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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.

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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 gained recognition in asymmetric synthesis,² the development of insecticides3 and small-molecule drug discovery4 (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 promise⁵ in terms of favorable physicochemical and pharmacokinetic properties. cyclo-roniciclib features improved permeability,

reduced efflux and lipophilicity while displaying potency, metabolic stability and solubility comparable to those of roniciclib (Fig. 1).

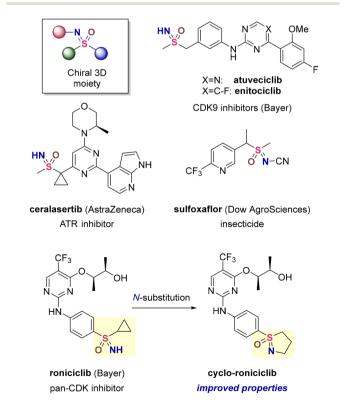


Fig. 1 Bioactive sulfoximines.

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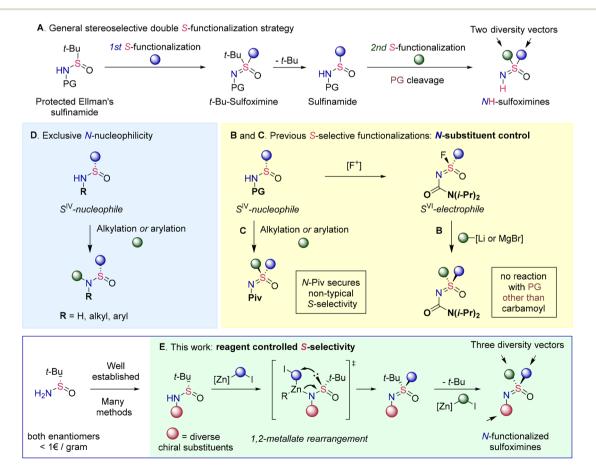
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The surge of recent applications has vigorously spurred interest in the synthetic community and a stream of novel methodologies has started to fill the previously underexplored chemical space surrounding sulfoximines. Especially, remarkable progress has been achieved in the development of the corresponding stereoselective approaches. Thus, advances in S-imidation methods have allowed the direct synthesis of sulfoximines from sulfoxides.8 Moreover, asymmetric imidation of thioethers affords enantiopure sulfimides, 66,9 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 NH-sulfoximines. The pioneering work of Jonson¹² on nucleophilic substitution at the S-atom in sulfonimidoyl derivatives has evolved13 into another class of powerful methodologies. Despite all these advances, most methodologies focus primarily on the synthesis of NH-sulfoximines, completely neglecting possible substitution at the N-atom.

Likewise, only NH-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-Bucleavage (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 carbamovl 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 conditions²⁰ using simplified tertbutyl sulfinamide 3a as a model substrate (Table 1). When

Scheme 2 Serendipitous discovery.

Table 1 Selected experiments for the optimization of reaction conditions

<u>t</u> -Bu HN∑S∑O	base (1.1 equiv) alkyl metal (x equiv) iodide (x equiv)	t-Bu Me N≤S⇒O	<u>t</u> -Bu Me ∑N S ∑O	
Ph Me	Solvent, 0°C, 30 min then aqueous workup	Ph Me 4aa	Ph Me Me-3a	

	Base	Carbenoid formation		Yield ^b , %			
Entry		Metal alkyl	Iodide	x	3a	4aa	Ме-3а
1	_	ZnEt ₂	CH_2I_2	2.5	100	_	
2	LiHMDS	$ZnEt_2$	$CH_2I_2^c$	2.5	3	86	_
3	<i>n</i> -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 $^{\circ}$ C and then sequentially treated with an alkyl metal and alkyl iodide. b ¹H NMR yield was measured against mesitylene as an internal standard. 6 No reaction with CH₂Br₂ instead of CH₂I₂ (see ref. 20).

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 ZnEt₂ (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).

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 CH2I2. However, the treatment of Li-3a with ZnEt2 results in the reversible formation of a 1:1 zincate complex Zn-3a.

Due to the known²¹ dynamic nature of ZnEt₂ 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 CH₂I₂ 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 1,2metalate rearrangement or engage in rapid complexation with Li-3a similarly to ZnEt₂ (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 mode²⁴ 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 CH2I2; 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

A LiN
$$\stackrel{t\text{-Bu}}{\overset{t}{\circ}}$$
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Scheme 3 NMR experiment and mechanistic hypothesis

ΔG, kcal/mol (M06-2X/Def2TZVP//M06-2X/Def2SV PCM_{THF})

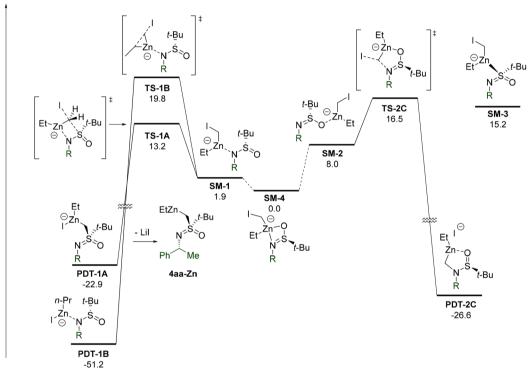


Fig. 2 The most kinetically favored transitions of the EtZnCH₂I-Li-3a complex.

(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 Etmigration 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 CH₂I₂ (5a) was confirmed in a scaled-up synthesis of 4aa. Gratifyingly, non-functionalized CH2I2 homologues 5b-g also readily engaged in the reaction. Steric crowding around the gemdiiodo 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 50-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

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^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

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 30 and N-acylated 3p displayed a noticeable drop in reactivity, whereas a number of sulfinamides²⁸ 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 known²⁹ 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 CH2I2 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 pro-

Table 4 Deprotection of tert-butyl sulfinamides

ductive 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.

Our focus then shifted to S-alkylation with other substituted diiodides. Using the ethylation of sulfinamide 1a as a model reaction, we evaluated³⁰ the efficacy of several diorganozinc reagents. While ZnEt2 still delivered the ethylsulfoximine

^a Performed at −30 °C for 16 h. ^b LiHMDS (2.2 equiv.) and ZnEt₂/CH₂I₂ (2.5 equiv.).

Table 5 Methylation of non-t-Bu-sulfinamides

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 nonmigratory³² dimethylsulfone fragment in diorganozine 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

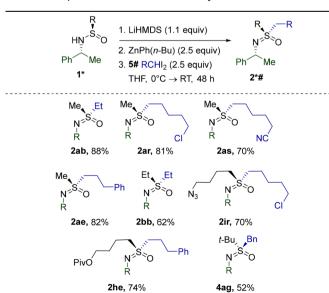


Table 7 Scope of diorganozinc 6 mediated alkylation

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

^a Performed in DME. ^b Over 16 h.

with a better yield. Alkylation with a homologue of CH₂I₂ 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 ZnEt2, 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,Sdialkyl 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.

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