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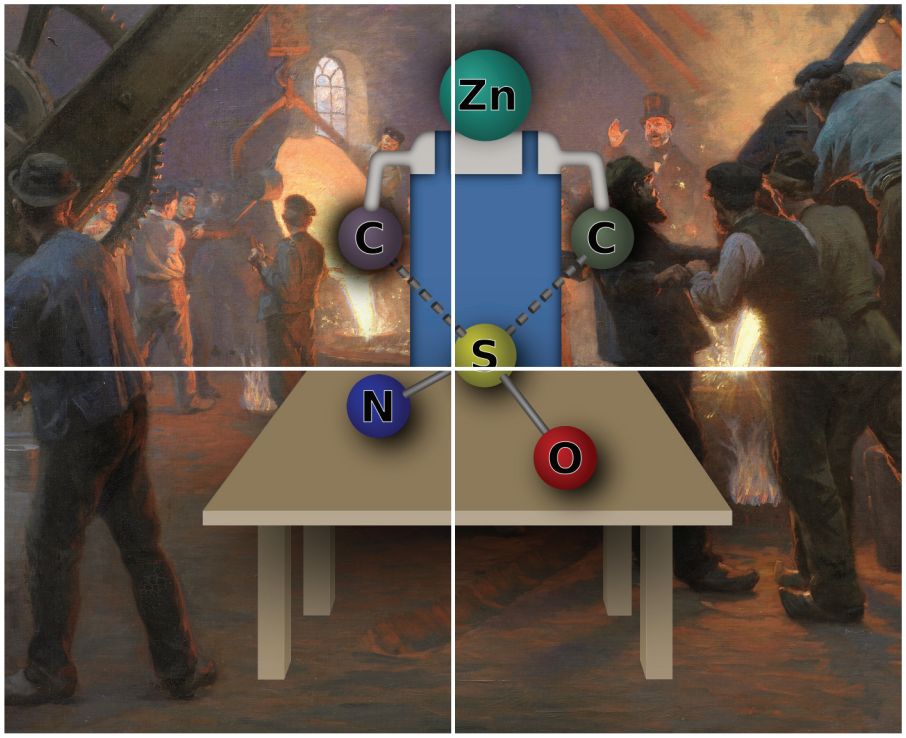

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S-Alkylation of sulfinamides with Zn-carbenoids: expanding stereoselective sulfoximine synthesis beyond NH derivatives†

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Sulfoximines are experiencing steadily increasing use in the development of pharmaceuticals and agrochemicals. Although recently a number of synthetic methods to access this versatile motif have been disclosed, only *NH*-sulfoximines have been considered as the ultimate targets. Here, we report an approach toward enantiopure *N*-substituted sulfoximines *via* direct stereoretentive *S*-alkylation of parent sulfinamides with zinc carbenoids. Mechanistically, a carbon–sulfur bond is formed in the course of 1,2-metallate rearrangement featuring an unusual migration of the S-atom in the transient zincate complex. The approach accommodates a large variety of differently substituted sulfinamides and features excellent functional group compatibility.

Introduction

Owing to their chemical stability and ease of synthesis, sulfonamides and sulfones are widely employed motifs in drug discovery, agrochemistry and materials science. Closely structurally related sulfoximines retain the beneficial properties of sulfonamides and sulfones while offering the additional advantage of three diversity vectors combined with a configurationally stable sulfur stereocentre. The enriched structural variability allows accessing 3D chemical space and renders sulfoximines particularly suitable for modular molecular design that is difficult to achieve with sulfonamides and sulfones.

Not surprisingly, sulfoximines have recently[1] gained recognition in asymmetric synthesis,[2] the development of insecticides[3] and small-molecule drug discovery[4] (Fig. 1). In the latter field, however, all recent clinical candidates exclusively feature *NH*-structures and the full substitution potential of the sulfoximine motif remains underutilized. On the other hand, a study conducted at Bayer demonstrated that *N*-alkylated sulfoximines indeed show promise[5] in terms of favorable physicochemical and pharmacokinetic properties. Thus, cyclo-roniciclib features improved permeability, reduced efflux and lipophilicity while displaying potency, metabolic stability and solubility comparable to those of roniciclib (Fig. 1).

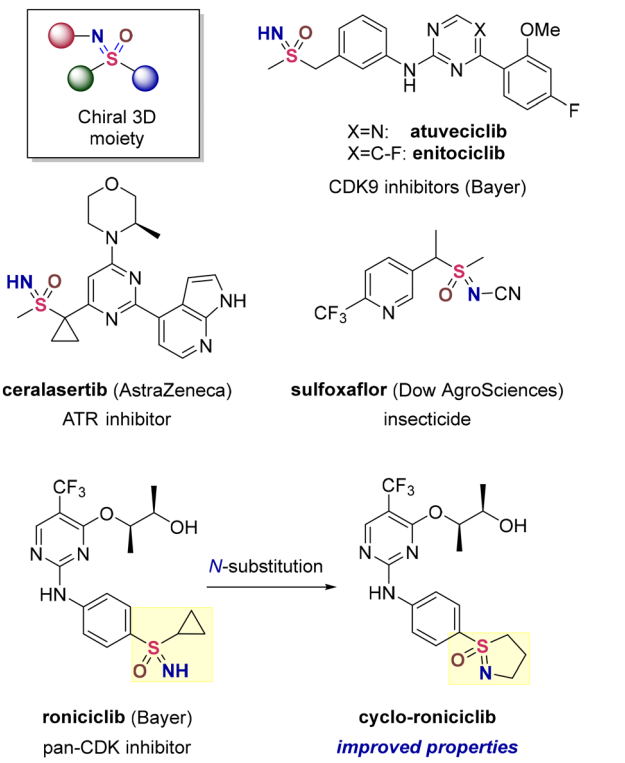

Fig. 1 Bioactive sulfoximines.

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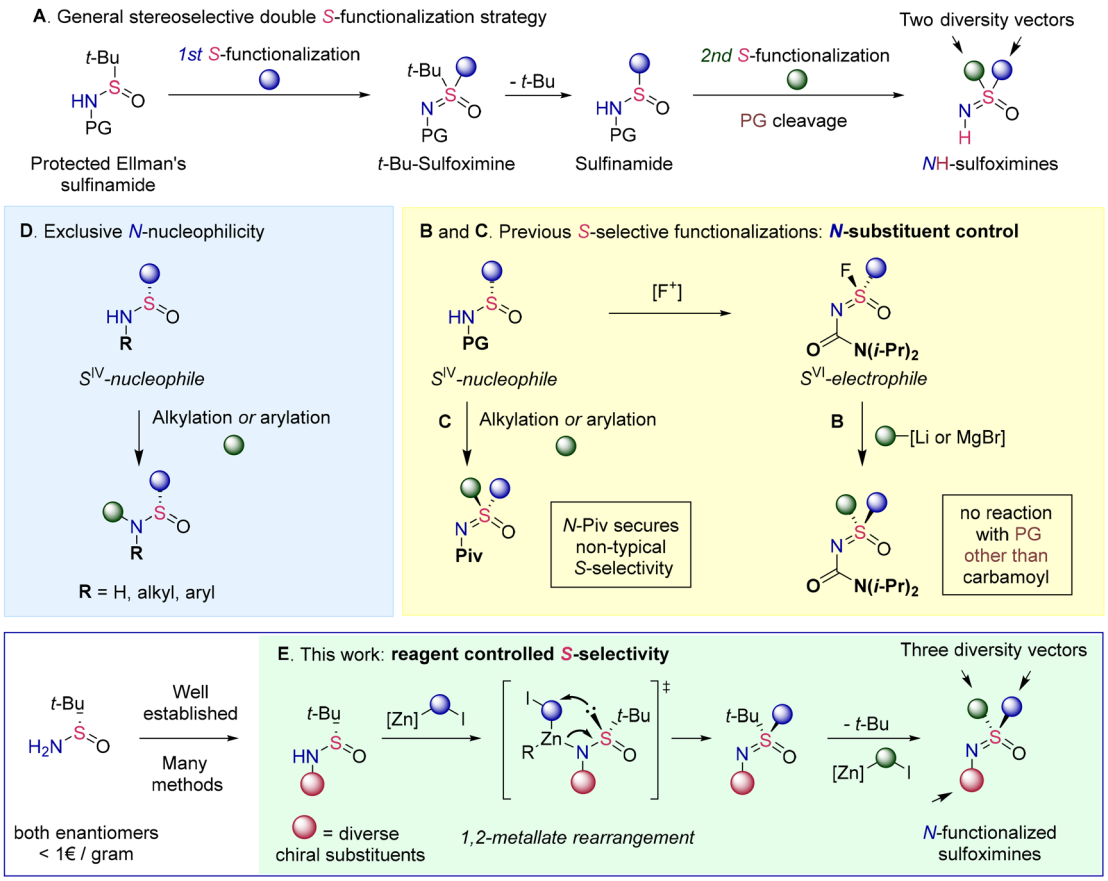
The surge of recent applications has vigorously spurred interest in the synthetic community and a stream of novel methodologies has started to fill the previously underexplored chemical space surrounding sulfoximines.[6] Especially, remarkable progress has been achieved in the development of the corresponding stereoselective approaches. Thus, advances in *S*-imidation[7] methods have allowed the direct synthesis of sulfoximines from sulfoxides.[8] Moreover, asymmetric imidation of thioethers affords enantiopure sulfimides,[6b,9] which in turn may be converted to sulfoximines *via* stereospecific oxidation. Enantiopure products are also accessible *via* desymmetrization[10] and kinetic resolution[11] of racemic *N*H-sulfoximines. The pioneering work of Jonson[12] on nucleophilic substitution at the S-atom in sulfonimidoyl derivatives has evolved[13] into another class of powerful methodologies. Despite all these advances, most methodologies focus primarily on the synthesis of *N*H-sulfoximines, completely neglecting possible substitution at the N-atom.

Likewise, only *N*H-sulfoximines are ultimately targeted by several general methods that borrow the stereogenic *SNO*-fragment from widely available Ellman's sulfinamide (Scheme 1). The common strategy of these approaches involves the consecutive introduction of substituents at the S-atom owing to the susceptibility of intermediate *t*-Bu-sulfoximines to *t*-Bu-cleavage (Scheme 1A). Thus, the addition of nucleophiles to sulfinamide derived *S*-electrophilic sulfonimidoyl fluorides allows access to a wide range of protected sulfoximines (Scheme 1B).[13c] Importantly, the carbamoyl protecting group plays a pivotal role as no addition occurs with other protecting groups. The inherent nucleophilic properties of sulfinamide derivatives have been exploited in another type of *S*-functionalization approach (Scheme 1C). Thus, both *S*-alkylation[14a,b] and *S*-arylation[14c–e] have been reported despite sulfinamides being ambident nucleophiles that predominantly exhibit *N*-specific reactivity (Scheme 1D).[15] The desired *S*-selective functionalization has required the introduction of an appropriate *N*-protecting group such as pivaloyl for the atypical *S*-nucleophilicity to manifest.

The necessity for *N*-protection limits the role of Ellman's sulfinamide simply to a convenient source of *S*-stereogenicity. However, the chemistry developed over the years around this versatile chiral auxiliary offers innumerable opportunities for *N*-functionalization.[16] Therefore, we realized that *N*-functionalized Ellman's sulfinamide derivatives could serve as excellent substrates for the modular synthesis of *tri-substituted* enantiopure sulfoximines. Such an approach would address the overlooked *N*-substitution and, considering the emerging usefulness of *N*-alkylated sulfoximines,[4a,5] would significantly expand the diversity of accessible structures.



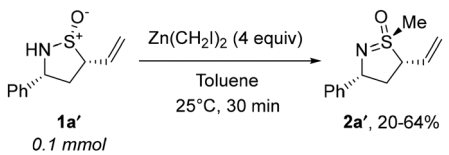
Scheme 1 Stereoselective approaches to sulfoximines from Ellman's sulfinamide.

Herein, we report the development of a general approach for chemo- and stereospecific *S*-alkylation of various *N*-substituted sulfinamides with Zn-carbenoids (Scheme 1E). Control experiments and DFT calculations provide strong evidence that the *S*-selective alkylation proceeds through stereospecific 1,2-metallate rearrangement. Overall, the developed modular synthesis of *tri-substituted* sulfoximines allows for the reliable introduction of a broad range of *N*-substituents and tolerates a wide range of functional groups.

Results and discussion

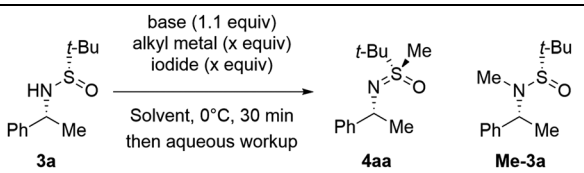
In 2022, we accidentally discovered[17] that the treatment of sulfinamide **1a′** with excess diethylzinc and diiodomethane delivers sulfoximine **2a′** rather than the anticipated cyclopropanation (Scheme 2). While *S*-alkylation of thioethers with Zn-carbenoids is precedented,[18] comparable reactivity of sulfinamides has been reported only once by Zercher *et al.* and was primarily regarded as a synthetic obstacle.[19]

Unfortunately, the depicted transformation of **1a′** suffered from reproducibility issues. Consequently, we undertook comprehensive optimization of conditions[20] using simplified *tert*-butyl sulfinamide **3a** as a model substrate (Table 1). When sequentially treated with excess diethylzinc and diiodomethane, **3a** failed to react and was quantitatively recovered. Gratifyingly, increasing the nucleophilicity of **3a** by deprotonation restored the reactivity and *S*-methylated derivative **4aa** was obtained in high yield. Irrespective of the nature of the base employed (entries 2 *vs.* 3), the Li-salt of **3a** afforded the best results in terms of both conversion and yield (entries 2, 4 and 5). Importantly, the treatment of lithiated **3a** with MeI produced *N*-methylation product **Me-3a** exclusively irrespective of the presence or absence of $ZnEt_2$ (entries 6 and 7). The determined optimal reagent system was efficient enough to conduct the transformation under slightly over-stoichiometric conditions additionally boosting the yield of **4aa** (entry 8).



Scheme 2 Serendipitous discovery.

Table 1 Selected experiments for the optimization of reaction conditions[a]



		Carbenoid formation			Yield[b], %		
Entry	Base	Metal alkyl	Iodide	*x*	**3a**	**4aa**	**Me-3a**
1	—	$ZnEt_2$	CH_2I_2	2.5	100	—	—
2	LiHMDS	$ZnEt_2$	CH_2I_2[c]	2.5	3	86	—
3	*n*-BuLi	$ZnEt_2$	CH_2I_2	2.5	4	82	—
4	NaHMDS	$ZnEt_2$	CH_2I_2	2.5	15	74	—
5	KHMDS	$ZnEt_2$	CH_2I_2	2.5	8	75	—
6	LiHMDS	$ZnEt_2$	MeI	2.5	5	—	89
7	LiHMDS	—	MeI	2.5	—	—	95
8	LiHMDS	$ZnEt_2$	CH_2I_2	1.2	0	95	—

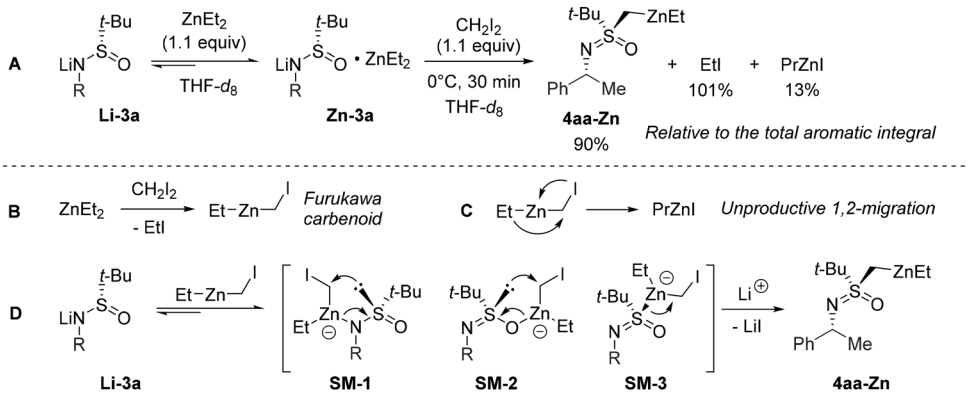
[a] Sulfinamide **3a** (0.1 mmol) was deprotonated using a base (0.11 mmol) in THF (1 mL) for 15 min at 0 °C and then sequentially treated with an alkyl metal and alkyl iodide. [b] ^1H NMR yield was measured against mesitylene as an internal standard. [c] No reaction with CH_2Br_2 instead of CH_2I_2 (see ref. 20).

To gain insight into the mechanistic aspects of the transformation, we performed a brief NMR investigation using a nearly stoichiometric variant of the identified conditions (Scheme 3A). To begin with it was established that separately prepared lithium salt **Li-3a** does not interact with CH_2I_2. However, the treatment of **Li-3a** with $ZnEt_2$ results in the reversible formation of a 1 : 1 zincate complex **Zn-3a**.

Due to the known[21] dynamic nature of $ZnEt_2$ complexation, we were unable to determine the exact binding mode of the Zn-atom in **Zn-3a** using NMR spectroscopy. On the other hand, attempts to crystallize **Zn-3a** resulted only in the formation of **Li-3a** crystals.[22] Nonetheless, upon the addition of CH_2I_2 to **Zn-3a**, a rapid reaction occurred. The obtained mixture contained the expected amount of EtI corresponding to quantitative I-Zn exchange leading to the formation of the Furukawa carbenoid (Scheme 3B). Next, the minor amount of PrZnI detected matched the decomposition of the excess of the formed carbenoid (Scheme 3C). The respective 1,2-metalate rearrangement is recognized as the major cause of instability in related species in coordinating media.[23] Finally, the major product resulting from **Li-3a** was determined to be dialkylzinc **4aa-Zn**.

The combined results of the NMR experiment and the optimization study allowed us to formulate a mechanistic hypothesis. Once formed in the reaction mixture, the Furukawa carbenoid will either undergo an irreversible 1,2-metalate rearrangement or engage in rapid complexation with **Li-3a** similarly to $ZnEt_2$ (Scheme 3C *vs.* 3D). The latter scenario should give rise to transient zincates **SM-1–3** analogous to **Zn-3a**. Irrespective of the realized Zn-binding mode[24] in **SM-1–3**, the anionic character of the ensuing 1,2-rearrangement renders[21a] the formation of **4aa-Zn** faster compared to the unproductive decomposition pathway (Scheme 3C). On the other hand, the migratory aptitude of the S-atom in **SM-1–3** apparently must exceed that of the Et substituent. We cannot rule out the possibility that I-Zn exchange may occur directly between the zincate **Zn-3a** and CH_2I_2; however, the same zincates **SM-1–3** would arise in this case.

To gain a deeper insight into the mechanism of the transformation, a computational study at the DFT level was performed.[25] Analysis of possible zincate complexes between **Li-3a** and the Furukawa carbenoid identified the *N*,*O*-bound adduct **SM-4** as the most thermodynamically stable configuration



Scheme 3 NMR experiment and mechanistic hypothesis.

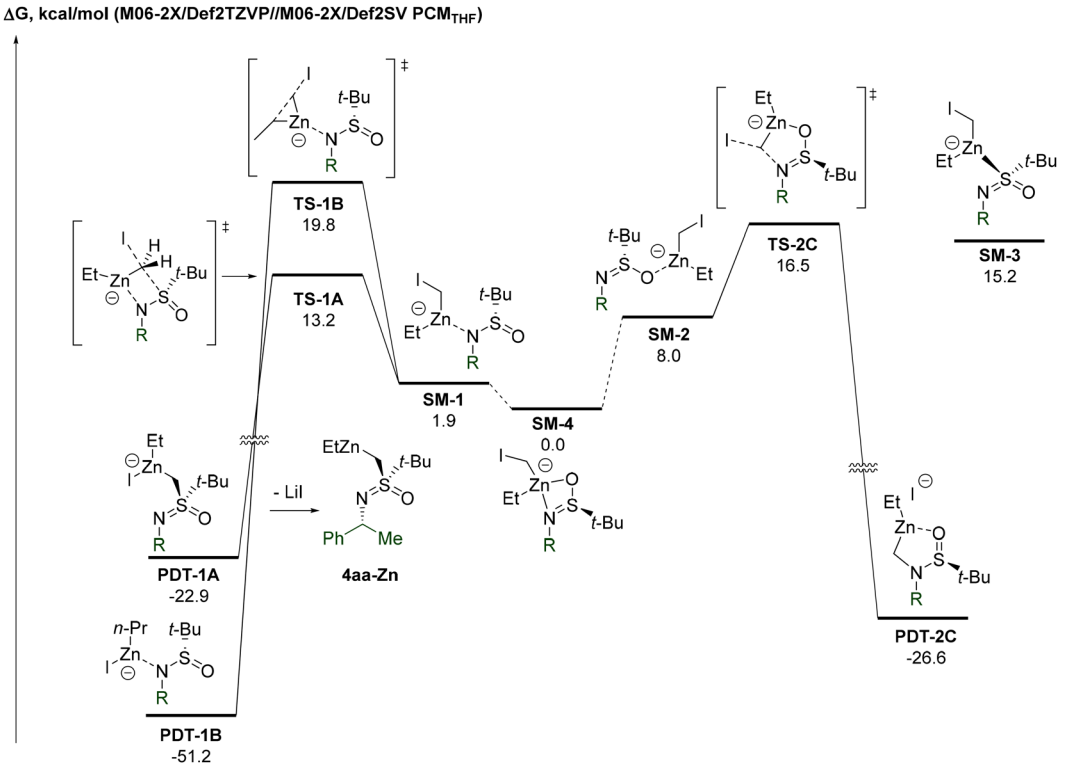
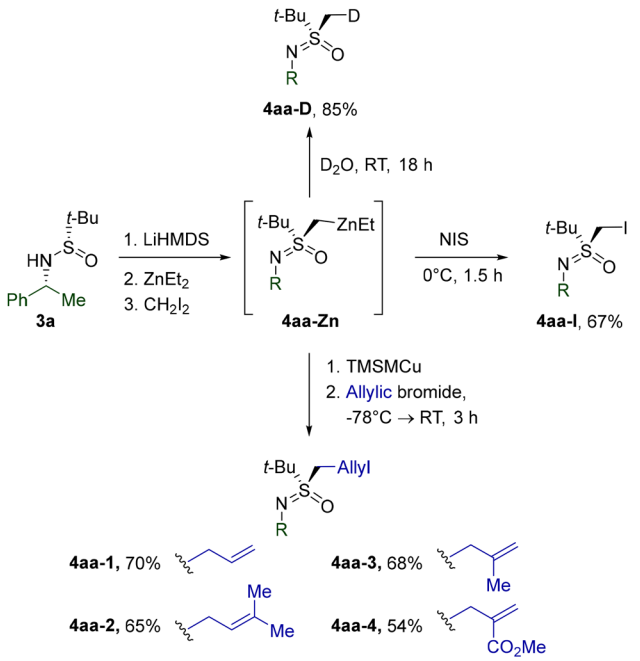


Fig. 2 The most kinetically favored transitions of the EtZnCH$_2$I–**Li-3a** complex.

(Fig. 2). In view of the minimal (<0.5 kcal mol^{-1}) energy difference between the two diastereomers of **SM-4**, it is represented by a single structure.

N-Bound **SM-1** was determined to be the second most populated isomer, whereas *O*- and *S*-bound **SM-2** and **SM-3** are far less energetically favored. Four-membered **TS-1A**, which ultimately leads to the observed product **4aa-Zn** *via* **PDT-1A**, possesses the lowest energy (13.2 kcal mol^{-1}) of all calculated transition states. The incorporation of an explicit Zn-bound THF molecule in **SM-1** and **TS-1A** results in only a minor decrease (9.9 *vs.* 11.3 kcal mol^{-1}) in the respective energy gap. Therefore, we assume that the omission of Zn-bound THF should not have a decisive impact on the overall calculated profile of the potential energy surface. The second lowest energy transition corresponds to the formation of *N*-alkylated **PDT-2C** *via* **TS-2C**, which is 3.3 kcal mol^{-1} higher compared to the observed *S*-alkylation **TS-1A**. Possible competitive Et-migration stands third in the order of increase in transition state energy. The corresponding **TS-1B** exceeds **TS-1A** by 6.6 kcal mol^{-1}. Thus, the computational study indeed confirms a significant kinetic preference for the observed S-atom migration.

The synthetic utility of dialkylzinc intermediate **4aa-Zn** was probed through a series of experiments (Scheme 4). Thus, deu-



Scheme 4 Synthetic utility of dialkylzinc intermediate **4aa-Zn**.

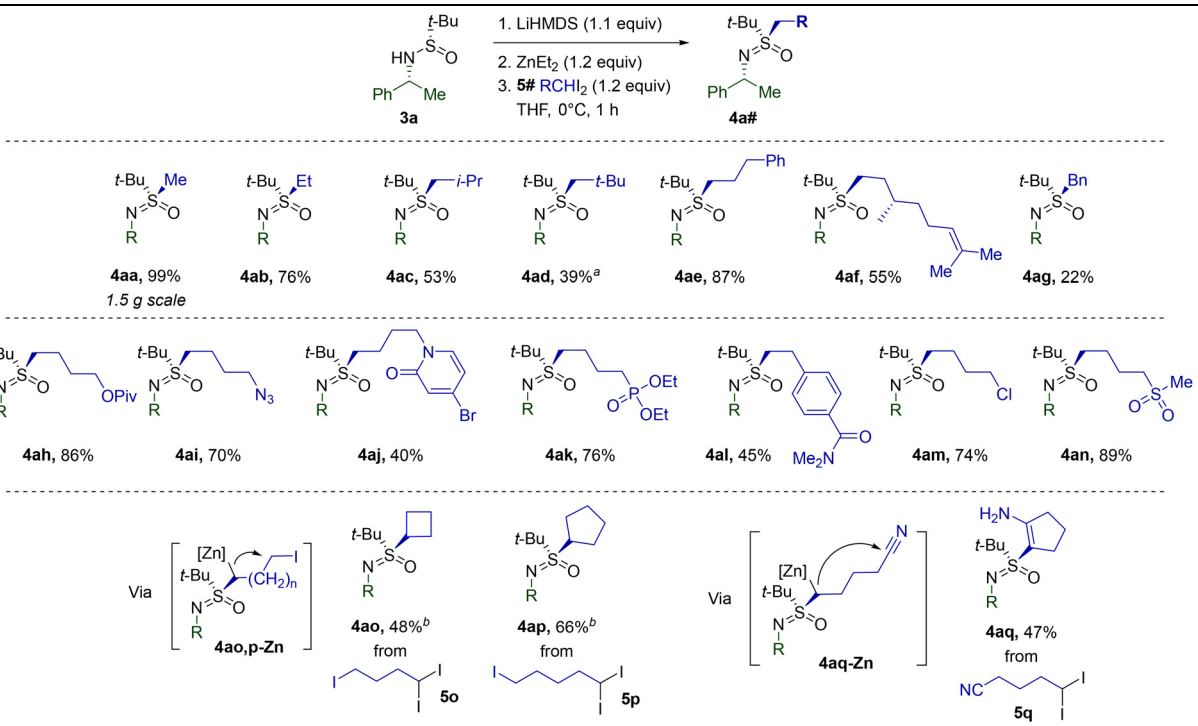
teration and iodination expectedly afforded the corresponding **4aa-D** and **4aa-I**. Moreover, transmetalation to [(trimethylsilyl) methyl]copper afforded mixed cuprates,[26] which smoothly delivered homoallylic derivatives **4aa-1–4** *via* coupling with the respective allylic bromides.

Next, we set out to explore the scope of the discovered sulfinamide alkylation with respect to geminal diiodides (Table 2). To begin with, the reliability of *S*-methylation with CH_2I_2 (**5a**) was confirmed in a scaled-up synthesis of **4aa**. Gratifyingly, non-functionalized CH_2I_2 homologues **5b–g** also readily engaged in the reaction. Steric crowding around the *gem*-diiodo carbon definitely suppressed the alkylation, as exemplified by the decreased yield of neopentylic **4ad**. Despite the presence of a double bond favorably aligned for intramolecular cyclopropanation,[27] **5f** afforded the expected sulfoximine **4af**. The low yield of **4ag** most probably arises from the acute susceptibility of the **5g**-derived benzylic carbenoid toward unproductive 1,2-metalate rearrangement.

The merits of the current methodology were most vividly revealed in reactions of **3a** with functionalized diiodides **5h–n**. The low basicity and nucleophilicity of the employed organozinc species allow for the introduction of a variety of functional groups. Additionally, the diiodides **5o–q** were found to react in a cascade manner *via* the dialkylzinc intermediates. While the corresponding **4ao-Zn** and **4ap-Zn** undergo intramolecular alkylation delivering alicyclic **4ao** and **4ap**, **4aq-Zn** engages in Blaise-type cyclization to **4aq**.

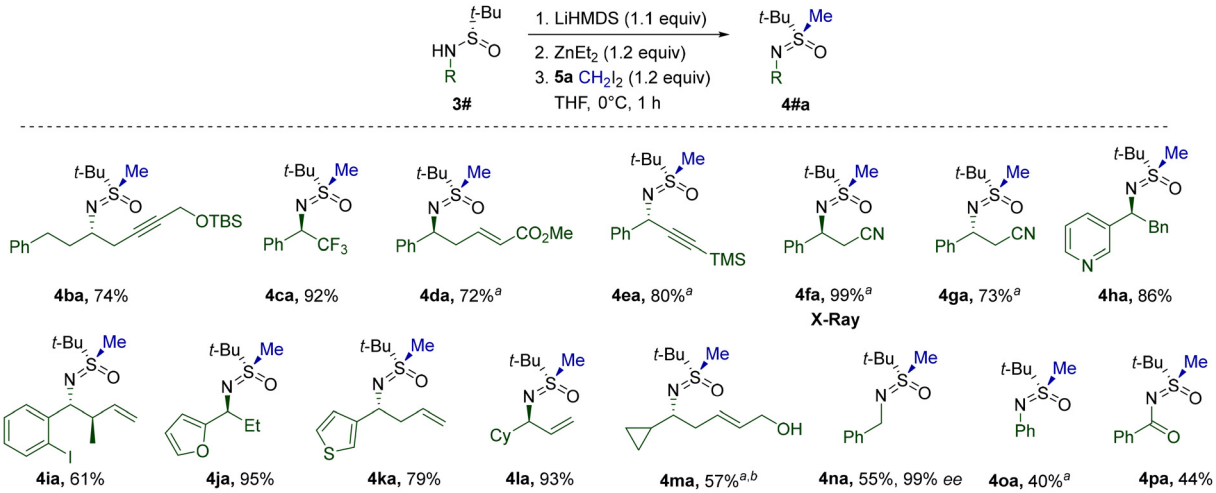
The high compatibility of the transformation with functional groups was further exploited during the investigation of possible patterns of α-*N*-substitution (Table 3). Sulfinamides **3b–p** were prepared using Ellman's auxiliary and methylated

Table 2 Scope of geminal diiodides



[a] The reaction was performed at 25 °C. [b] In the presence of LiBr (10 equiv.) over 16 h at 25 °C.

Table 3 Scope of α-*N*-substituents



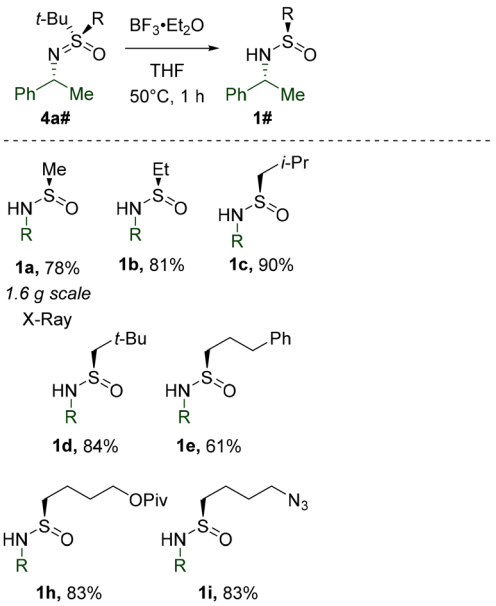
[a] Performed at −30 °C for 16 h. [b] LiHMDS (2.2 equiv.) and $ZnEt_2/CH_2I_2$ (2.5 equiv.).

analogously to **3a**. In most cases, the optimized conditions performed adequately without the need for additional modifications. However, a lower reaction temperature was found to be beneficial for several substrates in view of the limited stability of the corresponding Li-salts at 0 °C. The presence of a hydroxyl group in **3m** was successfully mitigated by higher loading of reagents. The configuration of the α-*N*-stereocenter apparently does not play a critical role in reaction performance, since both **4fa** and **4ga** were isolated with high yields. Moreover, the crystal structure obtained for **4fa** unambiguously confirmed the stereoretentive character of the alkylation. Primary alkyl groups at the N-atom of the starting sulfinamides are also tolerated, as evidenced by the reaction of **3n**. Notably, the corresponding **4na** was formed without any loss of enantiopurity. Less nucleophilic *N*-arylated **3o** and *N*-acylated **3p** displayed a noticeable drop in reactivity, whereas a number of sulfinamides[28] encumbered with tertiary *N*-alkyl substituents failed to deliver the expected products. In agreement with the computational analysis, the latter result suggests that the formation of *N*-bound zincate **SM-1** (Fig. 2) is pivotal for successful *S*-alkylation.

Having investigated the reactivity of *S*-*tert*-Bu-sulfinamides, we turned our attention to substrates with other substituents at the S-atom. To this end, a number of corresponding derivatives were prepared by literature known[29] *t*-Bu-cleavage (Table 4). The stereoretentive character of this transformation was confirmed by X-ray crystallography of **1a**.

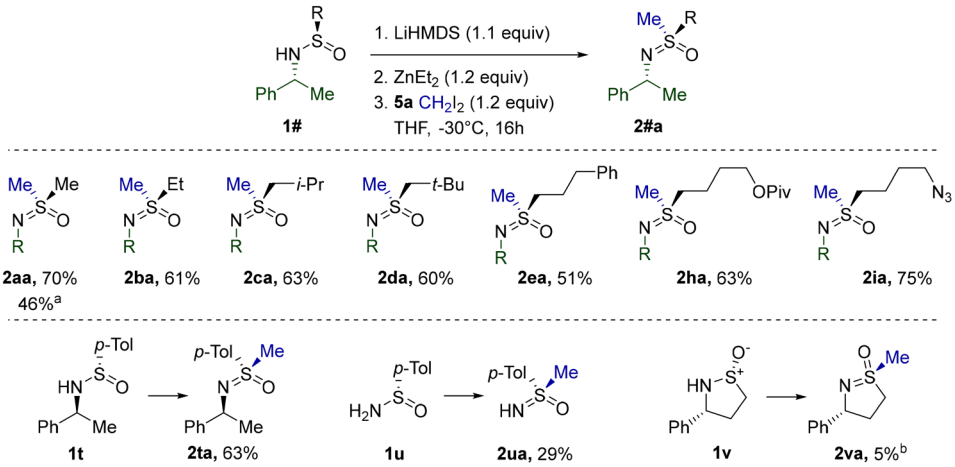
As before, *S*-methylation of the obtained substrates was performed first. The simplest Me-sulfinamide in the series, **1a**, was found to be moderately reactive toward the CH_2I_2 derived Furukawa reagent under standard conditions at 0 °C (Table 5). Apparently at this temperature, the rate of carbenoid decomposition is comparable with the rate of the requisite methylation. However, at −30 °C the stability of the carbenoid is improved sufficiently in order to participate predominantly in a productive interaction with **1a**. Therefore, homologues **1b–e**, **h**, **and i** were methylated at −30 °C and the corresponding sulfoximines were isolated in good yields. Additionally, the reaction was determined not to be limited to *S*-alkyl substrates, since *S*-arylated **1t**, derived from Davis' sulfinamide **1u**, performed equally well. However, the problematic methylation of **1u** and the exceedingly low reactivity of cyclic sulfinamide **1v** clearly denoted the restraints of the standard reagent system.

Table 4 Deprotection of *tert*-butyl sulfinamides



Our focus then shifted to *S*-alkylation with other substituted diiodides. Using the ethylation of sulfinamide **1a** as a model reaction, we evaluated[30] the efficacy of several diorganozinc reagents. While $ZnEt_2$ still delivered the ethylsulfoximine

Table 5 Methylation of non-*t*-Bu-sulfinamides



[a] Performed at 0 °C. [b] ^{1}H NMR yield was measured against mesitylene as an internal standard.

2ab in a fair yield, significant improvement was achieved using the unsymmetrical diorganozinc reagent ZnPh(*n*-Bu). As confirmed by a separate investigation,[31] ZnPh(*n*-Bu) combined the high reactivity of Zn-alkyls in I-Zn exchange with the low propensity of the Ph-substituent for migration, thus increasing the stability of intermediate carbenoid species.

The discovered efficiency of ZnPh(*n*-Bu) encouraged us to explore the alkylation of **2a** with homologues of **5b** employed previously (Table 6). Importantly, the excellent functional group compatibility of the transformation was completely retained. Alkylsulfinamides **1b**, **i**, and **h** with *S*-substituents besides methyl were also found to be competent substrates. Gratifyingly, the reaction of **3a** with benzal iodide **5g** mediated by ZnPh(*n*-Bu) afforded the corresponding **4ag** with a yield significantly superior to that obtained under the standard conditions (Table 2).

Disappointingly, the use of ZnPh(*n*-Bu) did not alleviate the unusually low reactivity of cyclic sulfinamides. Nevertheless, replacing the Ph group with the apparently completely non-migratory[32] dimethylsulfone fragment in diorganozinc **6** further reduced unproductive 1,2-migration and improved the performance of several cyclic sulfinamides and other previously challenging substrates (Table 7). Pleasingly, 5- and 6-membered **1v**, **a′**, and **w** reacted equally smoothly. Full retention of potentially epimerizable stereocenters in **2a′** and **2wa** clearly stresses the mildness of the procedure. As opposed to the initial conditions discovered for the methylation of **1a′** (Scheme 2), the current protocol afforded **2a′** reproducibly and

Table 6 Scope of ZnPh(*n*-Bu) mediated alkylation

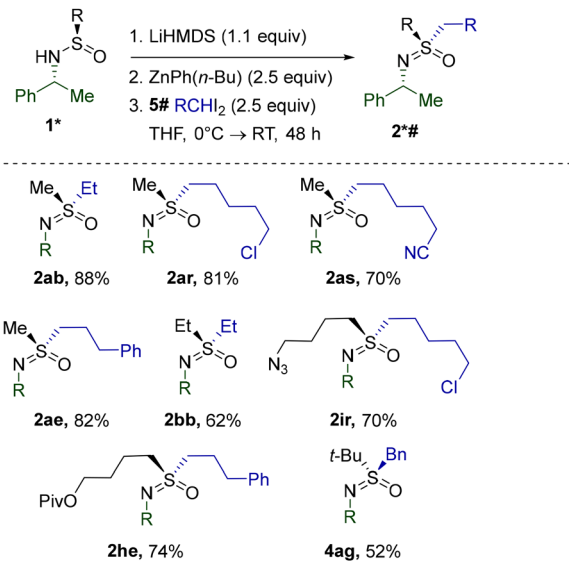
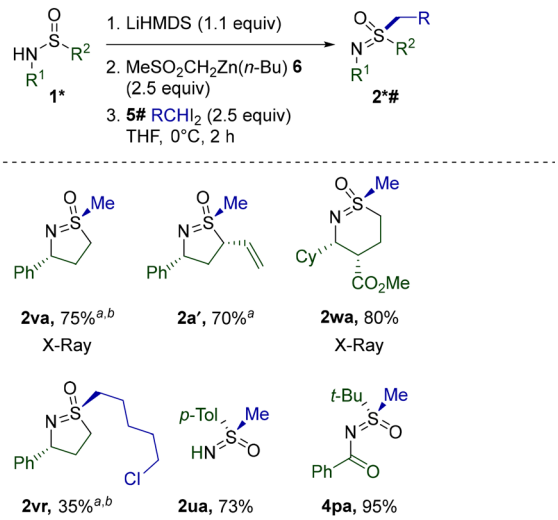


Table 7 Scope of diorganozinc **6** mediated alkylation



[a] Performed in DME. [b] Over 16 h.

with a better yield. Alkylation with a homologue of CH_2I_2 was also successfully realized in the reaction of **1v** with diiodide **5r**. Importantly, none of the currently existing synthetic methods (Scheme 1) possess the capacity for *S*-alkylation of cyclic sulfinamides. Unexpectedly, the diorganozinc **6** performed inferiorly to ZnPh(*n*-Bu) in the case of linear alkylsulfinamides (Table 6) and thus could not replace ZnPh(*n*-Bu) in this case.

Finally, methylation mediated by **6** was probed on the so far poorly reactive Davis' sulfinamide **1u** (Table 5) and *N*-acylated **3p** (Table 3). Gratifyingly, the corresponding sulfoximines **2vr** and **4pa** were obtained with much better yields. The particularly remarkable enhancement in the case of **4pa** is noteworthy.

Conclusions

In summary, we have developed a new synthesis of sulfoximines based on a hitherto unknown alkylation of sulfinamide salts with Furukawa-type carbenoids. This stereospecific transformation involves an anionic 1,2-metalate rearrangement of the corresponding zincate complex, which competes with mechanistically related unproductive carbenoid decomposition. Operating under a simple reagent system based on commercially available $ZnEt_2$, *t*-Bu-sulfinamides were found to be excellent substrates. Moreover, we have demonstrated the synthetic utility of the resulting organozinc intermediates. Coupled with mild *t*-Bu-cleavage, the transformation provides a new entry to variously *N*-substituted *S*-alkyl sulfinamides. Subsequent iterative application, on the other hand, seamlessly joins the chemistry around Ellman's auxiliary with *S*,*S*-dialkyl sulfoximines. The method may also be extended to *S*-arylated substrates, as illustrated by the use of Davis' sulfinamide derivatives. While the sulfinamide structure–reactivity relationship is still not fully understood, a solution for substrates that are resilient to alkylation under standard conditions has been successfully identified. The discovered modifications of the dialkylzinc precursor effectively suppress the unproductive carbenoid decomposition, hence enforcing the requisite alkylation. It is noteworthy that structures obtained *via* the corresponding transformation of cyclic sulfinamides are virtually inaccessible by other contemporary methods.

Data availability

Crystallographic data for **1a**, **2va**, **2wa**, **3a-Li**, and **4fa** have been deposited at the Cambridge Crystallographic Data Centre under 2374035–2374039.†

Experimental details, characterization data, DFT calculations, and NMR spectra have been included in the ESI.†

Author contributions

Conceptualization: G. J., P. A. D., and E. S.; investigation: G. J., D. M., and A. K.; supervision: P. A. D.; writing – original draft: G. J. and P. A. D.; writing – review & editing: G. J., P. A. D., and E. S.; funding acquisition – E. S. All authors have given approval for the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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