (10.0 mmol) of **2**, yielded 2.72 g (90%).

Method B. Starting from 0.167 g (1.0 mmol) of **1**, yielded 0.279 g (92% over two steps); starting from 1.67 g (10.0 mmol) of **1**, yielded 2.86 g (94% over two steps).

Method C. Starting from 0.050 g (0.23 mmol) of **8**, yielded 0.032 g (65%). Mp = 108−112 °C; ^{1}H NMR (400 MHz, chloroform-*d*): 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); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): 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; 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 (**3b**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:1) and obtained as a slightly yellow solid.

Method A. Starting from 0.044 g (0.20 mmol) of **2**, yielded 0.033 g (65%).

Method B. Starting from 0.167 g (1.0 mmol) of **1**, yielded 0.129 g (51% over two steps).

Method C. Starting from 0.050 g (0.23 mmol) of **8**, yielded 0.0292 g (72%). Mp = 106−110 °C; ^{1}H NMR (400 MHz, chloroform-*d*): 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); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 166.1, 152.4, 136.5, 132.5, 127.8, 127.6, 125.2, 122.3, 118.5, 46.5; 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 (**3c**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:3) and obtained as a colorless oil.

Method A. Starting from 0.044 g (0.20 mmol) of **2**, yielded 0.036 g (67%).

Method B. Starting from 0.167 g (1.0 mmol) of **1**, yielded 0.178 g (66% over two steps).

Method C. Starting from 0.050 g (0.23 mmol) of **8**, yielded 0.035 g (56%). ^{1}H NMR (400 MHz, chloroform-*d*): 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); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 166.2, 152.5, 136.6, 127.7, 127.6, 125.2, 122.3, 43.9, 31.9, 19.7, 13.6; 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.

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*N-(Furan-2-ylmethyl)benzo[d]thiazole-2-sulfonamide (**3d**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:1) and obtained as a colorless oil.

Method B. Starting from 0.167 g (1.0 mmol) of **1**, yielded 0.114 g (39% over two steps).

Method C. Starting from 0.050 g (0.23 mmol) of **8**, yielded 0.031 g (45%). ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.14−8.13 (m, 1H), 7.97−7.96 (m, 1H), 7.56 (ddd, J = 8.3, 7.3, 1.3 Hz, 1H), 7.61 (ddd, J = 8.3, 7.2, 1.3 Hz, 1H), 7.17 (m, 1H), 6.16 (dd, J = 3.1, 0.7 Hz, 1H), 6.13 (dd, J = 3.2, 1.9 Hz, 1H), 5.56−5.54 (m, 1H), 4.46 (d, J = 6.0 Hz, 2H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*): δ 165.9, 152.5, 148.9, 143.0, 136.5, 127.8, 127.6, 125.2, 122.3, 110.5, 108.9, 40.9; MS (ESI) m/z (%) 295: $[M + H]^+$ (100); HRMS (ESI) m/z: $[M + K]^+$ calcd for $C_{12}H_{10}KN_2O_3S_2$, 332.9764; found, 332.9767.

*tert-Butyl (2-(Benzo[d]thiazole-2-sulfonamido)ethyl)carbamate (**3e**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 2:3) and obtained as a white solid.

Method A. Starting from 0.221 g (1.0 mmol) of **2**, yielded 0.172 g (67%). Mp = 142−146 °C; ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.17 (ddd, J = 8.3, 1.5, 0.7 Hz, 1H), 7.97 (ddd, J = 7.6, 1.3, 0.6 Hz, 1H), 7.61 (ddd, J = 7.9, 7.2, 1.4 Hz, 1H), 7.56 (ddd, J = 7.9, 7.2, 1.5 Hz, 1H), 6.01 (bs, 1H), 5.05 (t, J = 5.2 Hz, 1H), 3.44−3.41 (m, 2H), 3.44−3.30 (m, 2H), 1.39 (s, 9H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 166.3, 156.7, 152.3, 136.5, 127.7, 127.5, 125.2, 122.3, 80.2, 44.8, 40.4, 28.4; MS (ESI) m/z (%) 356: $[M + H]^+$ (100); HRMS (ESI) m/z $[M + K]^+$ calcd for $C_{14}H_{19}N_3O_4S_2K$, 396.0449; found, 396.0452.

*N-(1-(4-Chlorophenyl)ethyl)benzo[d]thiazole-2-sulfonamide (**3f**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:10) and obtained as a colorless oil.

Method A. Starting from 0.044 g (1.0 mmol) of **2**, yielded 0.052 g (74%).

Method C. Starting from 0.050 g (0.23 mmol) of **8**, yielded 0.0196 g (24%). ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.07 (ddd, J = 8.2, 1.3, 0.6 Hz, 1H), 7.92 (ddd, J = 7.8, 1.3, 0.6 Hz, 1H), 7.60 (ddd, J = 8.2, 7.2, 1.4 Hz, 1H), 7.55 (ddd, J = 8.4, 7.3, 1.3 Hz, 2H), 7.12 (dt, J = 8.8, 2.0 Hz, 2H), 7.05 (dt, J = 8.9, 2.4 Hz, 2H), 5.74 (d, J = 7.4 Hz, 1H), 4.77 (p, J = 7.0 Hz, 1H), 1.53 (d, J = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 166.5, 152.2, 139.8, 136.5, 133.7, 128.7, 127.8, 127.7, 127.5, 125.0, 122.1, 54.2, 23.2; MS (ESI) m/z (%) 351: $[M + H]^+$ (100); HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{15}H_{14}ClN_2O_2S_2$, 353.0180; found, 353.0178.

*N-(Benzo[d][1,3]dioxol-5-ylmethyl)benzo[d]thiazole-2-sulfonamide (**3g**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 3:4) and obtained as a white solid.

Method B. Starting from 0.167 g (1.0 mmol) of **1**, yielded 0.150 g (43% over two steps). Mp = 140−141 °C; ^{1}H NMR (400 MHz, chloroform-*d*): 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 (bs, 1H), 4.32 (d, J = 5.5 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): 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; 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.

*(−)-(S)-N-(1-Hydroxy-3-methylbutan-2-yl)benzo[d]thiazole-2-sulfonamide ((−)-**3h**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:1) and obtained as a colorless oil.

Method A. Starting from 0.044 g (0.20 mmol) of **2**, yielded 0.038 g (64%).

Method B. Starting from 0.167 g (1.0 mmol) of **1**, yielded 0.135 g (45% over two steps). $[\alpha]_D^{21}$ = −335° (c 0.2, MeOH); ^{1}H NMR (400 MHz, chloroform-*d*): 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); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 167.9, 151.5, 136.3, 127.8, 127.7, 124.9, 122.3, 62.9, 30.4, 19.3, 18.6; 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 ((−)-**3i**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 4:5) and obtained as a white solid.

Method A. Starting from 0.044 g (0.20 mmol) of **2**, yielded 0.024 g (37%).

Method B. Starting from 0.167 g (1.0 mmol) of **1**, yielded 0.160 g (47% over two steps). Mp = 118−120 °C; $[\alpha]_D^{23}$ = − 144° (c 0.25, CH_2Cl_2); ^{1}H NMR (400 MHz, chloroform-*d*): 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); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): 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; 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.

*(S)-Diethyl (Benzo[d]thiazol-2-ylsulfonyl)glutamate ((−)-**3j**).* Method B (the method was slightly modified since hydrochloride salt was used): L-glutamate hydrochloride (0.215 g, 0.9 mmol) was suspended in CH_2Cl_2 (3 mL) at RT, and Et_3N (0.125 mL, 0.9 mmol, 9 equiv) followed by **1** (0.050 g, 0.3 mmol, 3 equiv) were added. After 5 min at RT, *N*-chlorosuccinimide (0.040 g, 0.3 mmol, 3.0 equiv) was added, and the resulting mixture was stirred at RT for 2 h. CH_2Cl_2 (20 mL) and H_2O (20 mL) were added, and the resulting layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The residue was suspended in EtOH (2 mL), and $(NH_4)_6M_7O_4{\cdot}4H_2O$ (0.123 g, 0.1 mmol, 0.1 equiv) was added. The resulting slurry was cooled to 0 °C (ice/water), and H_2O_2 in water (0.610 mL, 20 equiv; 30% in water) was added dropwise. The resulting mixture was stirred at 0 °C for 5 min before the cooling bath was removed. After 12 h at RT, the whole mixture was diluted with CH_2Cl_2 (20 mL) and H_2O (20 mL) and the resulting layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), and combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The purification of the crude product using flash column chromatography (SiO_2; EtOAc/petroleum ether = 1:3) yielded 0.114 g (66% over two steps) of **3j** as a viscose syrup. $[\alpha]_D^{20}$ = −112° (*c* 0.44, CH_2Cl_2); ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.11 (ddd, J = 8.2, 1.6, 0.6 Hz, 1H), 7.97 (ddd, J = 7.7, 1.6, 0.7 Hz, 1H), 7.62−7.53 (m, 2H), 5.80 (bs, 1H), 4.47 (dd, J = 8.8, 4.6 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 4.04−3.98 (m, 2H), 2.60−2.46 (m, 2H), 2.25 (dtd, J = 14.2, 7.5, 4.7 Hz, 1H), 2.00 (dddd, J = 14.3, 8.8, 7.8, 6.4 Hz, 1H), 1.25 (t, J = 7.2 Hz, 3H), 1.12 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 172.7, 171.0, 165.7, 152.4, 136.5, 127.8, 127.6, 125.1, 122.3, 62.3, 60.9, 56.3, 30.0, 28.5, 14.3, 14.1; MS (ESI) m/z (%) 401: $[M + H]^+$ (100); HRMS (ESI) m/z: $[M + K]^+$ calcd for $C_{16}H_{20}KN_2O_6S_2$, 439.0394; found, 439.0396.

*(−)-Methyl (Benzo[d]thiazol-2-ylsulfonyl)-L-phenylalaninate ((−)-**3k**).* Method B (the method was slightly modified since hydrochloride salt was used): Methyl L-phenylalaninate hydrochloride (0.193 g, 0.9 mmol) was suspended in CH_2Cl_2 (3 mL) at RT, and Et_3N (0.125 mL, 0.9 mmol, 9 equiv) followed by **1** (0.050 g, 0.3 mmol, 3 equiv) were added. After 5 min at RT, *N*-chlorosuccinimide (0.040 g, 0.3 mmol, 3.0 equiv) was added, and the resulting mixture was stirred at RT for 2 h. CH_2Cl_2 (20 mL) and H_2O (20 mL) were added, and the resulting layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The residue was suspended in EtOH (2 mL), and $(NH_4)_6M_7O_4{\cdot}4H_2O$ (0.123 g, 0.1 mmol, 0.1 equiv) was added. The resulting slurry was cooled to 0 °C (ice/water), and H_2O_2 in water (0.610 mL, 20 equiv; 30% in water) was added dropwise. The resulting mixture was stirred at 0 °C for 5

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min before the cooling bath was removed. After 12 h at RT, the whole mixture was diluted with CH_2Cl_2 (20 mL) and H_2O (20 mL) and the resulting layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), and combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The purification of the crude product using flash column chromatography (SiO_2; EtOAc/petroleum ether = 1:3) yielded 0.27 g (80% over two steps) of **3k** as a viscose syrup. $[\alpha]_D^{23} = -129°$ (*c* 0.51, CH_2Cl_2); ^1H NMR (400 MHz, chloroform-*d*): 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); $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*): 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; 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.

*(−)-Methyl (Benzo[d]thiazol-2-ylsulfonyl)alaninate ((−)-**3l**).* Method B (the method was slightly modified since hydrochloride salt was used): Methyl alaninate hydrochloride (0.125 g, 0.9 mmol) was suspended in CH_2Cl_2 (3 mL) at RT, and Et_3N (0.125 mL, 0.9 mmol, 9 equiv) followed by **1** (0.050 g, 0.3 mmol, 3 equiv) were added. After 5 min at RT, *N*-chlorosuccinimide (0.040 g, 0.3 mmol, 3.0 equiv) was added, and the resulting mixture was stirred at RT for 2 h. CH_2Cl_2 (20 mL) and H_2O (20 mL) were added, and the resulting layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The residue was suspended in EtOH (2 mL), and $(NH_4)_6M_7O_4{\cdot}4H_2O$ (0.123 g, 0.1 mmol, 0.1 equiv) was added. The resulting slurry was cooled to 0 °C (ice/water), and H_2O_2 in water (0.610 mL, 20 equiv; 30% in water) was added dropwise. The resulting mixture was stirred at 0 °C for 5 min before the cooling bath was removed. After 12 h at RT, the whole mixture was diluted with CH_2Cl_2 (20 mL) and H_2O (20 mL) and the resulting layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), and combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The purification of the crude product using flash column chromatography (SiO_2; EtOAc/petroleum ether = 1:3) yielded 0.059 g (66% over two steps) of **3l** as a viscose syrup. $[\alpha]_D^{20} = -18.2°$ (*c* 0.45, $CHCl_3$); ^1H NMR (400 MHz, chloroform-*d*): δ 8.14 (ddd, *J* = 8.3, 1.3, 0.6 Hz, 1H), 7.97 (ddd, *J* = 7.7, 1.4, 0.6 Hz, 1H), 7.58−7.65 (m, 1H), 7.50−7.60 (m, 1H), 5.84 (bs, 1H), 4.48 (bs, 1H), 3.61 (s, 3H), 1.51 (d, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*): δ 172.4, 165.9, 152.4, 136.5, 127.8, 127.6, 125.2, 122.4, 53.0, 52.6, 20.1; MS (ESI) *m*/*z* (%) 301: $[M + H]^+$ (100); HRMS (ESI) *m*/*z*: $[M + K]^+$ calcd for $C_{11}H_{12}KN_2O_4S_2$, 338.9870; found, 338.9873.

*N-(1-(Naphthalen-1-yl)ethyl)benzo[d]thiazole-2-sulfonamide (**3m**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:3) and obtained as a colorless oil.

Method A. Starting from 0.050 g (0.226 mmol) of **2**, yielded 0.029 g (36%). ^1H NMR (400 MHz, chloroform-*d*): δ 8.02−7.98 (m, 2H), 7.84−7.82 (m, 1H), 7.75−7.71 (m, 1H), 7.61 (d, *J* = 8.2 Hz, 1H), 7.56−7.48 (m, 2H), 7.44 (dd, *J* = 7.2, 1.1 Hz, 1H), 7.42−7.36 (m, 2H), 7.24 (dd, *J* = 8.2, 7.3 Hz, 1H), 5.65−5.63 (m, 1H), 1.72 (d, *J* = 6.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*): δ 166.5, 152.3, 137.1, 136.6, 133.9, 130.2, 128.9, 128.6, 127.6, 127.4, 126.6, 125.9, 125.2, 125.1, 123.6, 122.7, 122.1, 50.9, 23.2; MS (ESI) *m*/*z* (%) 370: $[M + H]^+$ (100); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{17}N_2O_4S_2$, 369.0726; found, 369.0734.

*(+)-N-((1R,2R)-2-(Benzo[d]thiazole-2-sulfonamido)cyclohexyl)-benzo[d]thiazole-2-sulfonamide ((+)-**3n**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:5 ≥ 1:3) and obtained as a viscose syrup.

Method A. Starting from 0.100 g (0.452 mmol, 2.2 equiv) of **2**, and (1R,2R)-cyclohexane-1,2-diamine (0.0235 g, 0.205 mmol, 1.0 equiv); yielded 0.031 g (30%). $[\alpha]_D^{21} = -5.63°$ (*c* 0.16, CH_2Cl_2); ^1H NMR (400 MHz, chloroform-*d*): δ 9.43 (d, *J* = 3.2 Hz, 2H), 8.31 (dt, *J* = 8.3, 1.0 Hz, 2H), 7.95−7.89 (m, 2H), 7.61 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 2H), 7.54 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 2H), 3.58−3.49 (m, 2H), 2.49 (dt, *J* = 14.0, 2.7 Hz, 2H), 1.79−1.67 (m, 2H), 1.64−1.45 (m, 4H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 168.6, 149.8, 136.1, 128.2, 128.13, 125.2, 122.3, 57.8, 35.9, 24.4; MS (ESI) *m*/*z* (%) 510: $[M + H]^+$ (100); HRMS (ESI) *m*/*z*: $[M + K]^+$ calcd for $C_{20}H_{21}N_4O_4S_4$, 509.0440; found, 509.0442.

*1-(Benzo[d]thiazol-2-ylsulfonyl)piperidin-4-ol (**4a**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:1 ≥ 4:3 ≥ 8:3) and obtained as a colorless oil.

Method A. Starting from 0.044 g (0.20 mmol) of **2**, yielded 0.045 g (76%). ^1H NMR (400 MHz, chloroform-*d*): δ 8.20−8.17 (m, 1H), 7.99−7.96 (m, 1H), 7.63−7.54 (m, 2H), 3.91−3.86 (m, 1H), 3.71−3.64 (m, 2H), 3.34−3.28 (m, 2H), 2.00−1.94 (m, 2H), 1.72−1.68 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*): δ 164.1, 152.8, 136.4, 127.7, 127.5, 125.4, 122.2, 65.8, 43.7, 33.4; MS (ESI) *m*/*z* (%) 290: $[M + H]^+$ (100); HRMS (ESI) *m*/*z*, $[M + H]^+$ calcd for $C_{12}H_{15}N_2O_3S_2$, 299.0519; found, 299.0521.

*2-(Piperidin-1-ylsulfonyl)benzo[d]thiazole (**4b**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/$CHCl_3$ = 1:1 ≥ 0:1) and obtained as a white solid.

Method A. Starting from 0.044 g (0.20 mmol) of **2**, yielded 0.031 g (55%). Method C: starting from 0.050 g (0.23 mmol) of **8**, yielded 0.0156 g (24%). Mp = 109−113 °C; ^1H NMR (400 MHz, chloroform-*d*): δ 8.20 (ddd, *J* = 8.2, 1.3, 0.7 Hz, 1H), 7.98 (ddd, *J* = 7.9, 1.4, 0.7 Hz, 1H), 7.61 (ddd, *J* = 8.2, 7.2, 1.4 Hz, 1H), 7.56 (ddd, *J* = 7.9, 7.2, 1.4 Hz, 1H), 3.40−3.37 (m, 4H), 1.71−1.66 (m, 4H), 1.56−1.50 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*): δ 164.6, 152.8, 136.4, 127.6, 127.4, 125.3, 122.2, 47.6, 25.4, 23.6; MS (ESI) *m*/*z* (%) 283: $[M + H]^+$ (100); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{12}H_{15}N_2O_2S_2$, 283.0569; found, 283.0570.

*N-Cyclohexyl-N-methylbenzo[d]thiazole-2-sulfonamide (**4c**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:3) and obtained as a white solid.

Method B. Starting from 0.167 g (1.0 mmol) of **1**, yielded 0.107 g (34%).

Method C. Starting from 0.050 g (0.23 mmol) of **8**, yielded 0.011 g (22%). Mp = 80−82 °C; ^1H NMR (400 MHz, chloroform-*d*): δ 8.18−8.16 (m, 1H), 7.97−7.95 (m, 1H), 7.59 (ddd, *J* = 8.3, 7.2, 1.4 Hz, 1H), 7.56−7.52 (m, 1H), 3.98 (tt, *J* = 11.6, 3.8 Hz, 1H), 2.98 (s, 3H), 1.77−1.59 (m, 5H), 1.43−1.29 (m, 4H), 1.07−0.98 (m, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*): δ 166.4, 152.8, 136.4, 127.5, 127.4, 125.3, 122.2, 58.1, 30.6, 29.5, 25.8, 25.4; MS (ESI) *m*/*z* (%) 311: $[M + H]^+$ (100); HRMS (ESI) *m*/*z*: $[M + K]^+$calcd for $C_{14}H_{19}N_2O_2S_2$, 311.0882; found, 311.0886.

Synthesis of Fully Protected Amino Alcohols 10. *3-(N-(Benzo[d]thiazol-2-ylsulfonyl)acetamido)propyl Acetate (**10a**) (Scheme 5B, **Equation 4**).* Prepared using the Method A from **2** (0.100 g, 0.45 mmol). The crude product obtained using the Method A was dissolved in pyridine (2 mL), and Ac_2O (0.128 mL, 1.35 mmol, 3.0 equiv) was added at RT. The resulting mixture was stirred for 12 h at RT before sat. aq. NH_4Cl (5 mL) was added. The resulting mixture was extracted with EtOAc (3 × 15 mL), and the resulting organic layers were combined and washed with brine (10 mL), dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The crude product was purified by flash column chromatography (SiO_2; EtOAc:hexane = 1:2) to yield 0.113 g (71% over two steps) of **10a** and obtained as a colorless oil. ^1H NMR (400 MHz, chloroform-*d*): δ 8.18−8.16 (m, 1H), 8.00−7.98 (m, 1H), 7.66−7.58 (m, 2H), 4.13 (t, *J* = 6.1 Hz, 2H), 4.00−3.96 (m, 2H), 2.58 (s, 3H), 2.11−2.08 (m, 2H), 2.04 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*): δ 171.2, 170.5, 164.1, 152.1, 136.6, 128.5, 128.0, 125.7, 122.3, 61.9, 45.1, 28.8, 25.6, 21.1; MS (ESI) *m*/*z* (%) 357: $[M + H]^+$ (100); HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{17}N_2O_5S_2$, 357.0573; found, 357.0576.

*N-(Benzo[d]thiazol-2-ylsulfonyl)-N-(6-((tert-butyldimethylsilyl)-oxy)hexyl)acetamide (**10b**) (Scheme 5B, **Equation 5**).* Prepared using the Method A from **2** (0.100 g, 0.45 mmol). The crude product

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obtained using the Method A was dissolved in DMF (9 mL) at RT, and imidazole (0.183 g, 2.7 mmol, 6 equiv) was added. After 5 min at RT, TBSCl (0.202 g, 1.35 mmol, 3.0 equiv) was added and the resulting mixture was stirred at RT for 12 h. The solvent was removed from the reaction mixture by a freeze-drying technique. The crude product was suspended in pyridine (4 mL), and Ac_2O (0.127 mL, 1.35 mmol, 3.0 equiv) was added at RT. The resulting mixture was stirred for an additional 12 h before sat. aq. NH_4Cl (10 mL) was added. The resulting mixture was extracted with CH_2Cl_2 (3 × 15 mL), and the resulting organic layers were combined, washed with brine (10 mL), dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The crude product was purified by flash column chromatography (SiO_2; EtOAc:hexane = 1:3) to yield 0.279 g (66% over 3 steps) of **10b** and obtained as a colorless oil. ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.17 (dd, J = 7.6, 1.6 Hz, 1H), 7.99 (dd, J = 7.5, 1.7 Hz, 1H), 7.65−7.57 (m, 2H), 3.87−3.84 (m, 2H), 3.58 (t, J = 6.5 Hz, 1H), 2.58 (s, 3H), 1.78−1.70 (m, 2H), 1.53−1.46 (m, 2H), 1.36−1.32 (m, 4H), 0.89−0.88 (m, 9H), 0.04−0.03 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 170.5, 164.5, 152.1, 136.7, 128.3, 127.9, 125.6, 122.3, 63.2, 47.9, 32.8, 29.7, 26.6, 26.1, 25.6, 25.5, 18.5, -5.2; MS (ESI) m/z (%) 472: $[M + H]^+$ (100); HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{21}H_{35}N_2O_4S_2Si$, 471.1802; found, 417.1805.

_N_-Alkylation of _N_-Monosubstituted Sulfonamides (Table 3). *General Procedure for Fukuyama−Mitsunobu Alkylation (FM Alkylation).* A sulfonamide **3** (0.18 mmol, 1.0 equiv) was dissolved in dry THF (4.5 mL) at RT in a 10 mL microwave vial, and alcohol (0.36 mmol, 2 equiv), PPh_3 (0.070 g, 0.27 mmol, 1.5 equiv) and DIAD (0.052 mL, 0.27 mmol, 1.5 equiv) were successfully added. The microwave vial was placed in the microwave reactor and heated for 10 min at 50 °C (100 W power). The resulting reaction mixture was placed in a 25 mL flask and the solvents were removed under reduced pressure to yield the crude product.

General Procedure for Base-Promoted Alkylation Using Alkyl Halides (Base-Promoted Alkylation). A sulfonamide (0.098 mmol, 1.0 equiv) was added to DMF (2 mL) at RT. The whole mixture was cooled to 0 °C and alkyl halide (0.196 mmol, 2.0 equiv) followed by the addition of K_2CO_3 (0.196 mmol, 2.0 equiv) were added. The resulting mixture was stirred at 0 °C for 5 min. The cooling bath was removed and the whole mixture was stirred for 12 h at rt (for primary alkyl halides) or at 50 °C (for secondary alkyl halides; external temperature, oil bath). Sat. aq. NH_4Cl (10 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (3 × 15 mL). Combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure to give the crude product.

*N-Benzyl-N-isopropylbenzo[d]thiazole-2-sulfonamide (**4d**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:3) and obtained as a colorless oil.

FM Alkylation. Starting from 0.030 g (0.09 mmol) of **3a**, yielded 0.030 g (90%).

Base-Promoted Alkylation. Starting from 0.030 g (0.09 mmol) of **3a**, carried out at 50 °C, yielded 0.032 g (97%). ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.18−8.17 (m, 1H), 7.97−7.95 (m, 1H), 7.62−7.58 (m, 1H), 7.56−7. 52 (m, 1H), 7.46−7.44 (m, 2H), 7.34−7.24 (m, 3H), 4.61 (s, 2H), 4.39 (hept, J = 6.8 Hz, 1H), 1.06 (d, J = 6.8 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 166.9, 152.7, 138.1, 136.5, 128.6, 128.0, 127.7, 127.6, 127.4, 125.3, 122.2, 51.8, 48.0, 21.5; MS (ESI) m/z (%) 347: $[M + H]^+$ (100); HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{19}N_2O_2S_2$, 347.0882; found, 347.0884.

*N-Benzyl-N-(prop-2-yn-1-yl)benzo[d]thiazole-2-sulfonamide (**4e**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:4) and obtained as a colorless oil.

FM Alkylation. Starting from 0.030 g (0.09 mmol) of **3a**, yielded 0.031 g (94%).

Base-Promoted Alkylation. Starting from 0.030 g (0.09 mmol) of **3a**, carried out at RT, yielded 0.024 g (72%). ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.23 (ddd, J = 8.2, 1.3, 0.6 Hz, 2H), 8.00 (ddd, J = 7.9, 1.4, 0.6 Hz, 2H), 7.67−7.60 (m, 1H), 7.60−7.54 (m, 1H), 7.42−7.32 (m, 5H), 4.74 (s, 2H), 4.06 (s, 2H), 1.87−1.86 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 164.8, 152.8, 136.5, 134.4, 129.0, 128.9, 128.5, 127.6, 127.5, 125.4, 122.2, 75.7, 74.3, 51.1, 36.4; MS (ESI) m/z (%) 343: $[M + H]^+$ (100); HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{18}H_{16}N_2O_2S_2$, 343.0569; found, 343.0571.

*N-Benzyl-N-(2-methylallyl)benzo[d]thiazole-2-sulfonamide (**4f**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:6 ≥ 1:3) and obtained as a colorless oil.

FM Alkylation. Starting from 0.055 g (0.18 mmol) of **3a**, yielded 0.026 g (40%).

Base-Promoted Alkylation. Starting from 0.055 g (0.18 mmol) of **3a**, carried out at RT, yielded 0.056 g (87%). ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.17 (ddd, J = 8.5, 1.3, 0.7 Hz, 2H), 7.96 (ddd, J = 7.9, 1.3, 0.6 Hz, 1H), 7.63−7.59 (m, 1H), 7.58−7.53 (m, 1H), 7.27−7.22 (m, 5H), 4.87−4.86 (m, 1H), 4.79−4.78 (m, 1H), 4.59 (s, 2H), 3.94 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 166.3, 152.5, 139.5, 136.3, 135.2, 129.0, 128.5, 128.0, 127.6, 127.4, 125.2, 122.2, 115.5, 54.2, 51.6, 19.9; MS (ESI) m/z (%) 359: $[M + H]^+$ (100); HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{21}H_{19}N_2O_2S_2$, 359.0882; found, 359.0880.

*N,N-Dibenzylbenzo[d]thiazole-2-sulfonamide (**4g**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:3) and obtained as a colorless oil.

FM Alkylation. Starting from 0.070 g (0.23 mmol) of **3a**, yielded 0.065 g (72%);

Base-Promoted Alkylation. Starting from 0.030 g (0.09 mmol) of **3a**, carried out at RT, yielded 0.031 g (81%). ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.17 (ddd, J = 8.3, 1.2, 0.5 Hz, 1H), 7.97 (ddd, J = 7.9, 1.3, 0.5 Hz, 1H), 7.62 (ddd, J = 8.2, 7.3, 1.4 Hz, 1H), 7.57 (ddd, J = 7.9, 7.2, 1.3 Hz, 1H), 7.21−7.15 (m, 10H), 4.55 (s, 4H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 166.4, 152.5, 136.3, 134.9, 128.9, 128.6, 128.0, 127.6, 127.4, 125.2, 122.2, 51.5; MS (ESI) m/z (%) 395: $[M + H]^+$ (100); HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{21}H_{19}N_2O_2S_2$, 395.0882; found, 395.0885.

*N-Butyl-N-isopropylbenzo[d]thiazole-2-sulfonamide (**4h**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 2:5) and obtained as a colorless oil.

FM Alkylation. Starting from 0.045 g (0.17 mmol) of **3c**, yielded 0.049 g (88%);

Base-Promoted Alkylation. Starting from 0.024 g (0.09 mmol) of **3c**, carried out at 50 °C, yielded 0.028 g (94%). ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.16 (ddd, J = 8.4, 1.3, 0.6 Hz, 1H), 7.96 (ddd, J = 7.8, 1.4, 0.6 Hz, 1H), 7.61−7.55 (m, 1H), 7.53 (ddd, J = 8.0, 7.3, 1.4 Hz, 3H), 4.35 (hept, 1H), 3.31−3.27 (m, 2H), 1.76−1.68 (m, 2H), 1.35 (sext, 2H), 1.17 (d, 6H), 0.94 (t, 3H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 167.00, 152.7, 136.4, 127.4, 127.3, 125.2, 122.1, 51.1, 44.0, 34.0, 21.5, 20.3, 13.8; MS (ESI) m/z (%) 313: $[M + H]^+$ (100); HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{21}N_2O_2S_2$, 313.1039; found, 313.1041.

*N-Allyl-N-(prop-2-yn-1-yl)benzo[d]thiazole-2-sulfonamide (**4i**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:3) and obtained as a colorless oil.

FM Alkylation. Starting from 0.025 g (0.098 mmol) of **3b**, yielded 0.022 g (77%).

Base-Promoted Alkylation. Starting from 0.023 g (0.09 mmol) of **3b**, carried out at RT, yielded 0.024 g (86%). ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.20 (ddd, J = 8.2, 1.4, 0.7 Hz, 1H), 7.98 (ddd, J = 7.9, 1.5, 0.7 Hz, 1H), 7.61 (ddd, J = 8.2, 7.2, 1.4 Hz, 1H), 7.56 (ddd, J = 7.9, 7.2, 1.4 Hz, 1H), 5.78 (ddt, J = 17.1, 10.0, 6.5 Hz, 1H), 5.36 (dq, J = 17.1, 1.4 Hz, 1H), 5.28 (dq, J = 10.1, 1.2 Hz, 1H), 4.22 (d, J = 2.5 Hz, 2H), 4.18 (d, J = 6.5, 2H), 1.90 (t, J = 2.5 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 164.9, 152.7, 136.5, 131.4, 127.6, 127.4, 125.3, 122.2, 120.7, 76.0, 73.9, 50.2, 36.6; MS (ESI) m/z (%) 293: $[M + H]^+$ (100); HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{13}H_{13}N_2O_2S_2$, 293.0413; found, 293.0416.

*(S)-N-Benzyl-N-(octan-2-yl)benzo[d]thiazole-2-sulfonamide ((−)-**4j**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:8) and obtained as a colorless oil.

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FM Alkylation. Starting from 0.060 g (0.18 mmol) of **3a** and (*R*)-octan-2-ol (0.057 mL, 0.36 mmol, e.r. ≥ 99:1), yielded 0.051 g (62%), e.r. ≥ 98:2;

Base-Promoted Alkylation. Starting from 0.060 g (0.18 mmol) of **3a** and (±)-2-bromooctan (0.063 mL, 036 mmol), carried out at 50 °C, yielded 0.068 g (91%), e.r. = 51:49. $[\alpha]_D^{22}$ = −183° (*c* 0.3, CH_2Cl_2); ^{1}H NMR (400 MHz, chloroform-*d*): 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); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): 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; 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).

*N-Butyl-N-(oxiran-2-ylmethyl)benzo[d]thiazole-2-sulfonamide (**4k**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:35) and obtained as a colorless oil.

FM Alkylation. Starting from 0.048 g (0.18 mmol) of **3c**, yielded 0.043 g (74%). ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.16 (ddd, *J* = 8.5, 1.3, 0.6 Hz, 1H), 7.98 (ddd, *J* = 8.0, 1.5, 0.8 Hz, 1H), 7.63−7.59 (m, 1H), 7.58−7.53 (m, 1H), 4.00 (dd, *J* = 15.1, 3.0 Hz, 1H), 3.56−3.45 (m, 1H), 3.34−3.36 (m, 1H), 3.24−3.22 (m, 1H), 3.16 (dd, *J* = 15.0, 6.6 Hz, 1H), 2.81 (t, *J* = 4.3 Hz, 1H), 2.59 (ddd, *J* = 4.6, 2.5, 1.0 Hz, 1H), 1.71−1.61 (m, 2H), 1.41−1.29 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 165.7, 152.6, 136.3, 127.6, 127.5, 125.2, 122.2, 51.8, 50.9, 50.0, 45.2, 30.6, 19.8, 13.7; MS (ESI) *m*/*z* (%) 327: $[M + H]^+$ (100); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{14}H_{19}N_2O_3S_2$, 327.0832; found, 327.0838.

*Ethyl N-(Benzo[d]thiazol-2-ylsulfonyl)-N-benzylalaninate ((−)-**4l**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:4) and obtained as a slightly yellow oil.

FM Alkylation. Starting from 0.054 g (0.17 mmol) of **3a**, yielded 0.066 g (92%). $[\alpha]_D^{23}$ = − 440° (*c* 0.25, CH_2Cl_2); ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.19−8.17 (m, 1H), 7.99−7.96 (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), 7.44−7.42 (m, 2H), 7.34−7.24 (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), 3.70−3.88 (m, 2H), 1.34 (d, *J* = 7.4 Hz, 1H), 0.96 (t, *J* = 7.1 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 170.7, 165.6, 152.7, 137.0, 136.5, 128.6, 128.2, 127.9, 127.7, 127.5, 125.2, 122.2, 61.6, 56.4, 50.3, 16.9, 13.8; 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.

*Methyl N-(Benzo[d]thiazol-2-ylsulfonyl)-N-butyl-L-alaninate ((−)-**4m**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:3) and obtained as a colorless solid.

FM Alkylation. Starting from 0.048 g (0.17 mmol) of **3c** and methyl (*R*)-2-hydroxypropanoate (0.032 mL, 0.34 mmol, e.r. ≥ 99:1), yielded 0.053 g (84%, e.r. ≥ 98:1). Mp = 53−55 °C; $[\alpha]_D^{23}$ = −101° (*c* 0.25, CH_2Cl_2); ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.17−8.15 (m, 1H), 7.98−7.95 (m, 1H), 7.61−7.57 (m, 1H), 7.56−7.52 (m, 1H), 4.85 (q, *J* = 7.3 Hz, 2H), 3.57 (ddd, *J* = 15.6, 10.9, 5.2 Hz, 1H), 3.45 (s, 3H), 3.22 (ddd, *J* = 15.2, 10.9, 5.5 Hz, 1H), 1.84 − 1.73 (m, 1H), 1.68−1.58 (m, 1H), 1.51 (d, *J* = 7.3 Hz, 3H), 1.40−1.27 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 171.6, 165.6, 152.6, 136.4, 127.6, 127.4, 125.2, 122.2, 56.2, 52.5, 46.9, 33.3, 20.2, 16.7, 13.8; MS (ESI) *m*/*z* (%) 358: $[M + H]^+$ (100); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{15}H_{21}N_2O_4S_2$, 357.0937; found, 357.0936; HPLC (Chiralpak IE3, CO_2/MeOH = 95/5, flow rate = 2.2 mL/min, I = 272 nm) tR = 5.50 min (minor), 5.89 min (major).

*Methyl N-(Benzo[d]thiazol-2-ylsulfonyl)-N-((R)-1-methoxy-1-oxopropan-2-yl)-L-alaninate (meso-**4n**).* The crude product was purified using flash column chromatography (SiO_2; acetone/petroleum ether = 1:2) and obtained as a colorless oil.

FM Alkylation. Starting from 0.023 g (0.08 mmol) of **3m** and methyl (*R*)-2-hydroxypropanoate (0.016 mL, 0.16 mmol, e.r. ≥ 99:1), yielded 0.010 g (33%, d.r. ≥ 20:1). $[\alpha]_D^{23}$ = 0° (*c* 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.13 (ddd, *J* = 8.2, 1.4, 0.6 Hz, 1H), 7.97 (ddd, *J* = 7.8, 1.5, 0.6 Hz, 1H), 7.62−7.58 (m, 1H), 7.57−7.53 (m, 1H), 4.82 (q, *J* = 7.3 Hz, 1H), 3.67 (s, 6H), 1.56 (d, *J* = 7.3 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 171.4, 167.2, 152.4, 136.4, 127.7, 127.5, 125.1, 122.3, 55.3, 52.7, 17.0; MS (ESI) *m*/*z* (%) 387: $[M + H]^+$ (100); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{15}H_{19}N_2O_4S_2$, 387.0679; found, 387.0684.

*(5R,5aR,8aS,9S)-9-(Benzo[d]thiazol-2-yl(benzyl)amino)-5-(3,4,5-trimethoxyphenyl)-5,8,8a,9-tetrahydrofuro[3′,4′:6,7]naphtho[2,3-d][1,3]dioxol-6(5aH)-one ((−)-**4o**).* The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:8) and obtained as a colorless solid.

FM Alkylation. Starting from 0.096 g (0.32 mmol) of **3a**, yielded 0.067 g (30%, d.r. ≥ 20:1) as a white solid. Mp = 139-141 °C; $[\alpha]_D^{21}$ = −64.6° (*c* 3.51, CH_2Cl_2); ^{1}H NMR (500 MHz, chloroform-*d*): δ 8.35−8.33 (m, 1H), 8.09−8.06 (m, 1H), 7.75−7.65 (m, 2H), 7.35−7.33 (m, 3H), 7.05−7.03 (m, 2H), 6.78 (s, 1H), 6.50 (s, 1H), 6.11 (s, 2H), 5.98−5.97 (m, 2H), 5.78 (d, *J* = 5.1 Hz, 1H), 4.87 (d, *J* = 15.5 Hz, 1H), 4.47 (dd, *J* = 9.2, 7.5 Hz, 1H), 4.26 (dd, *J* = 11.0, 9.2 Hz, 1H), 4.06 (d, *J* = 5.5 Hz, 1H), 3.77 (s, 3H), 3.71 (s, 3H), 3.60 (d, *J* = 15.4 Hz, 1H), 2.82 (dddd, *J* = 14.7, 10.9, 7.6, 5.0 Hz, 1H), 1.51 (dd, *J* = 14.7, 5.5 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*): δ 174.1, 165.5, 152.7, 152.6, 149.1, 147.7, 137.3, 137.2, 136.6, 134.8, 134.8, 129.4, 129.3, 129.2, 128.3, 128.2, 125.3, 124.2, 122.5, 110.7, 109.8, 108.2, 101.9, 69.8, 60.9, 58.9, 56.4, 49.5, 43.7, 40.6, 37.6; MS (ESI) *m*/*z* (%) 701: $[M + H]^+$ (100); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{36}H_{33}N_2O_9S_2$, 701.1622; found, 701.1625.

Intramolecular Cyclization of Aminoalcohol Based on *N*-BT-Sulfonylation/Intramolecular Fukuyama−Mitsunobu Alkylation (Table 3B). *2-(Azepan-1-ylsulfonyl)benzo[d]thiazole (**5**).* Sulfinic salt **2** (0.200 g, 0.9 mmol, 1.0 equiv) was added to a mixture of THF (8 mL) and H_2O (2 mL) at RT, and the resulting mixture was stirred for 5 min. 6-Aminohexan-1-ol (0.107 g, 1 mmol, 1.1 equiv) followed by NBS (0.318 g, 1.8 mmol, 2.0 equiv) were added. After 10 min at RT, the whole mixture was diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL) and the resulting layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The crude product was placed into a microwave reaction vessel and dissolved in THF (8 mL). DIAD (0.264 mL, 1.35 mmol, 1.5 equiv) and PPh_3 (0.262 g, 1.35 mmol, 1.5 mmol) were added and the reaction mixture was heated in a microwave reactor for 10 min at 50 °C (100 W). The reaction mixture was transferred to a flask and the solvents were removed under reduced pressure. The resulting crude product was purified by flash column chromatography (SiO_2; EtOAc/hexane = 3:8) to yield the desired cyclized sulfonamide **5** (0.139 g, 59% over two steps) in the form of colorless oil. ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.17 (ddd, *J* = 8.2, 1.2, 0.6 Hz, 2H), 7.97 (ddd, *J* = 7.8, 1.3, 0.6 Hz, 2H), 7.62−7.58 (m, 1H), 7.56−7.52 (m, 1H), 3.55−3.52 (m, 4H), 1.83−1.76 (m, 4H), 1.64−1.61 (m, 4H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 165.6, 152.7, 136.3, 127.4, 127.3, 125.2, 122.2, 49.1, 29.2, 27.0; MS (ESI) *m*/*z* (%) 297: $[M + H]^+$ (100); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{13}H_{17}N_2O_2S_2$, 297.0726; found, 297.0728.

***N*-Benzylbenzo[*d*]thiazol-2-amine (7a) Synthesis (Scheme 3B, Equation 6).** A solution of sulfonamide **3a** (0.127 g, 0.42 mmol, 1.0 equiv) and Cs_2CO_3 (0.274 g, 0.84 mmol, 2.0 equiv) were added to 1,4-dioxane (5 mL), and the resulting mixture was degassed using the freeze−pump−thaw technique (three times). $(PPh_3)_2PdCl_2$ (0.059 g, 0.084 mmol, 0.2 equiv) was added and the resulting mixture was heated at 100 °C (external temperature, oil bath) for 24h. The resulting mixture was cooled to RT, diluted with CH_2Cl_2 (25 mL), and filtered through a pad of Celite. The filter cake was washed with additional CH_2Cl_2 (3 × 25 mL) and the combined filtrates were

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evaporated under reduced pressure. The residue was purified by flash column chromatography (SiO_2; EtOAc/petroleum ether = 1:5 ≥ 1:2 ≥ 1:1) to yield the desired product **7a** (0.077 g, 76%) as a colorless solid. Mp = 163−165 °C (164−168 °C lit[58]); ^{1}H NMR (500 MHz, chloroform-*d*): δ 7.58 (d, *J* = 7.9 Hz, 1H), 7.33−7.20 (m, 7H), 7.06 (t, *J* = 7.8 Hz, 1H), 6.84 (broad s, 1H), 4.64 (s, 2H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*): δ 165.9, 153.3, 136.6, 129.3, 128.8, 128.0, 127.9, 123.9, 121. 9, 121.1, 119.8, 50.5; MS (ESI) *m*/*z* (%) 241: [M + H]$^+$ (100); HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{14}H_{13}N_2S$, 241.0794; found, 241.0796.

General Procedure for Chan−Lam Coupling. Sulfonamide **3** (0.1 mmol, 1 equiv) was dissolved in dry DCE (2.0 mL, 0.05 M), and boronic acid (0.2 mmol, 2 equiv), TMEDA (0.06 mL, 0.4 mmol, 4 equiv), and $[Cu(CH_3CN)_4]PF_6$ (0.015 g, 0.04 mmol, 0.4 equiv) were added. The resulting mixture was placed under an atmosphere of O_2 (1 atm) and stirred for 4h at RT. The whole mixture was filtered over a pad of Celite, and the filter cake was washed with CH_2Cl_2 (3 × 25 mL). The resulting filtrates were combined and the solvents were removed under reduced pressure.

*N-Benzyl-N-phenylbenzo[d]thiazole-2-sulfonamide (**6a**).* Prepared starting from sulfonamide **3a** (0.030 g, 0.09 mmol) and phenylboronic acid (0.022 g, 0.18 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:3) to yield 0.025 g (67%) of **6a** obtained as a colorless oil. ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.31 (ddd, *J* = 8.2, 1.3, 0.7 Hz, 1H), 7.99 (ddd, *J* = 8.1, 1.3, 0.7 Hz, 1H), 7.68 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.61 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H), 7.33−7.23 (m, 8H), 7.17−7.12 (m, 2H), 5.13 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 165.7, 152.6, 138.2, 136.7, 135.6, 129.3, 128.9, 128.7, 128.6, 128.1, 127.7, 127.5, 125.4, 122.3, 56.9; MS (ESI) *m*/*z* (%) 381: [M + H]$^+$ (100); HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{20}H_{17}N_2O_2S_2$, 381.0726; found, 381.0728

*N-Allyl-N-phenylbenzo[d]thiazole-2-sulfonamide (**6b**).* Prepared starting from sulfonamide **3b** (0.024 g, 0.09 mmol) and phenylboronic acid (0.022 g, 0.18 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:3) to yield 0.020 g (63%) of **6b** obtained as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.25−8.23 (m, 1H), 7.95−7.93 (m, 1H), 7.63 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.56 (ddd, *J* = 8.3, 7.1, 1.2 Hz, 1H), 7.34−7.30 (m, 3H), 7.23−7.21 (m, 2H), 5.87 (ddt, *J* = 16.6, 10.2, 6.4 Hz, 1H), 5.15 (dd, *J* = 17.0, 1.5 Hz, 1H), 5.11 (dd, *J* = 9.7, 1.4 Hz, 1H), 4.54 (dt, *J* = 6.5, 1.3 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 165.6, 152.6, 138.3, 136.7, 132.6, 129.4, 129.2, 128.7, 127.7, 127.5, 125.4, 122.3, 119.6, 55.6; MS (ESI) *m*/*z* (%) 331: [M + H]$^+$ (100); HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{16}H_{15}N_2O_2S_2$, 331.0569; found, 331.0573.

*N-Butyl-N-phenylbenzo[d]thiazole-2-sulfonamide (**6c**).* Prepared starting from sulfonamide **3c** (0.062 g, 0.22 mmol) and phenylboronic acid (0.054 g, 0.44 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:4) to yield 0.044 g (58%) of **6c** obtained as a colorless oil. ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.24−8.22 (m, 1H), 7.95−7.92 (m, 1H), 7.62 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 7.55 (ddd, *J* = 8.3, 7.3, 1.3 Hz, 1H), 7.34−7.30 (m, 3H), 7.23−7.20 (m, 2H), 3.92 (t, *J* = 7.1 Hz, 2H), 1.53−1.47 (m, 2H), 1.43−1.34 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 165.5, 152.7, 138.4, 136.6, 129.4, 129.2, 128.7, 127.6, 127.4, 125.4, 122.2, 52.5, 30.7, 19.7, 13.7; MS (ESI) *m*/*z* (%) 347: [M + H]$^+$ (100); HRMS (ESI) *m*/*z*: calcd for $C_{17}H_{19}N_2O_2S_2$, 347.0882; found, 347.0885.

*N-Benzyl-N-(3-methoxyphenyl)benzo[d]thiazole-2-sulfonamide (**6d**).* Prepared starting from sulfonamide **3a** (0.030 g, 0.09 mmol) and 3-methoxyphenylboronic acid (0.027 g, 0.18 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:5 ≥ 1:3) and the collected fractions containing the product were concentrated under reduced pressure. The resulting crude product was purified by semiprep HPLC (MeCN/buffer, gradient 9:1 to 3:2 over 6 min) to yield 0.0155 g (42%) of **6d** obtained as a colorless oil. ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.28−8.25 (m, 1H), 7.98−7.95 (m, 1H), 7.67−7.63 (m, 1H), 7.60−7.55 (m, 1H), 7.30−7.23 (m, 5H), 7.11 (ddd, *J* = 8.3, 7.9, 0.8 Hz, 1H), 6.77 (ddd, *J* = 8.4, 2.3, 1.1 Hz, 1H), 6.69−6.66 (m, 2H), 5.07 (s, 2H), 3.62 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 165.8, 160.1, 152.6, 139.3, 136.7, 135.7, 129.8, 128.9, 128.6, 128.1, 127.7, 127.5, 125.4, 122.3, 121.3, 115.2, 114.7, 56.9, 55.4; MS (ESI) *m*/*z* (%) 411: [M + H]$^+$ (100); HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{21}H_{19}N_2O_3S_2$, 411.0832; found, 411.0833.

*N-Benzyl-N-(4-chlorophenyl)benzo[d]thiazole-2-sulfonamide (**6e**).* Prepared starting from sulfonamide **3a** (0.030 g, 0.09 mmol) and 4-chlorophenylboronic acid (0.028 g, 0.18 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/petroleum ether = 1:6) to yield 0.026 g (65%) of **6e** obtained as a colorless oil. ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.27 (d, *J* = 8.1 Hz, 1H), 7.97 (d, *J* = 8.2 Hz, 1H), 7.66 (ddd, *J* = 8.3, 7.3, 1.3 Hz, 1H), 7.59 (ddd, *J* = 8.2, 7.3, 1.2 Hz, 1H), 7.30−7.19 (m, 7H), 7.15 (t, *J* = 7.9 Hz, 1H), 7.03 (ddd, *J* = 7.9, 2.0, 1.2 Hz, 1H), 5.05 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 165.2, 152.6, 139.4, 136.6, 135.1, 134.7, 130.2, 129.6, 129.0, 128.9, 128.7, 128.3, 127.9, 127.7, 127.6, 125.5, 122.3, 56.7; MS (ESI) *m*/*z* (%) 415: [M + H]$^+$ (100); HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{20}H_{16}ClN_2O_2S_2$, 415.0336; found, 415.0341.

*N-Benzyl-N-(3-fluorophenyl)benzo[d]thiazole-2-sulfonamide (**6f**).* Prepared starting from sulfonamide **3a** (0.030 g, 0.09 mmol) and 3-fluorophenylboronic acid (0.025 g, 0.18 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/petroleum ether = 1:3) to yield 0.017 g (45%) of **6f** obtained as a colorless oil. ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.27 (dd, *J* = 9.2, 0.9 Hz, 1H), 7.97 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.66 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.59 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H), 7.28−7.23 (m, 5H), 7.19 (td, *J* = 8.2, 6.3 Hz, 1H), 6.97−6.90 (m, 3H), 5.07 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 165.3, 162.66 (d, *J* = 248.6 Hz), 152.6, 139.6 (d, *J* = 9.7 Hz), 136.6, 135.2, 130.3 (d, *J* = 9.0 Hz), 128.9, 128.7, 128.3, 127.9, 127.7, 125.5, 125.0 (d, *J* = 3.3 Hz), 122.3, 116.7 (d, *J* = 22.8 Hz), 115.9 (d, *J* = 20.8 Hz), 56.8; ^{19}F{^{1}H} NMR (376 MHz, chloroform-*d*): δ -110.8; MS (ESI) *m*/*z* (%) 399: [M + H]$^+$ (100); HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{21}H_{35}N_2O_4S_2Si$, 399.0632; found, 399.0635.

*N-Benzyl-N-(4-bromophenyl)benzo[d]thiazole-2-sulfonamide (**6g**).* Prepared starting from sulfonamide **3a** (0.030 g, 0.09 mmol) and 4-bromophenylboronic acid (0.036 g, 0.18 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/hexane = 1:3) and the collected fractions containing the product were concentrated under reduced pressure. The resulting crude product was purified by semiprep HPLC (MeCN/buffer, gradient 9:1 to 3:2 over 6 min) to yield 0.0107 g (26%) of **6g** obtained as a colorless oil. ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.26 (ddd, *J* = 8.3, 1.2, 0.7 Hz, 1H), 7.97 (ddd, *J* = 8.0, 1.3, 0.7 Hz, 1H), 7.66 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 7.59 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.36−7.33 (m, 2H), 7.27−7.25 (m, 9H), 7.02−6.98 (m, 2H), 5.05 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 165.3, 152.6, 137.2, 135.2, 132.6, 130.9, 128.9, 128.8, 128.3, 127.9, 127.7, 125.5, 122.8, 122.3, 56.8; MS (ESI) *m*/*z* (%) 459: [M + H]$^+$ (100); HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{20}H_{16}BrN_2O_2S_2$, 458. 9831; found 458.9833.

*N-([1,1′-Biphenyl]-4-yl)-N-benzylbenzo[d]thiazole-2-sulfonamide (**6h**).* Prepared starting from sulfonamide **3a** (0.030 g, 0.09 mmol) and [1,1′-biphenyl]-4-ylboronic acid (0.036 g, 0.18 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/petroleum ether = 1:3) to yield 0.026 g (65%) of **6h** obtained as a colorless oil. ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.27 (d, *J* = 8.2 Hz, 1H), 7.95 (d, *J* = 8.6 Hz, 1H), 7.66−7.62 (m, 1H), 7.59−7.55 (m, 1H), 7.49−7.35 (m, 6H), 7.32−7.24 (m, 6H), 7.17−7.15 (m, 2H), 5.12 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 165.6, 152.6, 141.4, 139.9, 137.2, 136.6, 135.6, 129.5, 128.9, 128.6, 128.0, 127.9, 127.8, 127.6, 127.5, 127.1, 125.4, 122.2, 56.8; MS (ESI) *m*/*z* (%) 457: [M + H]$^+$ (100); HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{26}H_{21}N_2O_2S_2$, 457.1039; found 457.1040.

*N-([1,1′-Biphenyl]-4-yl)-N-allylbenzo[d]thiazole-2-sulfonamide (**6i**).* Prepared starting from sulfonamide **3b** (0.030 g, 0.09 mmol) and [1,1′-biphenyl]-4-ylboronic acid (0.036 g, 0.18 mmol). The crude product was purified using flash column chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and the collected fractions containing

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the product were concentrated under reduced pressure. The resulting crude product was purified by semiprep HPLC (MeCN/buffer, gradient 9:1 to 3:2 over 6 min) to yield 0.026 g (72%) of **6i** obtained as a colorless oil. ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.26 (ddd, *J* = 8.3, 1.3, 0.7 Hz, 1H), 7.96 (ddd, *J* = 8.0, 1.3, 0.7 Hz, 1H), 7.65 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 7.58 (ddd, *J* = 8.1, 7.2, 1.3 Hz, 1H), 7.52 (ddd, *J* = 7.8, 1.8, 1.1 Hz, 1H), 7.43 (td, *J* = 2.0, 0.4 Hz, 2H), 7.41−7.30 (m, 6H), 7.20 (ddd, *J* = 7.9, 2.1, 1.1 Hz, 1H), 5.90 (ddt, *J* = 16.5, 10.2, 6.4 Hz, 1H), 5.17 (ddd, *J* = 16.9, 2.6, 1.3 Hz, 1H), 5.13 (ddd, *J* = 10.1, 2.3, 1.1 Hz, 1H), 4.56 (dt, *J* = 6.4, 1.3 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 165.6, 152.7, 142.6, 140.0, 138.8, 136.7, 132.6, 129.7, 129.0, 128.0, 127.9, 127.9, 127.7, 127.6, 127.4, 127.2, 125.4, 122.3, 119.7, 55.7; MS (ESI) *m*/*z* (%) 407: $[M + H]^+$ (100); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{22}H_{19}N_2O_2S_2$, 407.0882; found, 407.0886.

Benzo[d]thiazol-2-ylsulfonyl Group Cleavage (Scheme 6C). Ethanethiolysis (Scheme 6C, Equation 6). *N*,*N*-Dibenzylsulfonamide **4g** (0.050 g, 0.12 mmol) was dissolved in CH_3CN (1.2 mL) at RT, and EtSLi (0.024 g, 0.36 mmol, 3.0 equiv) was added. The resulting mixture was stirred at RT for 12 h. Solvents were removed under reduced pressure, and the resulting crude product was purified with flash column chromatography (SiO_2; EtOAc/hexane = 1:1) to yield compound **11** (0.022 g, 95%) as a yellowish oil.

$NaBH_4$ Reduction (Scheme 6C, Equation 7). *N*,*N*-Dibenzylsulfonamide **4g** (0.129 g, 0.33 mmol) was dissolved in EtOH (2 mL) at RT, and $NaBH_4$ (0.049 g, 1.3 mmol, 4.0 equiv) was added. The resulting mixture was stirred at RT for 12 h. The whole mixture was diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 ×15 mL), and the organic layers were combined, washed with brine (10 mL), dried over Na_2SO_4, filtered, and the solvents were removed under reduced pressure. The crude product was purified by flash column chromatography (SiO_2; EtOAc/hexane = 1:1) to give the desired compound **11** (0.063 g, 98%) as a yellowish oil.

Dibenzylamine (11). ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.37−7.32 (10H), 3.82 (4 H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*): δ 140.3, 128.6, 128.3, 127.1, 53.2; MS (ESI) *m*/*z* (%) 198: $[M + H]^+$ (100); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{14}H_{16}N$, 198.1277; found 198.1277.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00317.

Relevant optimization tables; discussion related to the proposed reaction mechanisms; and a copy of ^{1}H and ^{13}C{^{1}H} NMR spectra (PDF)

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Author Contributions

F.Z. performed most of the experiments and analyzed the experimental data. O.K. carried out the experiments and analyzed the experimental data. F.Z., E.L., and O.K. performed and optimized Chan−Lam coupling. F.Z., O.K., and N.S. performed and optimized SuFEX experiments. F.Z. partially designed the experimental plans. J.P. initiated the project, led the project team, designed the experiments, and analyzed results. F.Z. and J.P. co-wrote the paper with input from all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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