

RESEARCH ARTICLE

View Article Online
View Journal | View IssueCite this: *Org. Chem. Front.*, 2025, **12**, 6556

Structurally divergent reactivity of 2,2-disubstituted azetidines – mechanistic insights and stereochemical implications of amide coupling and ring expansion to 5,6-dihydro-4*H*-1,3-oxazines

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Azetidines have gained traction in drug discovery for their ability to introduce conformational constraint and modulate physicochemical properties. Strategies that enable their selective functionalization or controlled expansion into more complex scaffolds provide opportunities for molecular diversification to rapidly access new chemical space. Subjecting 2,2-disubstituted azetidines to amide coupling with carboxylic acids is found to effect either *N*-acylation or ring expansion to spiro and 6,6-disubstituted 5,6-dihydro-4*H*-1,3-oxazine, dependent on reaction conditions. A diverse range of topologically interesting heterocycles, which hold significant potential for pharmaceutical screening, have been prepared using this divergent reaction manifold. A mechanistic framework, supported by additive screening and trapping experiments, is presented to account for the ring expansion and racemization that accompanies these transformations when the substrate allows formation of a ring-opened azafulvenium intermediate.

Received 22nd May 2025,
Accepted 26th August 2025
DOI: 10.1039/d5qo00804b

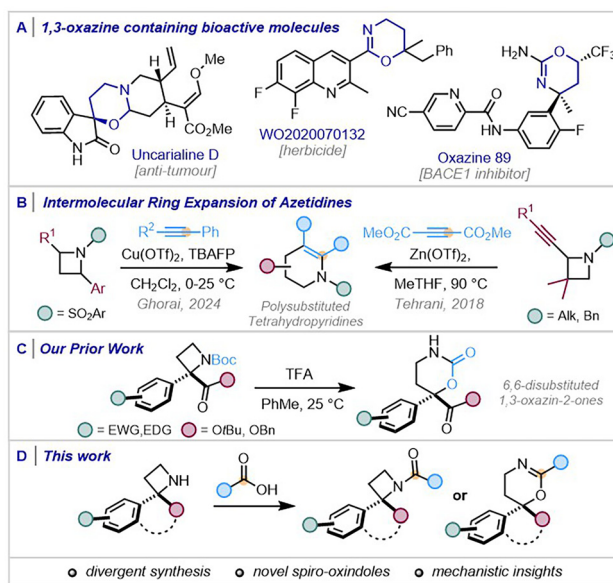
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Introduction

The ring-opening and ring-expansion of small-ring aza-heterocycles driven by relief of strain is a powerful strategy for generating new acyclic and cyclic architectures.¹ Such transformations can allow for the generation of complex molecular structures in a single step. While aziridines have been extensively studied in this context,² their four-membered counterparts, azetidines, are relatively underexplored.^{3,4} This disparity likely reflects the difficulty in synthesizing azetidines and the relatively higher energy barrier to achieve ring-opening *via* σ -C–N bond cleavage, particularly in non-activated (*i.e.*, N–H and *N*-alkyl) systems.⁵ These derivatives exhibit remarkable stability despite bearing similar ring strain energies to aziridines (105 vs. 114 kJ mol⁻¹).⁶

Recent advances have addressed challenges associated with the accessibility of azetidines and opened new avenues to harness their unique reactivity.^{7–9} For instance, Ghorai has disclosed regioselective Cu-catalysed ring expansion of activated *N*-sulfonylazetidines with alkynes (Scheme 1B).^{9b} Similarly,

Tehrani has shown non-activated azetidines undergo Zn-catalysed cycloaddition with DMAD, albeit requiring 2-alkynyl substitution.^{9c} Ring expansion of azetidines using a pendant



Scheme 1 Context of the work reported here.

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internal nucleophile constitutes an alternate strategy.¹⁰ Indeed, simple *N*-acylazetidines are known to undergo acid-^{10a-c} and base-mediated^{10d,e} ring expansion to isomeric dihydrooxazine products. Additionally, we previously demonstrated that *N*-Boc-2,2-disubstituted azetidines undergo TFA-mediated, irreversible, intramolecular ring expansion to form 1,3-oxazin-2-ones (Scheme 1C).¹⁰ⁱ

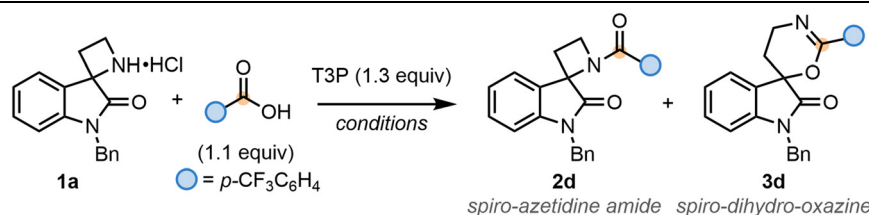
Building on these findings, we sought to explore whether σ -C–N cleavage of 2,2-disubstituted azetidines could be orchestrated in a potentially reversible fashion to generate zwitterionic intermediates capable of *intermolecular* trapping by nucleophiles/dipolarophiles. Herein, we disclose divergent reactivity of *N*-unsubstituted azetidines with carboxylic acids, wherein either *N*-acylation or ring expansion to spiro- and 6,6-disubstituted dihydro-1,3-oxazines occurs, dependent on the reaction conditions. These latter ring-systems are widely found in agrochemicals such as herbicides,¹¹ and medicinal leads *e.g.*, in aspartyl β -secretase (BACE1) inhibitor ‘oxazine 89’, which is a therapeutic target for Alzheimer’s disease,¹² and spiro-oxindole natural product uncarialine D, which exhibits promise as an anti-tumour agent¹³ (Scheme 1A).

The substrate for our initial investigations was *N*-H spiro-oxindole azetidine hydrochloride **1a** (Table 1). This compound was prepared in quantitative yield from its *N*-Boc counterpart¹³ upon treatment with 4 N HCl in dioxane. No ring expansion to the spiro-1,3-oxazin-2-one was observed under these conditions, consistent with our previous findings.¹⁴ Subsequent attempted amide coupling reactions of **1a** with *p*-CF₃ benzoic acid using EDC·HCl and Et₃N in CH₂Cl₂ yielded two products:

the expected spiro-azetidine amide and the ring expanded spiro dihydro-1,3-oxazine in 4 : 1 ratio (entry 1). A similar ratio albeit with improved total yield was obtained by switching to T3P as coupling agent (entry 2). The formation of the latter product was attributed to σ -C–N bond cleavage (aided by electron donation from the oxindole nitrogen), amide N-to-O tautomerism and subsequent 6-*exo-trig* spirocyclization of the amide oxygen onto the putative azafulvenium intermediate (*vide infra*, Scheme 4). This mechanism is consistent with prior reports of azetidine to dihydrooxazine ring expansions.^{10a-c}

Intrigued, we sought to delineate conditions to selectively furnish either the spiro-azetidine amide **2d** or the spiro dihydro-1,3-oxazine **3d** (Table 1). Initial screening revealed a pronounced influence of the solvent on product distribution. Using THF favoured the formation of **2d** (18 : 1 ratio **2d** : **3d**, entry 3) in 71% yield. By contrast, MeCN shifted the selectivity (2 : 1 ratio **2d** : **3d**, entry 4). Further refinement of the reaction parameters, including an increase in the base equivalents, a reduction in the initial reaction temperature, and an extension of the reaction duration from 4 to 6 h, yielded the spiro-azetidine amide **2d** with high selectivity [29 : 1 ratio (**2d** : **3d**)] and an 88% yield (entry 8). To enhance the formation of the spiro dihydro-1,3-oxazine **3d**, the reaction was conducted with 5 equiv. DBU (*cf.* 3 equiv. Et₃N) at elevated temperature over an extended reaction time of 18 h which gave **3d** with good selectivity (1 : 11 ratio **2d** : **3d**) and in 62% yield (entry 12). The protonated base may aid the azetidine ring expansion by H-bond-interactions during the tautomerisation/proton-trans-

Table 1 Optimization of amide coupling and ring expansion



Entry ^a	Base (x equiv.)	Solvent	Temp. (°C)	Time (h)	2d ^b , (%)	3d ^b , (%)	2d : 3d
1 ^c	Et ₃ N (2.5 equiv.)	CH ₂ Cl ₂	25	4	58	15	4 : 1
2	Et ₃ N (2.5 equiv.)	CH ₂ Cl ₂	25	4	64	22	3 : 1
3	Et ₃ N (2.5 equiv.)	DCE	25	4	69	17	4 : 1
4	Et ₃ N (2.5 equiv.)	THF	25	4	71	4	18 : 1
5	Et ₃ N (2.5 equiv.)	MeCN	25	4	55	28	2 : 1
6	Et ₃ N (2.5 equiv.)	EtOAc	25	4	41	3	14 : 1
Change from entry 4 – spiro-azetidine amide optimisation							
7	Et ₃ N (3 equiv.)	THF	25	4	82	4	21 : 1
8	Et ₃ N (3 equiv.)	THF	0–25	6	88 (77) ^d	3	29 : 1
Change from entry 5 – spiro-dihydro-oxazine optimisation							
9	Et ₃ N (5 equiv.)	MeCN	25	4	44	31	1.4 : 1
10	DBU (5 equiv.)	MeCN	25	4	46	36	1.3 : 1
11	Et ₃ N (5 equiv.)	MeCN	40	18	18	56	1 : 3
12	DBU (5 equiv.)	MeCN	40	18	6	62 (54) ^d	1 : 11

^a Reactions were carried out on 0.017 mmol. ^b Yields are determined by *in situ* ¹⁹F NMR spectroscopy with respect to PhCF₃ as an internal standard. ^c Using EDC·HCl. ^d Isolated yield on 0.1 mmol scale.



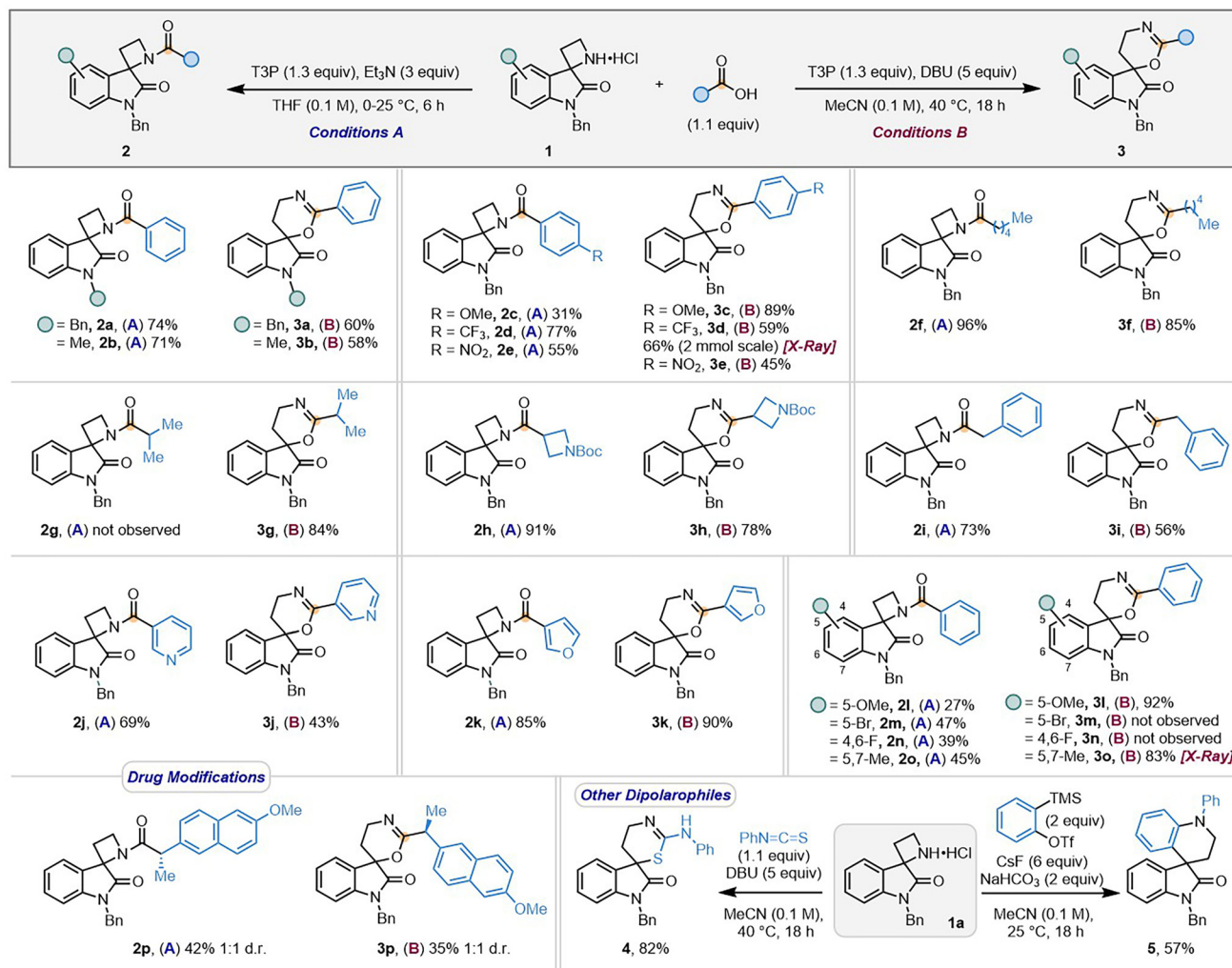
fer. A time-course study confirmed the rapid formation of the spiro-azetidine amide as the kinetic product. Over time, under conditions conducive to ring expansion, this intermediate underwent conversion to the thermodynamically favoured spiro dihydro-1,3-oxazine product (see SI).

With optimized conditions established for each product, the scope of this divergent reactivity was explored. An array of carboxylic acids was evaluated which in most cases could be selectively converted to both product classes (Scheme 2). Coupling with benzoic acid afforded both spiro-azetidine amide and spiro dihydro-1,3-oxazine products in good yields (**2a**, **3a**). Switching the *N*-protecting group from benzyl to methyl on the spiro-oxindole also delivered both **2b** and **3b**, the latter of which has previously been isolated by Muñiz and co-workers.¹⁵ Aryl electronics influenced the product distribution with substituted benzoic acids. Electron-rich *p*-anisic acid gave a higher yield of spiro dihydro-1,3-oxazine **3c**,

whereas electron-deficient aryl acids *p*-trifluoromethyl and *p*-nitrobenzoic acids, afforded both spiro-azetidine amides **2d**, **2e** and spiro dihydro-1,3-oxazines **3d**, **3e** in good yields.

The reactivity of alkyl carboxylic acids was influenced by both steric and electronic effects. Hexanoic acid provided products **2f** and **3f** in moderate yields whereas isobutyric acid exhibited a preference for the ring-expanded spiro dihydro-1,3-oxazine **3g**, which was isolated in 84% yield. In contrast, the use of azetidine-3-carboxylic acid delivered both spiro-azetidine amide **2h** and spiro dihydro-1,3-oxazine **3h** in good yields, suggesting that steric factors may play a role in influencing selectivity. Phenylacetic acid afforded both regioisomeric products **2i** and **3i** in 73% and 56% yields under the respective sets of conditions.

Heteroaromatic carboxylic acids coupled divergently to give pyridyl and furan-containing products (**2–3j**, **2–3k**), the former of which constitutes nicotine derivatives. The reaction scope



Scheme 2 Scope of divergent coupling of carboxylic acids with *N*-H spiro-oxindole azetidines to form spiro-azetidine amides or ring expanded products.



was further expanded by exploring substitutions on the oxindole scaffold. The introduction of a 5-methoxy substituent led to marked preference for the ring expanded spiro dihydro-1,3-oxazine **3l**. In contrast, and somewhat unexpectedly, the 5-bromo and 4,6-difluoro analogues afforded exclusively spiro-azetidine amides **2m** and **2n**. 5,7-Dimethyl substituents on the spiro-oxindole scaffold afforded both products (**2–3o**) in moderate yields. Spiro-azetidine amide **2p** and spiro dihydro-1,3-oxazine **3p** derivatives of Naproxen were obtained in comparable yields, both as 1 : 1 mixture of diastereomers. Pleasingly, other dipolarophiles proved to be compatible delivering novel spiro-thiazine oxindole **4** and *N*-aryl spiro-tetrahydroquinoline oxindole **5**.

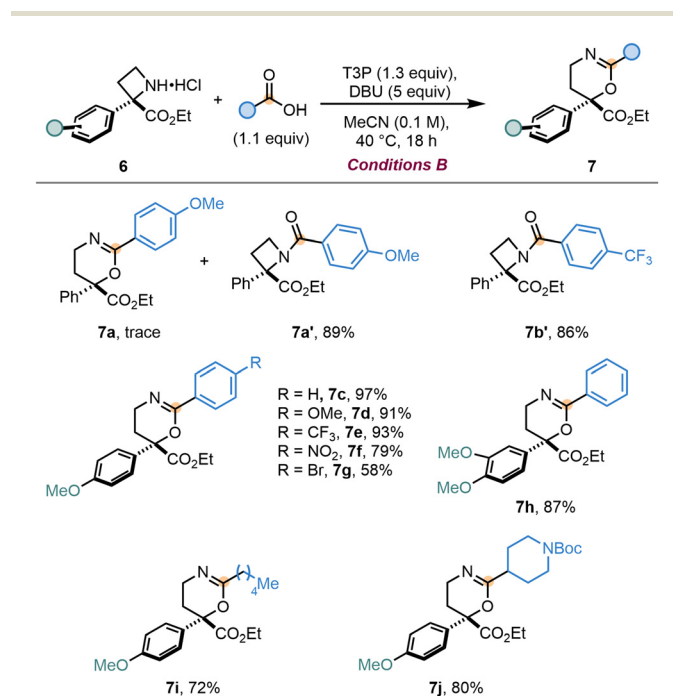
Having examined the scope with spiro-oxindole scaffolds, we sought to determine whether non-spirocyclic compounds could similarly undergo the ring-expansion process. To this end, 2,2-disubstituted azetidines were subjected to the optimized ring-expansion conditions (Scheme 3). 2-Phenyl-2-carboxylethyl-azetidine **6a** coupled with *p*-anisic acid and *p*-trifluoromethyl-benzoic acid to give azetidine amides **7a'** and **7b'** as major products. Only trace amounts of dihydro-1,3-oxazine **7a** were observed in the former case. Switching to the corresponding 2-*p*-anisyl-2-carboxylethyl azetidine **6b** allowed access to ring-expanded dihydro-1,3-oxazine products in high yields with an array of carboxylic acid coupling partners with varying electronic demands (**7c–g**). The 1,2-dimethoxy derivative **6c** reacted cleanly to afford the corresponding 6,6-disubstituted dihydro-1,3-oxazine **7h**. Furthermore, both primary and secondary alkyl carboxylic acids, exemplified by hexanoic acid and piperidine-4-carboxylic acid respectively, successfully deli-

vered the dihydro-1,3-oxazines **7i** and **7j** in excellent yields. Overall, these findings demonstrate the utility of 2,2-disubstituted azetidines as intermediates *en route* to various substituted dihydro-1,3-oxazines, which are valuable building blocks for further exploration in medicinal and materials chemistry.

During these studies, it was observed that when highly enantiomerically enriched spiro-oxindole azetidine **1a** (4 : 96 er) was reacted with *p*-trifluoromethyl-benzoic acid, both spiro-azetidine amide **2d** and spiro dihydro-1,3-oxazine **3d** were obtained with significantly eroded enantiomeric excess (40 : 60 and 45 : 55, respectively). Loss of stereochemical integrity was expected for the dihydro-1,3-oxazine **3d**,^{10c} but had not been anticipated for amide **2d** which retains the intact azetidine ring. This unexpected racemization of **2d** prompted a mechanistic investigation. Chiral HPLC analysis of the spiro-oxindole azetidine hydrochloride salt **1a** obtained by *N*-Boc deprotection with 4 N HCl in dioxane revealed negligible racemization. By contrast, attempted *N*-Boc deprotection using TFA led exclusively to the spiro-oxazinone product (76 : 24 er), consistent with our previously reported findings.¹⁴ Precipitation of the product from the reaction mixture as it progresses under the former conditions likely explains these contrasting stereochemical outcomes.

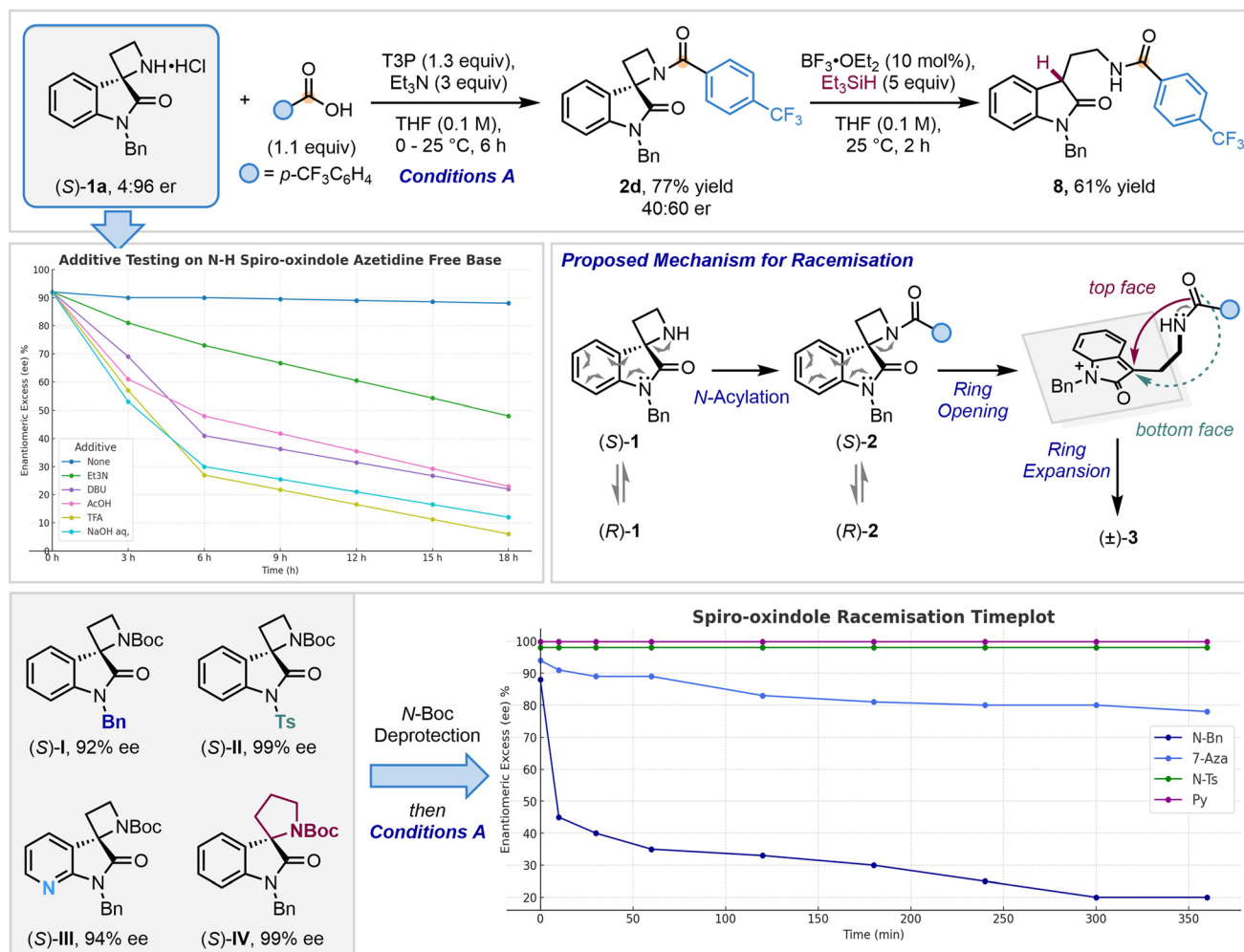
The spiro-oxindole azetidine HCl salt **1a** was then exposed to acids and bases in solution to assess racemization. Over 18 h, most conditions led to significant loss of enantiopurity, especially with acids. Carefully free-basing **1a** with NaOH yielded the *N*-H spiro-oxindole azetidine with minimal racemization, but this form proved more susceptible to racemization, again most notably with acids. We hypothesised that the lability of the spiro-oxindole stereocenter in the *N*-Boc-deprotected spiro-oxindole azetidine **1a** likely resulted from rapid ring opening and closing of the azetidine ring *via* an azafulvenium salt intermediate (Scheme 4). Support for this hypothesis came from treating spiro-azetidine amide **2d** with BF₃·Et₂O and Et₃SiH, which afforded ring-opened acylated intermediate **8** presumably resulting from hydride capture at C3 of the azafulvenium salt.

Recognizing the importance of maintaining the azetidine stereochemical integrity for medicinal chemistry applications and to accrue further evidence to support the racemisation hypothesis, we prepared a series of further spiro-oxindole azetidines **II–IV**. The *N*-Ts and 7-aza derivatives were designed to retard azetidine ring-opening by destabilising the proposed azafulvenium salt intermediate. Additionally, a spiro-pyrrolidine homologue was synthesized as a control to evaluate the impact of ring strain in promoting the racemization process. These were prepared as racemates and separated using chiral SFC. Subjecting the modified spiro-oxindole azetidines **II–IV** to one-pot *N*-Boc deprotection followed by optimized amide coupling conditions revealed a significant reduction in racemization, with their enantiomeric purities being maintained over the 6 h period of evaluation. The pyrrolidine **IV** also did not racemise under these conditions. These findings support the proposed mechanism of racemisation and provide a method



Scheme 3 Dihydro-1,3-oxazine formation from other 2,2-disubstituted azetidines.





Scheme 4 Studies to investigate racemization during reactions of spiro-oxindole azetidines with carboxylic acid.

of preventing it by counter-balancing the inherent ring strain with an electron-deficient oxindole framework.[†]

Racemisation (or epimerization) at C3 of spiro-oxindoles *via* azafulvenium ion intermediates has been proposed previously for aziridine-based systems.^{16a–c} In particular, Hajra has shown that spiro-oxindole aziridines (and epoxide) undergo ring-opening and ring-expansion reactions, generally with retention of stereochemistry at C3, but sometimes with varying degrees of epimerization.¹⁶ The stereoretentive pathway was

[†]Studies were also conducted on salt 1a to assess whether *N*-alkylation proceeded with retention of enantiopurity. Treatment of enantiopure *N*-Boc-deprotected spiro-oxindole azetidine 1a with 3,5-difluorobenzyl bromide under $\text{S}_{\text{N}}2$ conditions yielded the desired product with significantly diminished er. A side product was isolated and characterized as the bis-alkylated ammonium salt, which intriguingly retained the spiro-azetidine ring. Reductive amination conditions using 3,5-difluorobenzaldehyde furnished exclusively the mono-alkylated product. However, this also resulted in substantial erosion of enantiopurity. As in the *N*-acylation process, racemization is likely attributable to the facile ring-opening of the spiro-oxindole azetidine. Furthermore, we found that *N*-alkylation could also be successfully achieved with suitable Michael acceptors such as ethyl acrylate and phenyl vinyl sulfone (see S1).

postulated to proceed with anchimeric assistance from the lactam nitrogen (*i.e.* double inversion *via* a tricyclic α -lactam intermediate), with epimerization proceeding *via* an azafulvenium ion intermediate (as proposed in this study) for electron-rich oxindoles or upon addition of Lewis acids.^{16df} We found no evidence for the anchimeric assistance pathway in our work, but like Hajra have found that the propensity of these strained spiro oxindoles to spring open *via* azafulvenium ions is dependent on the electron demand of the aryl ring in the oxindole: electron neutral and rich derivatives undergo this ring-opening readily, electron deficient congeners less so.

Conclusions

In summary, we have developed a divergent, condition-controlled coupling protocol to access spiro-azetidine amides and the corresponding spiro dihydro-1,3-oxazine from the reaction of *N*-H-spiro-oxindole azetidines with carboxylic acids. We have also extended the scope beyond spirocyclic systems to 2,2-disubstituted azetidines, which serve as versatile linchpins for



molecular editing/scaffold hopping. Mechanistic investigations revealed partial racemisation of the spirocentre under the amide coupling conditions. Additive screening and trapping studies suggested that this proceeds *via* a ring-opened azafulvenium salt intermediate. These studies reinforce that care should be taken to monitor the enantiopurity of enantio-enriched oxindole derivatives through reaction sequences. However, rational modifications to the spiro-oxindole framework enables the synthesis of spiro-azetidone amide products with retention of enantiopurity. Ongoing efforts are focused on developing an asymmetric variant of the ring expansion process to access enantioenriched spiro- and non-spiro dihydro-1,3-oxazine products.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the SI: experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra; full details of reaction optimization, X-ray crystallography data (cif & cif-check files), HPLC traces for enantioenriched compounds. Schemes were drawn using Chemdraw v20.1.1. See DOI: <https://doi.org/10.1039/d5qo00804b>.

CCDC 2442548 and 2442549 contain the supplementary crystallographic data for this paper.^{17a,b}

Acknowledgements

We gratefully acknowledge EPSRC [EPSRC Centre for Doctoral training in Next Generation Synthesis and Reaction Technology (EP/S023232/1) for a studentship (to A. K. S.); EP/Y007859/1], the Royal Society [URF\R\201019 for J. A. B.] and Mr Alex Brien and Dr Daniel Hamza at Sygnature Discovery for helpful discussions and facilitating chiral SFC.

References

- For selected reviews see: (a) J. D. Mack and J. T. Njardarson, Recent advances in the metal-catalyzed ring expansions of three- and four-membered rings, *ACS Catal.*, 2013, **3**, 272–286; (b) C.-Y. Huang and A. G. Doyle, The chemistry of transition metals with three-membered ring heterocycles, *Chem. Rev.*, 2014, **114**, 8153–8198; (c) E. A. Ilardi and J. T. Njardarson, Ring expansions of vinyloxiranes, -thiiranes, and -aziridines: synthetic approaches, challenges, and catalytic success stories, *J. Org. Chem.*, 2013, **78**, 9533–9540; (d) R. Li, B. Li, H. Zhang, C.-W. Ju, Y. Qin, X.-S. Xue and D. Zhao, A ring expansion strategy towards diverse azaheterocycles, *Nat. Chem.*, 2021, **13**, 1006–1016; (e) H. Mughal and M. Szostak, Recent advances in the synthesis and reactivity of azetidines: strain-driven character of the four-membered heterocycle, *Org. Biomol. Chem.*, 2021, **19**, 3274–3286.
- For selected reviews on ring opening/expansion of aziridines see: (a) W. McCoull and F. A. Davis, Recent synthetic applications of chiral aziridines, *Synthesis*, 2000, 1347–1365; (b) J. B. Sweeney, Aziridines: epoxides' ugly cousins?, *Chem. Soc. Rev.*, 2002, **31**, 247–258; (c) S. Stanković, M. D'hooghe, S. Catak, H. Eum, M. Waroquier, V. V. Speybroeck, N. D. Kimpe and H.-J. Ha, Regioselectivity in the ring opening of non-activated aziridines, *Chem. Soc. Rev.*, 2012, **41**, 643–665.
- Ring expansion of azetidines *via* azetidinium ions. For selected reviews see: (a) F. Couty and G. Evano, Azetidines: new tools for the synthesis of nitrogen heterocycles, *Synlett*, 2009, 3053–3064; (b) J. Dolfen, N. N. Yadav, N. De Kimpe, M. D'hooghe and H. Ha, Bicyclic aziridinium ions in aza-heterocyclic chemistry – preparation and synthetic application of 1-azoniabicyclo[n.1.0]alkanes, *Adv. Synth. Catal.*, 2016, **358**, 3485–3511 For selected examples see: (c) F. Outurquin, X. Pannecoucke, B. Berthe and C. Paulmier, Stereocontrolled synthesis of 1,2-dialkyl-4-halopyrrolidines through PhSeX-induced cyclization of secondary homoallylamines, *Eur. J. Org. Chem.*, 2002, 1007–1014; (d) F. Couty, F. Durrat and D. Prim, Highly stereoselective ring expansion of enantiopure α -hydroxyalkyl azetidines, *Tetrahedron Lett.*, 2003, **44**, 5209–5212; (e) W. Van Brabant, R. Van Landeghem and N. De Kimpe, Ring transformation of 2-(haloalkyl)azetidines into 3,4-disubstituted pyrrolidines and piperidines, *Org. Lett.*, 2006, **8**, 1105–1108; (f) A. Feula, L. Male and J. S. Fossey, Diastereoselective preparation of azetidines and pyrrolidines, *Org. Lett.*, 2010, **12**, 5044–5047; (g) B. Drouillat, I. V. Dorogan, M. Kletskii, O. N. Burov and F. Couty, Competitive ring expansion of azetidines into pyrrolidines and/or azepanes, *J. Org. Chem.*, 2016, **81**, 6677–6685; (h) *Via* ammonium ylides: F. Couty, F. Durrat, G. Evano and J. Marrot, Ring expansions of 2-alkenylazetidinium salts – a new route to pyrrolidines and azepanes, *Eur. J. Org. Chem.*, 2006, 4214–4223; (i) T. M. Bott, J. A. Vanecko and F. G. West, One-carbon ring expansion of azetidines *via* ammonium ylide [1,2]-shifts: a simple route to substituted pyrrolidines, *J. Org. Chem.*, 2009, **74**, 2832–2836; (j) *Via* ring opening cascade: P. Nocquet, D. Hazelard and P. Compain, Synthesis of spirocyclopropyl γ -lactams by a highly stereoselective tandem intramolecular azetidone ring-opening/closing cascade reaction, *Eur. J. Org. Chem.*, 2011, 6619–6623; (k) T. Shimizu, S. Koya, R. Yamasaki, Y. Mutoh, I. Azumaya, K. Katagiri and S. Saito, Acid-mediated ring-expansion reaction of N-aryl-2-vinylazetidines: synthesis and unanticipated reactivity of tetrahydrobenzazocines, *J. Org. Chem.*, 2014, **79**, 4367–4377; (l) Cu-catalyzed ring expansion: M. K. Ghorai, D. Shukla and A. Bhattacharyya, Syntheses of chiral β - and γ -amino ethers, morpholines, and their homologues *via* nucleophilic ring-



- opening of chiral activated aziridines and azetidines, *J. Org. Chem.*, 2012, **77**, 3740–3753.
- 4 (a) B. Drouillat, K. Wright, O. David and F. Couty, Insight into the regioselectivity of nucleophilic ring-opening of azetidinium ions containing quaternary carbon atoms, *Eur. J. Org. Chem.*, 2012, 6005–6012; (b) Z. Wang, F. K. Sheong, H. H. Y. Sung, I. D. Williams, Z. Lin and J. Sun, Catalytic enantioselective intermolecular desymmetrization of azetidines, *J. Am. Chem. Soc.*, 2015, **137**, 5895–5898; (c) J. Luginina, J. Uzuleņa, D. Posevins and M. Turks, Ring-opening of carbamate-protected aziridines and azetidines in liquid sulfur dioxide, *Eur. J. Org. Chem.*, 2016, 1760–1771; (d) K. Wright, B. Drouillat, L. Menguy, J. Marrot and F. Couty, The von Braun reaction applied to azetidines, *Eur. J. Org. Chem.*, 2017, 7195–7201; (e) W. Cai, S. Wang, H. B. Jalani, J. Wu, H. Lu and G. Li, Oxidative cascade reaction of N-aryl-3-alkylideneazetidines and carboxylic acids: access to fused pyridines, *Org. Lett.*, 2018, **20**, 3833–3837; (f) D. Qian, M. Chen, A. C. Bissember and J. Sun, Counterion-induced asymmetric control in ring-opening of azetidiniums: facile access to chiral amines, *Angew. Chem., Int. Ed.*, 2018, **57**, 3763–3766; (g) G. Masson, D. Gomez Pardo and J. Cossy, Ring-opening of azetidiniums by nucleophiles: synthesis of polysubstituted linear amines, *Chirality*, 2021, **33**, 5–21; (h) M. Andresini, M. Colella, R. S. Dibenedetto, E. Graziano, G. Romanazzi, A. Aramini, L. Degennaro and R. Luisi, Sustainable continuous flow synthesis of β -aminocarbonyls via acid-catalyzed hydration of N-Boc-2-azetidines, *React. Chem. Eng.*, 2023, **8**, 3203–3209; (i) J. J. Gair, M. Isomura, C. C. Wagen, D. A. Strassfeld and E. N. Jacobsen, Enantioselective ring opening of azetidines via charge recognition in hydrogen-bond-donor catalysis, *J. Am. Chem. Soc.*, 2025, **147**, 6378–6383.
- 5 F. Couty and O. R. P. David, Ring expansions of nonactivated aziridines and azetidines, in *Synthesis of 4- to 7-membered Heterocycles by Ring Expansion*, ed. M. D'hooghe and H.-J. Ha, Springer International Publishing, Cham, 2015, vol. 41, pp. 1–47.
- 6 (a) H. D. Banks, The profound effect of fluorine substitution on the reactivity and regioselectivity of nucleophilic substitution reactions of strained heterocycles. A study of aziridine and its derivatives, *J. Org. Chem.*, 2006, **71**, 8089–8097; (b) N. De Rycke, O. David and F. Couty, Assessing the rates of ring-opening of aziridinium and azetidinium ions: a dramatic ring size effect, *Org. Lett.*, 2011, **13**, 1836–1839.
- 7 (a) A. Brandi, S. Cicchi and F. M. Cordero, Novel syntheses of azetidines and azetidines, *Chem. Rev.*, 2008, **108**, 3988–4035; (b) G. S. Singh, Chapter one – advances in synthesis and chemistry of azetidines, in *Advances in Heterocyclic Chemistry*, ed. E. F. V. Scriven and C. A. Ramsden, Academic Press, 2020, vol. 130, pp. 1–74; (c) A. A. Kirichok, I. O. Shton, I. M. Pishel, S. A. Zozulya, P. O. Borysko, V. Kubyshekin, O. A. Zaporozhets, A. A. Tolmachev and P. K. Mykhailiuk, Synthesis of multifunctional spirocyclic azetidines and their application in drug discovery, *Chem. – Eur. J.*, 2018, **24**, 5444–5449; (d) A. J. Boddy, D. P. Affron, C. J. Cordier, E. L. Rivers, A. C. Spivey and J. A. Bull, Rapid assembly of saturated nitrogen heterocycles in one-pot: diazo-heterocycle “stitching” by N–H insertion and cyclization, *Angew. Chem., Int. Ed.*, 2019, **58**, 1458–1462; (e) V. Zadsirjan and F. Soleimani, Recent advances in the synthesis of azetidines, *Tetrahedron*, 2025, **169**, 134383.
- 8 For selected reviews see: (a) F. G. West and T. M. Bott, *Heterocycles*, 2012, **84**, 223–264; (b) F. Couty, B. Drouillat, G. Evano and O. David, 2-Cyanoazetidines and azetidinium ions: scaffolds for molecular diversity, *Eur. J. Org. Chem.*, 2013, 2045–2056; (c) V. Mehra, I. Lumb, A. Anand and V. Kumar, Recent advances in synthetic facets of immensely reactive azetidines, *RSC Adv.*, 2017, **7**, 45763–45783.
- 9 For intermolecular ring expansion of azetidines: (a) S. K. Pawar, D. Vasu and R. Liu, Gold- and silver-catalyzed [4 + 2] cycloadditions of ynamides with oxetanes and azetidines, *Adv. Synth. Catal.*, 2014, **356**, 2411–2416; (b) D. Shukla, S. Singh, A. K. Sharma, B. Singh, A. Bhattacharyya, R. Talukdar and M. K. Ghorai, Lewis acid catalyzed domino ring-opening cyclization of azetidines with alkynes: synthesis of tetrahydropyridines, *Synlett*, 2024, 2459–2464; (c) S. A. Shehzadi, K. Kushwaha, H. Sterckx and K. Abbaspour Tehrani, Zn(OTf)₂-catalyzed synthesis of 2-alkynylazetidines and their ring expansion to functionalized 1,4,5,6-tetrahydropyridines, *Adv. Synth. Catal.*, 2018, **360**, 4393–4401; (d) G. Goswami, B. Singh, I. A. Wani, A. Mal and M. K. Ghorai, A synthetic route to tetrahydro-1H-azepino[4,3,2-cd]indoles via ring-opening cyclization of activated azetidines with 4-bromoindole: toward a vasopressin V2 receptor antagonist, *J. Org. Chem.*, 2024, **89**, 11576–11587.
- 10 (a) Y. Iwakura, A. Nabeya, T. Nishiguchi and Y. Ichikawa, Isomerization of Azetidine Derivatives, *J. Org. Chem.*, 1965, **30**, 3410–3413; (b) D. Black and K. Watson, Nitrones and Oxaziridines. X. Photorearrangement of Some Bicyclic Oxaziridines, *Aust. J. Chem.*, 1973, **26**, 2505–2513; (c) A. Nabeya, T. Endo, T. Nishiguchi and K. Hori, Study on the Isomerization of 1-Acylazetidine. A Comparative Study with the Case of 1-Acylaziridine, *J. Org. Chem.*, 1999, **64**, 5686–5690; (d) K. C. Nicolaou, T. K. Chakraborty, Y. Ogawa, R. A. Danes, N. S. Simpkins and G. T. Furst, Chemistry of Amphotericin B. Degredation studies and preparation of amphoteronolide B, *J. Am. Chem. Soc.*, 1988, **110**, 4660–4672; (e) M. Coffinet, S. Lamy, F. Jaroschik and J.-L. Vasse, Cyclopent-2-enylaluminum as allylzinc precursor for the diastereoselective allylmethallation of non-racemic imines: applications to the synthesis of enantiomerically enriched heterocycles, *Org. Biomol. Chem.*, 2016, **14**, 69–73; (f) N. Ishida, D. Nečas, Y. Masuda and M. Murakami, Enantioselective construction of 3-hydroxypiperidine scaffolds by sequential action of light and rhodium upon N-allylglyoxylamides, *Angew. Chem., Int. Ed.*, 2015, **54**, 7418–7421; (g) G. Bai, T. N. O'Connell, M. A. Brodney, C. R. Butler, L. C. Czabaniuk, A. M. Gilbert,



- E. A. LaChapelle, C. Li, L. A. McAllister, K. Ogilvie, L. Philippe, R. Salomon-Ferrer, M. J. Shapiro, J. T. Starr, D. P. Uccello, J. M. Withka, J. Yan and M. F. Brown, Intramolecular ring-opening decomposition of aryl azetidines, *ACS Med. Chem. Lett.*, 2021, **12**, 1585–1588; (h) I. Brekalo, Z. M. Ištuk, M. Mesić, M. Čičak, I. J. Elenkov, A. Cuzzolin, F. Rancati and A. Accetta, Spotting the unforeseen in the preparation of N-(azetidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine derivatives, *Tetrahedron Lett.*, 2025, **155**, 155427–155432; (i) A. J. Boddy, C. J. Cordier, K. Goldberg, A. Madin, A. C. Spivey and J. A. Bull, Acid-mediated ring expansion of 2,2-disubstituted azetidine carbamates to 6,6-disubstituted 1,3-oxazinan-2-ones, *Org. Lett.*, 2019, **21**, 1818–1822; (j) M. Dolna, J. Narodowicz, O. Staszewska-Krajewska, P. Szcześniak and B. Furman, Remotely controlled flow photo-Fries-type rearrangement of N-vinylazetidines: an efficient route to structurally diverse 2,3-dihydro-4-pyridones, *React. Chem. Eng.*, 2023, **8**, 784–789.
- 11 F. Bou Hamdan, M. Weiss and L. Quaranta, Microbiocidal quinoline dihydro-[thiazine]oxazine derivatives, WO2020/070132A1, 2020.
- 12 (a) H. Hilpert, W. Guba, T. J. Woltering, W. Wostl, E. Pinard, H. Mauser, A. V. Mayweg, M. Rogers-Evans, R. Humm, D. Krummenacher, T. Muser, C. Schnider, H. Jacobsen, L. Ozmen, A. Bergadano, D. W. Banner, R. Hochstrasser, A. Kuglstatter, P. David-Pierson, H. Fischer, A. Polara and R. Narquizian, β -Secretase (BACE1) inhibitors with high in vivo efficacy suitable for clinical evaluation in Alzheimer's disease, *J. Med. Chem.*, 2013, **56**, 3980–3995; (b) A. K. Ghosh and H. L. Osswald, BACE1 (β -secretase) inhibitors for the treatment of Alzheimer's disease, *Chem. Soc. Rev.*, 2014, **43**, 6765–6813; (c) R. Machauer, R. Lueoend, K. Hurth, S. J. Veenstra, H. Rueeger, M. Voegtler, M. Tintelnot-Blomley, J.-M. Rondeau, L. H. Jacobson, G. Laue, K. Beltz and U. Neumann, Discovery of Umibecestat (CNP520): a potent, selective, and efficacious β -secretase (BACE1) inhibitor for the prevention of Alzheimer's disease, *J. Med. Chem.*, 2021, **64**, 15262–15279.
- 13 (a) X.-F. Cao, J.-S. Wang, X.-B. Wang, J. Luo, H.-Y. Wang and L.-Y. Kong, Monoterpene indole alkaloids from the stem bark of *Mitragyna diversifolia* and their acetylcholine esterase inhibitory effects, *Phytochemistry*, 2013, **96**, 389–396; (b) L. Fan, X.-J. Huang, C.-L. Fan, G.-Q. Li, Z.-L. Wu, S.-G. Li, Z.-D. He, Y. Wang and W.-C. Ye, Two new oxindole alkaloid glycosides from the leaves of *Nauclea officinalis*, *Nat. Prod. Commun.*, 2015, **10**, 2087–2090; (c) J.-H. Liang, Z.-L. Luan, X.-G. Tian, W.-Y. Zhao, Y.-L. Wang, C.-P. Sun, X.-K. Huo, S. Deng, B.-J. Zhang, Z.-J. Zhang and X.-C. Ma, Uncaralins A–I, monoterpene indole alkaloids from *Uncaria rhynchophylla* as natural agonists of the 5-HT_{1A} receptor, *J. Nat. Prod.*, 2019, **82**, 3302–3310; (d) A. Eichhorst, M. Gallhof, A. Voss, A. Sekora, L. Eggers, L. T. Huyen, C. Junghanss, H. Murua Escobar and M. Brasholz, Spirooxindol-1,3-oxazine alkaloids: highly potent and selective antitumor agents evolved from iterative structure optimization, *ChemMedChem*, 2022, **17**, e202200162; (e) K.-P. Huang, L.-L. Xu, S. Li, Y.-L. Wei, L. Yang, X.-J. Hao, H.-P. He and Y. Zhang, Uncaralins A–E, new alkaloids from *Uncaria rhynchophylla* and their anticoagulant activity, *Nat. Prod. Bioprospect.*, 2023, **13**, 13.
- 14 A. J. Boddy, A. K. Sahay, E. L. Rivers, A. J. P. White, A. C. Spivey and J. A. Bull, Enantioselective phase-transfer-catalyzed synthesis of spirocyclic azetidine oxindoles, *Org. Lett.*, 2024, **26**, 2079–2084.
- 15 A. E. Bosnidou, A. Millán, J. Ceballos, C. Martínez and K. Muñiz, Iodine(III)-mediated selective intermolecular C–H amination for the chemical diversification of tryptamines, *J. Org. Chem.*, 2016, **81**, 6496–6504.
- 16 (a) S. Hajra, S. Singha Roy, S. M. Aziz and D. Das, Catalyst-free “on-water” regio- and stereospecific ring-opening of spiroaziridine oxindole: enantiopure synthesis of unsymmetrical 3,3'-bisindoles, *Org. Lett.*, 2017, **19**, 4082–4085; (b) S. Hajra, S. Singha Roy, A. Biswas and S. A. Saleh, Catalyst-free ring opening of spiroaziridine oxindoles by heteronucleophiles: an approach to the synthesis of enantiopure 3-substituted oxindoles, *J. Org. Chem.*, 2018, **83**, 3633–3644; (c) S. Hajra, A. Hazra and P. Mandal, Stereocontrolled nucleophilic fluorination at the tertiary sp³-carbon center for enantiopure synthesis of 3-fluoro-oxindoles, *Org. Lett.*, 2018, **20**, 6471–6475; (d) S. Hajra, S. Maity, S. Roy, R. Maity and S. Samanta, Brønsted acid promoted regioselective C-3 arylation and heteroarylation of spiro-epoxyoxindoles for the construction of all carbon quaternary centres: a detailed study, *Eur. J. Org. Chem.*, 2019, 969–987; (e) S. Hajra and A. Biswas, Catalyst-free stereocontrolled formal [3 + 2]-cycloaddition of CO₂ for the synthesis of enantiopure spiro[indoline-3,5'-oxazolidine]-2,2'-diones under aqueous and ambient conditions, *Org. Lett.*, 2020, **22**, 4990–4994; (f) S. A. Saleh, A. Hazra and S. Hajra, Regioselective hydroperoxylation of aziridines and epoxides only with aqueous hydrogen peroxide, *Adv. Synth. Catal.*, 2022, **364**, 391–404; (g) S. A. Saleh, A. Hazra, M. S. Singh and S. Hajra, Selective C3-allylation and formal [3 + 2]-annulation of spiro-aziridine oxindoles: synthesis of 5'-substituted spiro[pyrrolidine-3,3'-oxindoles] and coerule-scine, *J. Org. Chem.*, 2022, **87**, 8656–8671; (h) A. Biswas and S. Hajra, Regio- and stereospecific desulfinylative chlorination of spiroaziridine oxindoles at spiro-center for formal [3 + 2]-cycloaddition with CS₂: sequential one-pot synthesis of (–)-spirobrassinin, *Adv. Synth. Catal.*, 2022, **364**, 3035–3304.
- 17 (a) A. K. Sahay, C. S. Begg, X. Zhang, J. A. Bull and A. C. Spivey, CCDC 2442548: Experimental Crystal Structure Determination, 2025, DOI: [10.5517/ccdc.csd.cc2mznw5](https://doi.org/10.5517/ccdc.csd.cc2mznw5); (b) A. K. Sahay, C. S. Begg, X. Zhang, J. A. Bull and A. C. Spivey, CCDC 2442549: Experimental Crystal Structure Determination, 2025, DOI: [10.5517/ccdc.csd.cc2mznx6](https://doi.org/10.5517/ccdc.csd.cc2mznx6).

