Synthesis and Functionalization of Sulfoximine-Bicyclo[1.1.0]butanes: Functionalizable, Tuneable and Cysteine-Selective Chiral Warheads

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Abstract: Electrophilic covalent warheads with appropriate reactivity and selectivity are crucial to the investigation of protein function and the discovery of therapeutics. Here we report the synthesis of sulfoximine bicyclo[1.1.0]butanes (BCBs) as novel thiol reactive chiral warheads, achieved in one-pot from methylsulfoximines. Unusually the warhead can then be derivatized, keeping the BCB intact, over 3 vectors: i) sulfoximine N-modification instills a broad range of strain-release reactivity; ii) sp^2-cross-coupling reactions on aryl-BCB-sulfoximines allows direct diversification, and iii) functionalization of the BCB motif itself is achieved by metalation and trapping with electrophiles. The BCB sulfoximines are shown to react selectively with cysteine including in a protein model (CDK2) under biocompatible conditions. Preliminary data indicate suitability for chemoproteomic applications, and enantioselective cysteine-labelling. The reactivity of sulfoximine BCBs with electron withdrawing groups on nitrogen is comparable to acrylamides with low to moderate reactivity.

Selective protein modification is essential in the investigation of the function of proteins and in the discovery of therapeutics.[1] Electrophilic small molecules provide opportunities to form selective covalent linkages with nucleophilic amino acids with the reactivity of the warhead critical to the intended application.[2] For targeted therapeutics, sufficient warhead reactivity is required to effectively modify the target residue, whereas over-reactivity can be associated with off-target effects and rapid metabolism. Acrylamides have been successfully incorporated into FDA approved drugs such as Ibrutinib (Fig 1).[3] Chemical probes and screening libraries necessarily encompass different ranges of intrinsic reactivity.[2] Moreover, the structure of the warhead itself can afford protein interactions and influence target specificity and proteome coverage by providing alternative geometries and selectivities.[2,4] Recently, Cravatt demonstrated the application of enantiomeric pair probes to achieve differential interaction between small molecules and proteins in cells.[5] This poses interesting potential for intrinsically chiral warheads, which has yet to be realised. The approach of 'electrophile first' proteomic screening, ensures that ligandable residues (often cysteine) are identified, from which targeted affinity elements can then be developed to ensure selective protein labelling. However, there are few synthetic strategies available to directly modify reactive warheads to grow a hit compound. Indeed, synthetic manipulation of covalent fragments for late-stage modification is extremely challenging due to the nature of the reactive groups. Installation of the warhead in the last step in a sequence is often required, limiting the rapid production of analogues to determine structure-activity relationships. Thus, there is considerable demand for new warheads which can offer both tuneable reactivity and synthetic tractability to enable fragment growth or late-stage diversification.

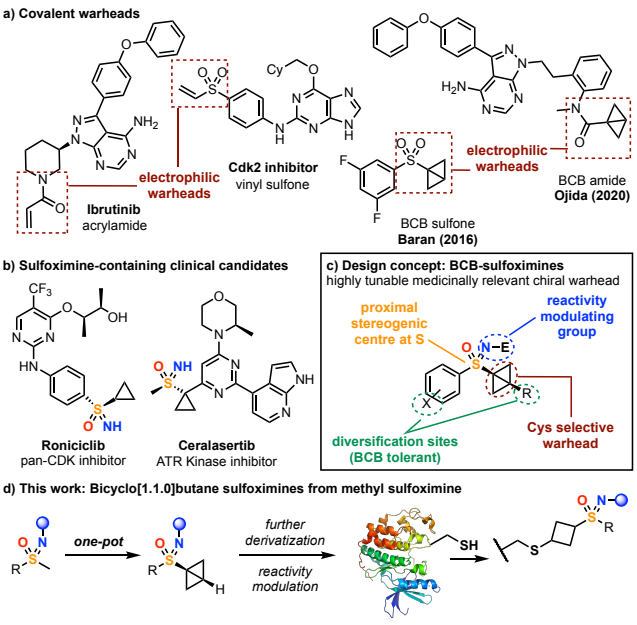


Figure 1. Covalent warheads and sulfoximines.

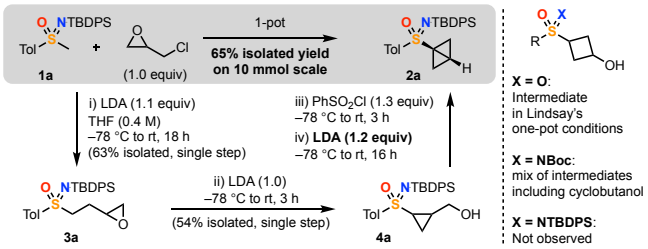
In 2016 Baran reported bicyclo[1.1.0]butane (BCB) aryl sulfones, which displayed selective reactions with cysteine residues in

peptides.[6] Recently, Ojida reported BCB amide derivatives as cysteine-directed electrophiles for covalent inhibitor development (Fig 1a).[7] In parallel, the strain release reactivity of BCBs has seen significant development to form cyclobutanes, through the addition of anions,[8] radicals,[9] and electrophiles,[10] and to form larger ring sizes.[11,12] Among synthetic developments,[6,12,13] Lindsay recently developed a one-pot process to generate BCB sulfones from methyl sulfones.[14] However, there remain few examples of functionalization of intact BCB derivatives: Anderson reported metallation for bridgehead and bridge functionalization on specific sterically hindered amide-BCB derivatives.[15]

We envisaged that the novel combination of BCBs and sulfoximines would present attractive, tuneable and chiral 3-D warheads with an increased range of electrophilicity that could be more directly controlled with potential for rapid diversification. Sulfoximines have emerged in recent years in clinical candidates as attractive chiral aza-analogues of sulfones or sulfonamides (Fig 1b).[16,17] Specifically, the sulfoximine nitrogen atom introduces a proximal chiral center and additional vector to allow broader exploration of 3-D chemical space and offers the potential to tune the chemical features.[18]

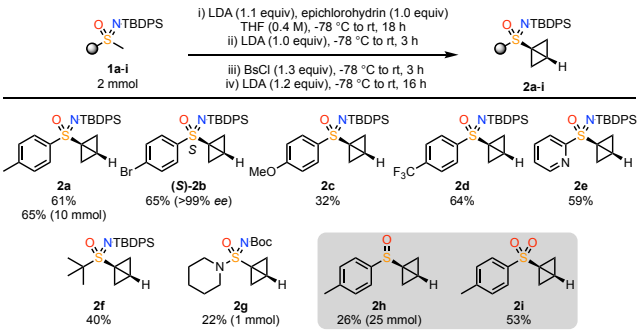
Here we report the efficient one-pot synthesis of chiral BCB-sulfoximines (Fig 1c and 1d). Further derivatization is demonstrated in the presence of the BCB warhead through *N*- and *C*-vectors including cross-coupling reactions and bridgehead deprotonation. The additional tuneable *N*-vector allows considerably broader strain-release reactivity than BCB sulfones. Moreover, we demonstrate cysteine-selective labelling in whole proteins, and potential for selective labelling in cell lysates.

We first investigated the preparation of sulfoximine-BCBs aiming for a 1-pot process. Initial studies used readily prepared *N*-Boc and *N*-silyl-methylsulfoximine derivatives.[19] Conditions reported by Lindsay with methyl sulfones, using *n*-Bu_2Mg as base for reaction with epichlorohydrin, were ineffective for both sulfoximine derivatives. *N*-Boc-sulfoximines also performed poorly using Li bases, giving incomplete conversion of the sulfoximine and mixtures of cyclopropanol and cyclobutanol products.[20] The use of *N*-TBDPS-sulfoximine **1a** allowed a well-behaved deprotonation and reaction with epichlorohydrin (to form **3a**, Scheme 1).[20] Optimization of the base dosing showed that 3 additions of LDA, a total of 3.3 equivalents for 3 deprotonation steps, was most suitable to achieve the conversion of **1a** to BCB sulfoximine **2a** via cyclopropane **4a** (see SI for further details). The individual steps were optimized, and a subsequent one-pot process formed **2a** in a 75% yield (by ^{1}H NMR) and a 65% isolated yield on a 10 mmol scale.



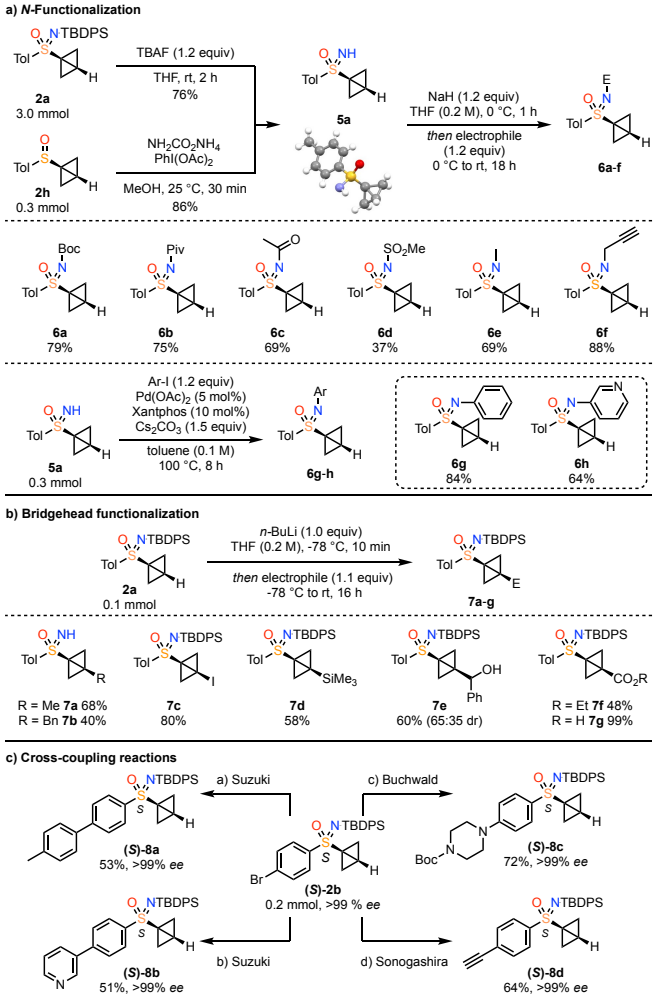
Scheme 1. One pot formation of BCB sulfoximines.

A series of BCB-sulfoximines and related derivatives was then prepared on a 2 mmol scale (Scheme 2). Enantioenriched BCB-sulfoximine **(*S*)-2b** gave complete retention of the stereochemical information of the substrate.[21] High yields of BCB-sulfoximines were achieved with arenes bearing electron-withdrawing aryl substituents though electron rich 4-methoxyphenyl derivative was also tolerated (**2c** and **2d**), further indicating the significance of the α-proton p*Ka* on the success of the BCB formation. 2-Pyridyl derivative **2e** similarly gave a good yield. Other BCB derivatives were prepared using the developed reaction conditions, including *t*Bu-BCB-sulfoximine **2f** and sulfonimidamide-BCB **2g**. Previously reported sulfoxide and sulfone-BCB derivatives **2h** and **2i** were also successfully prepared through this 1-pot process.[6,9a]



Scheme 2. Substrate scope of sulfur-containing BCB compounds.

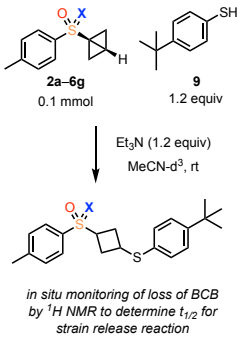
The difficult functionalization of fragments in the presence of covalent warheads limits synthetic flexibility and late-stage diversification and slows design-make-test cycles. We considered that the N-silyl BCB-sulfoximine may facilitate further diversification. Pleasingly, the TBDPS group could be readily removed from **2a** with TBAF to form BCB-NH-sulfoximine **5a** in high yield and maintaining the BCB integrity (Scheme 3). The same NH sulfoximine **5a** was also prepared by NH transfer to BCB-sulfoxide **2h** using diacetoxyiodobenzene and ammonium carbamate.[19a] The NH sulfoximine was characterized by X-ray crystallography indicating a sterically minimized conformation with the BCB ring sitting between sulfoximine nitrogen and oxygen atoms. The bridgehead C-C bond length is 1.498(3) Å, similar to reported bond lengths in other BCB derivatives.[22] Deprotonating the sulfoximine-NH with NaH followed by trapping with various electrophiles enabled a variety of N-functionalization with Boc, Piv, acetyl and mesyl groups (**6a**–**6d**), as well as alkylation with methyl and propargyl groups (**6e**–**6f**), the latter installing a click handle. Moreover, BCB-NH-sulfoximine **5a** underwent palladium-catalyzed *N*-arylation to afford *N*-aryl and *N*-heteroaryl BCB sulfoximines in good yields (**6g**–**6h**), presenting a viable route to install more complex aryl halides and significantly broadening the types of BCB sulfoximines that could be accessed.



Scheme 3. Scope of N-functionalization, bridgehead functionalization and C-substituent functionalization.

We envisaged that the sulfoximine motif may stabilize lithiated derivatives for bridgehead functionalization by coordination and steric protection. Indeed, treating TBDPS-protected BCB sulfoximine with *n*-BuLi led to successful bridgehead lithiation and functionalization with a range of electrophiles. Methyl (**7a**, MeI) and benzyl (**7b**, BnBr) BCB sulfoximines were isolated in good yields after in situ TBDPS deprotection. The lithiated BCB also reacted with I_2, TMSCl, benzaldehyde and ethyl chloroformate to afford the corresponding products **7c**–**7f**. Trapping the lithiated intermediate with carbon dioxide generated carboxylic acid **7g** directly in excellent yield, providing a handle for potential further diversification and reactivity modification. Using enantioenriched *p*-bromophenyl BCB sulfoximine **(*S*)-2b** tolyl and pyridyl substituents were successfully installed by palladium-catalyzed Suzuki-Miyaura cross-coupling, affording **(*S*)-8a** and **(*S*)-8b** in moderate yields and retention of *ee*. Buchwald amination conditions were applied using *N*-Boc piperazine to generate the aniline product **(*S*)-8c**. Sonogashira coupling followed by deprotection gave alkyne **(*S*)-8d**. The excellent tolerance of the BCB motif itself under basic conditions at elevated temperatures is notable.

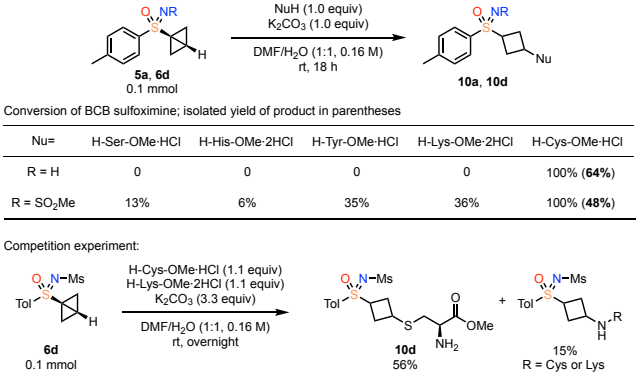
The potential to control the strain-release reactivity of BCB sulfoximines with different N-groups was first investigated using 4-*tert*-butylthiophenol as the nucleophile in the presence of triethylamine in MeCN.[23] The consumption of the BCB substrates was monitored by ^{1}H NMR with calculation of the half-life using the predicted curve of best fit. The more electron withdrawing N-substituents gave faster reactions with $t_{1/2}$ spanning from 460 min to <3 min. The strain-release reactivity was correlated to the ^{13}C NMR chemical shift of the BCB terminal bridgehead position to provide a predictor for strain-release reactivity (Figure 2).[24] By comparison, Baran's *p*-tolyl substituted BCB sulfone **2i** had 13-minute half-life (^{13}C NMR δ 12.4 ppm), which demonstrated good agreement with the correlation. BCB-sulfoximines with adjustable *N*-functionality provided a tuneable and a much broader range of strain-release reactivity and without reliance on modification of the arene.[25]



Entry	X		$t_{1/2}$ (min)	^{13}C δ (ppm)
1	NTBDPS	**2a**	**460**	11.2
2	NMe	**6e**	**57**	11.9
3	NH	**5a**	**52**	12.1
4	O	**2i**	**13**	12.4
5	NPh	**6g**	**4**	12.9
6	NBoc	**6a**	**< 3**	13.8
7	NPiv	**6b**	**< 3**	14.0
8	NAc	**6c**	**< 3**	14.2
9	NMs	**6d**	**< 3**	15.6

Figure 2. Strain release reactivity with different nitrogen protecting groups.

We next examined the warhead reactivity against a panel of amino acid derivatives (Ser, His, Tyr, Lys and Cys) in aqueous conditions (Scheme 4). NH sulfoximine **5a** gave complete recovery of the starting material for all except for cysteine which showed complete conversion (64% isolated yield). When switching to the more reactive N-mesyl BCB-sulfoximine **6d** low consumption of the BCB substrate was observed after 18 h with several amino acid nucleophiles. On the other hand, the reaction with cysteine gave complete conversion. A competition experiment reacted mesyl-protected BCB sulfoximine **6d** with cysteine and lysine methyl esters in a 1:1 ratio. The thiol nucleophile outcompeted the three NH_2 sites (56% vs 15% yield by ^{1}H NMR).



Scheme 4. Strain-release reactions under aqueous conditions and competition experiment.

The rates of reaction of four representative BCB compounds to conjugation with glutathione were established using a qIT (quantitative irreversible tethering) assay over a range of concentrations and benchmarked against that of acrylamides (Figure 3).[26] BCB-sulfoximines bearing electron-withdrawing groups demonstrated intrinsic reactivities (**6d, 6e**, **6i**, $t_{1/2}$ (GSH) = 1.2–13 h), comparable to that of a moderately reactive acrylamide ($t_{1/2}$ (GSH) = 9.4 h).[27,28] This moderate electrophilicity positions BCB-sulfoximines within a promising range for biological applications.

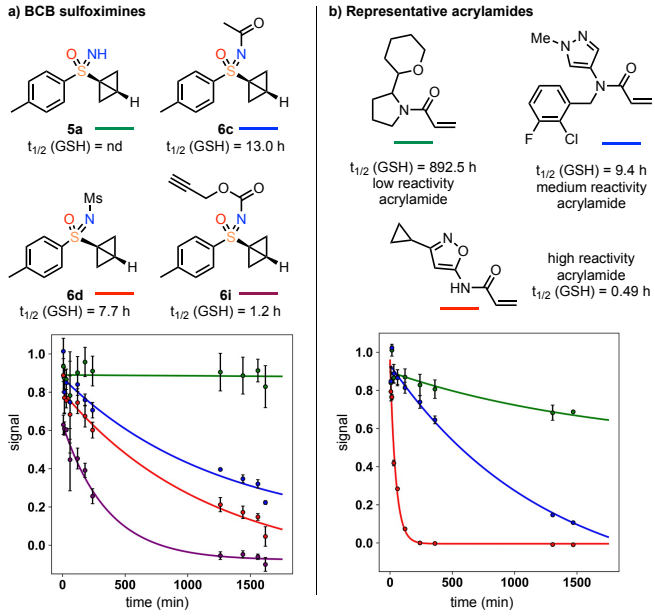


Figure 3. Comparison of the reaction rate constants for the reaction of GSH (5 μM) reaction with a) BCB-sulfoximines (500 μM), and b) a representative selection of acrylamides (500 μM), demonstrating the range of reactivity.

We next examined whether the BCB-sulfoximines would label proteins in a cysteine-selective manner under biocompatible conditions. The GSH rate data was used to estimate appropriate BCB concentrations to apply in protein models over a 24 h reaction period. A series of BCB-sulfoximines was then reacted with recombinantly expressed CDK2 (cyclin-dependent kinase 2) possessing a single surface cysteine C177 (CDK2 WT), and its Cys-deficient mutant CDK2 C177A as a model system to confirm reactivity and Cys selectivity of the compounds (Figure 4a).[26] CDK2 WT adducts with the N-acetyl (**6c**), and N-mesyl BCBs (**6d**) were observed in high percentage conversions.[29] CDK2 C177A did not react with any of the BCB sulfoximines tested nor with Cys-selective electrophile iodoacetamide control (Fig S15-S22). This is notably different reactivity to that reported for a targeted vinyl sulfone CDK2 inhibitor (see Figure 1a) which displayed selectivity for a reactive lysine residue.[3a] Treatment with the less reactive NH, NMe and NPh sulfoximines resulted in no observed reactivity with the protein. We prepared BCB sulfoximine **6i**[30] containing a propargyl carbamate to model a fully functionalized probe, exploiting the N-vector. This displayed a useful level of intrinsic reactivity with CDK2 with 50% conversion in a 24 h period to the mono-labelled protein and no reaction with CDK2 C177A (Figure 4b).

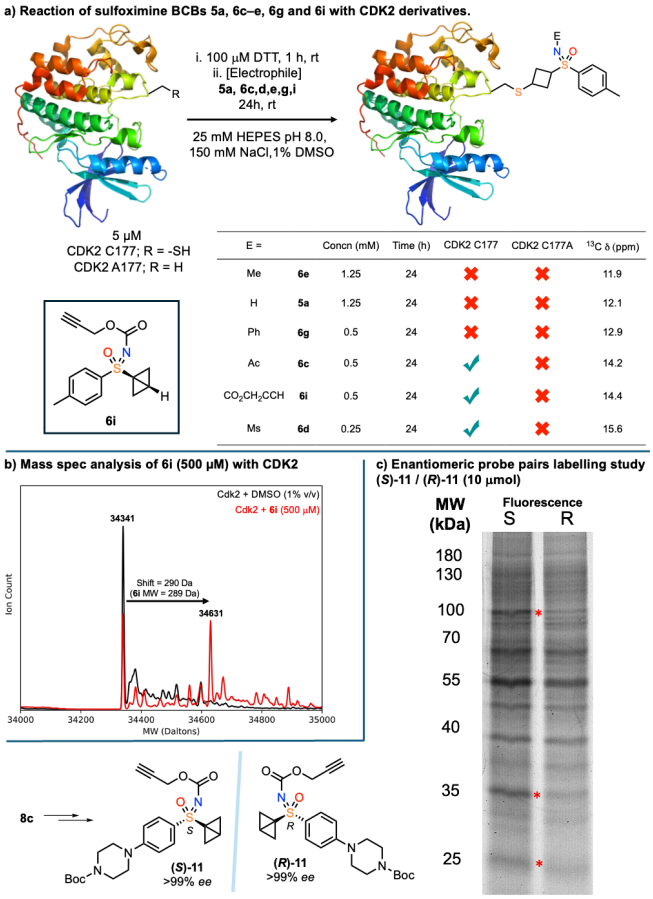


Figure 4. Reaction of sulfoximine BCBs with CDK2 derivatives (a,b) and whole cell lysates (c).

Next, we used gel-based chemoproteomic activity-based protein profiling (ABPP) methods to assess the proteome-selectivity for subset of BCB-sulfoximine probes. Covalent

warhead selectivity is ideally governed by non-covalent interactions and thus electrophiles which demonstrate differences in labelling selectivity when appended to varied scaffolds are promising for use within covalent ligand discovery. Alkyne-functionalised BCB-sulfoximine probes were incubated with HEK293 cell lysates (100 μM, 3h), conjugated to TAMRA-azide using copper-catalyzed azide alkyne cycloaddition (CuAAC) chemistry, and fluorescent bands visualized via gel scanning (See SI for full details). Pleasingly, in this preliminary study, BCB-sulfoximines with variation in N-functionality (*N*-propargyl or *N*-propargyl carbamate) and in arene substitution labelled different proteins (See Fig S21) indicating that proteome selectivity can be manipulated. Finally, we envisaged that the BCB-sulfoximines would provide promising warheads for use within enantioprobe pair screening studies due to the central stereogenic center and the ability to access analogues without the need for downstream warhead installation. Cravatt has demonstrated the value of using enantioprobe pairs within ABPP experiments, as factors which distort proteome-selectivity results are controlled for, allowing high confidence in the identification of ligandable cysteines.[5] In a preliminary study, enantioprobe pair **(*S*)-11** and **(*R*)-11** displayed enantioselective protein labelling when incubated with HEK 293 cell lysates (10 μM, 3 h), as visualized by clear differences in the fluorescence intensity of select bands (Figure 4c).

In conclusion, we report the efficient one-pot synthesis of a series of BCB-sulfoximines and diversification with the intact 3-D warhead structure. The modification of the N-substituent provided tuneable strain-release reactivity across a broad reactivity range, which will allow the reactivity to be tailored to applications. BCB-bridgehead functionalization and aryl cross-coupling reactions will allow rapid diversification and fragment growth, and also facilitate their incorporation into screening collections. BCB sulfoximines demonstrated selective strain-release reactivity towards cysteine nucleophiles under biocompatible conditions. N-Acyl, N-sulfonyl and N-carbamoyl sulfoximine BCBs possess reactivity sufficient for a range of potential uses. We demonstrate the potential for enantioselective labelling in cell lysates. We anticipate these reagents will add another opportunity to screen warheads in an electrophile first strategy, and for screening of enantiopair probes. Tuning to lower reactivity may find application in targeted inhibitors. Further studies to exploit these reactivity profiles are underway in our labs.

Supporting Information

The authors have cited additional references within the Supporting Information (Ref. [31-45])

Acknowledgements

For financial support, we gratefully acknowledge The Royal Society [University Research Fellowship URF\R\201019 (to J.A.B.)], Institute of Chemical Biology (Imperial College London, UK), the UK Engineering and Physical Sciences Research Council (EP/S023518/1; EP/Y007859/1), Sarcoma UK (SUK06.2019).

Keywords: sulfoximine • strained ring • bicyclobutane • protein labelling • warheads

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[25] Baran reported a range of ^{13}C NMR shifts on varying the aryl group from 3,5-difluorophenyl 13.7 ppm to 4-methoxyphenyl substituent 12.5 ppm [tolyl 12.6 ppm], and changing the aryl group of the sulfone afforded some limited variation in electrophilicity of the BCB (See ref 6).

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[27] G. B. Craven, D. P. Affron, T. Kösel, T. L. M. Wong, Z. H. Jukes, C.-T. Liu, R. M. L. Morgan, A. Armstrong, D. J. Mann, *ChemBioChem* **2020**, *21*, 3417.

[28] Acrylamide reactivity is known to vary over a wide range, M. E. Flanagan, J. A. Abramite, D. P. Anderson, A. Aulabaugh, U. P. Dahal, A. M. Gilbert, C. Li, J. Montgomery, S. R. Oppenheimer, T. Ryder, B. P. Schuff, D. P. Uccello, G. S. Walker, Y. Wu, M. F. Brown, J. M. Chen, M. M. Hayward, M. C. Noe, R. S. Obach, L. Philippe, V. Shanmugasundaram, M. J . Shapiro, J. Starr, J. Stroh, Y. Che, *J. Med. Chem.* **2014**, *57*, 10072. Here a 174-fold difference in reactivity was noted between the most reactive (**S3**, k_{obs} = 0.0329 min^{-1}) and least reactive (**S1**, k_{obs} = 0.000189 min^{-1}) acrylamides. Whereas the reactivity of acrylamides is affected by the amide group, S(VI) derivatives appear relatively little affected by changes to the C-substituent, but considerably influenced by the N-R group.

[29] Unpredicted minor adducts were also observed on some of the CDK2 C177 mass spectra with some of these compounds. For further discussion and full MS data see SI pages S23–S45).

[30] Prepared from **2h**: Z. Zhong, J. Chesti, A. Armstrong, J. A. Bull, *J. Org. Chem.* **2022**, *87*, 16115.

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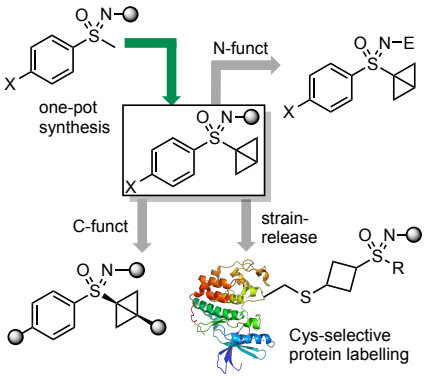

Sulfoximine substituted bicyclo[1.1.0]butanes are prepared in one-pot and then diversified through 3 vectors. N-Functionalization allows controlled variation in the electrophilicity of the BCB in strain release processes including in protein labelling under biocompatible conditions, and the proximal stereocenter allows stereoselective protein labelling.

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