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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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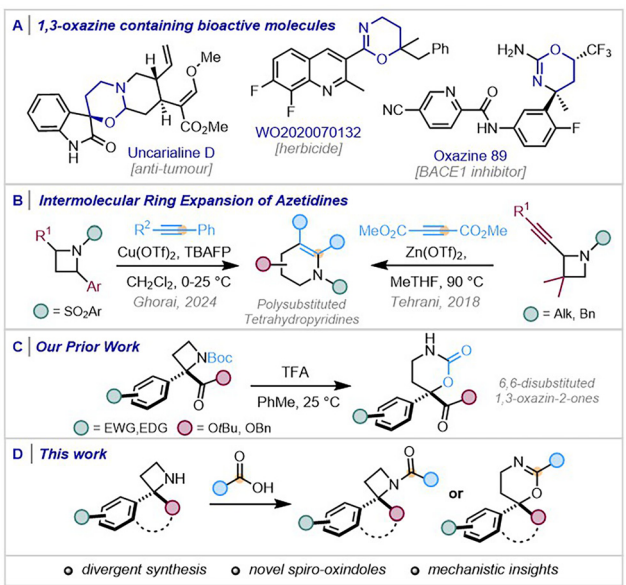
Azetidines have gained traction in drug discovery for their ability to introduce conformational constraint and modulate physiochemical properties. Strategies that enable their selective functionalization or controlled expansion into more complex scaffolds provide opportunities for molecular diversification 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.

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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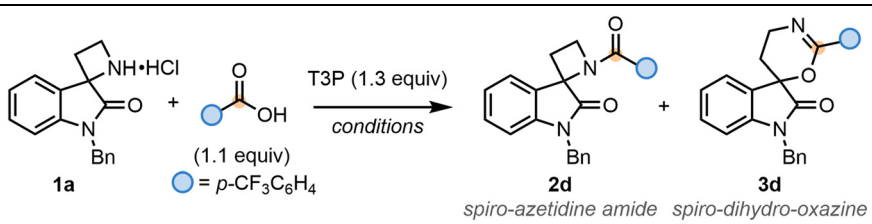
internal nucleophile constitutes an alternate strategy.[10] Indeed, simple *N*-acylazetidines are known to undergo acid-[10a–c] and base-mediated[10d,e] ring expansion to isomeric dihydrooxazine products. Additionally, we previously demonstrated that *N*-Boc-2,2-disubstituted azetidines undergo TFA-mediated, 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 *inter*molecular 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 agent[13] (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 counterpart[13] 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*-CF_3 benzoic acid using EDC·HCl and Et_3N in CH_2Cl_2 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 **3d** 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. Et_3N) 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_3N (2.5 equiv.)	CH_2Cl_2	25	4	58	15	4 : 1
2	Et_3N (2.5 equiv.)	CH_2Cl_2	25	4	64	22	3 : 1
3	Et_3N (2.5 equiv.)	DCE	25	4	69	17	4 : 1
4	Et_3N (2.5 equiv.)	THF	25	4	71	4	18 : 1
5	Et_3N (2.5 equiv.)	MeCN	25	4	55	28	2 : 1
6	Et_3N (2.5 equiv.)	EtOAc	25	4	41	3	14 : 1
	Change from entry 4 – spiro-azetidine amide optimisation						
7	Et_3N (3 equiv.)	THF	25	4	82	4	21 : 1
8	**Et_3N (3 equiv.)**	**THF**	**0–25**	**6**	**88 (77)[d]**	**3**	**29 : 1**
	Change from entry 5 – spiro-dihydro-oxazine optimisation						
9	Et_3N (5 equiv.)	MeCN	25	4	44	31	1.4 : 1
10	DBU (5 equiv.)	MeCN	25	4	46	36	1.3 : 1
11	Et_3N (5 equiv.)	MeCN	40	18	18	56	1 : 3
12	**DBU (5 equiv.)**	**MeCN**	**40**	**18**	**6**	**62 (54)[d]**	**1 : 11**

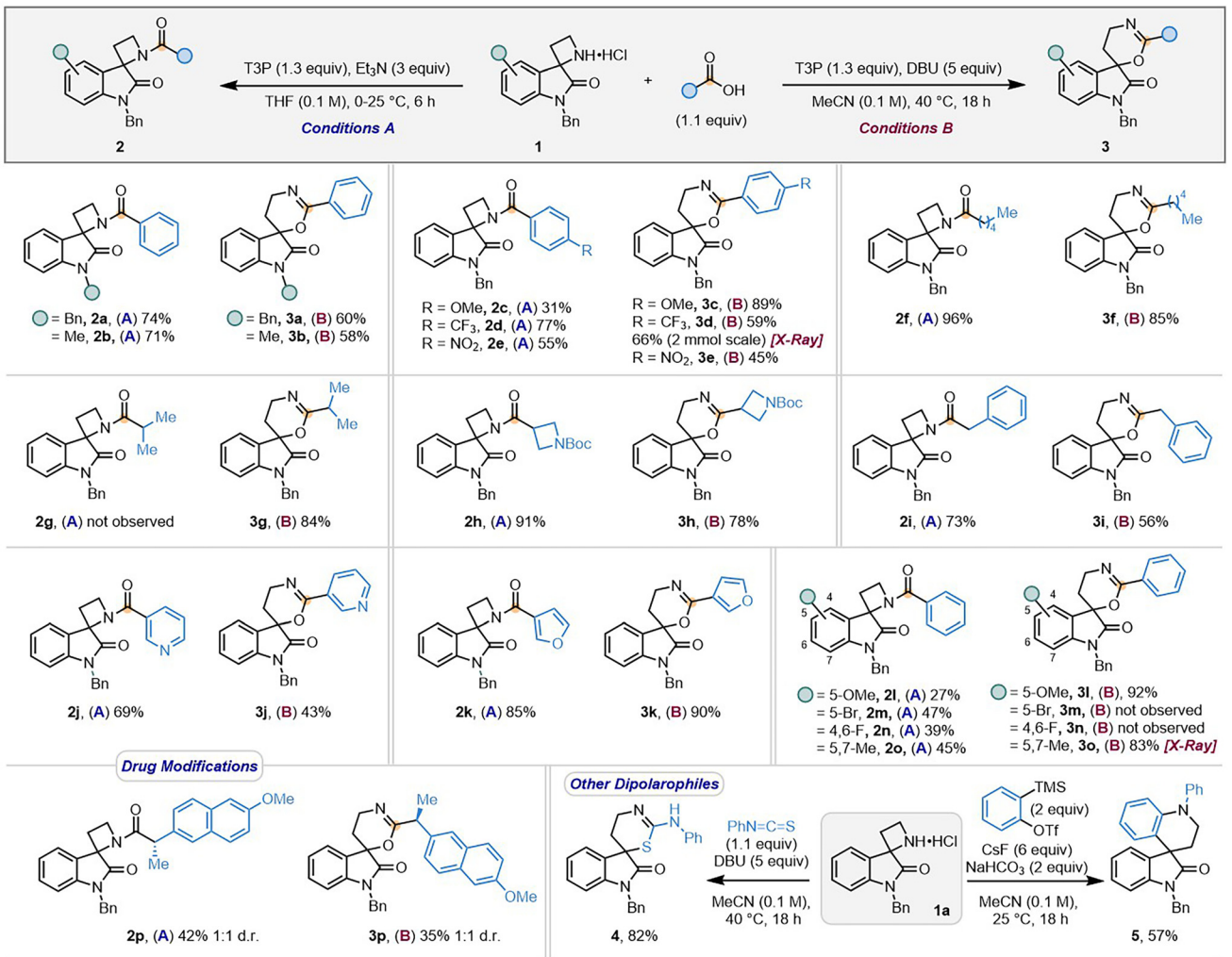
[a] Reactions were carried out on 0.017 mmol. [b] Yields are determined by *in situ* ^{19}F NMR spectroscopy with respect to $PhCF_3$ as an internal standard. [c] Using EDC·HCl. [d] Isolated yield on 0.1 mmol scale.

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.

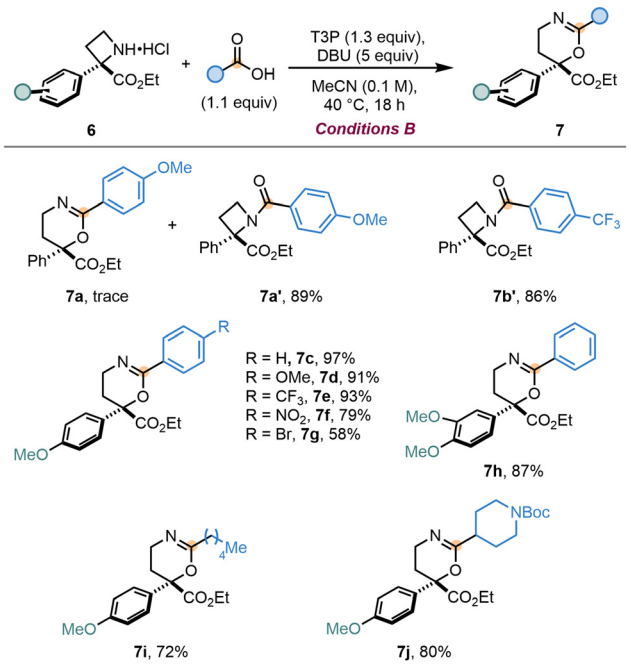
Heteroaromatic carboxylic acids coupled divergently to give pyridyl and furan-containing products (**2–3j**, **2–3k**), the former of which constitutes nicotinate derivatives. The reaction scope



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 delivered 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.

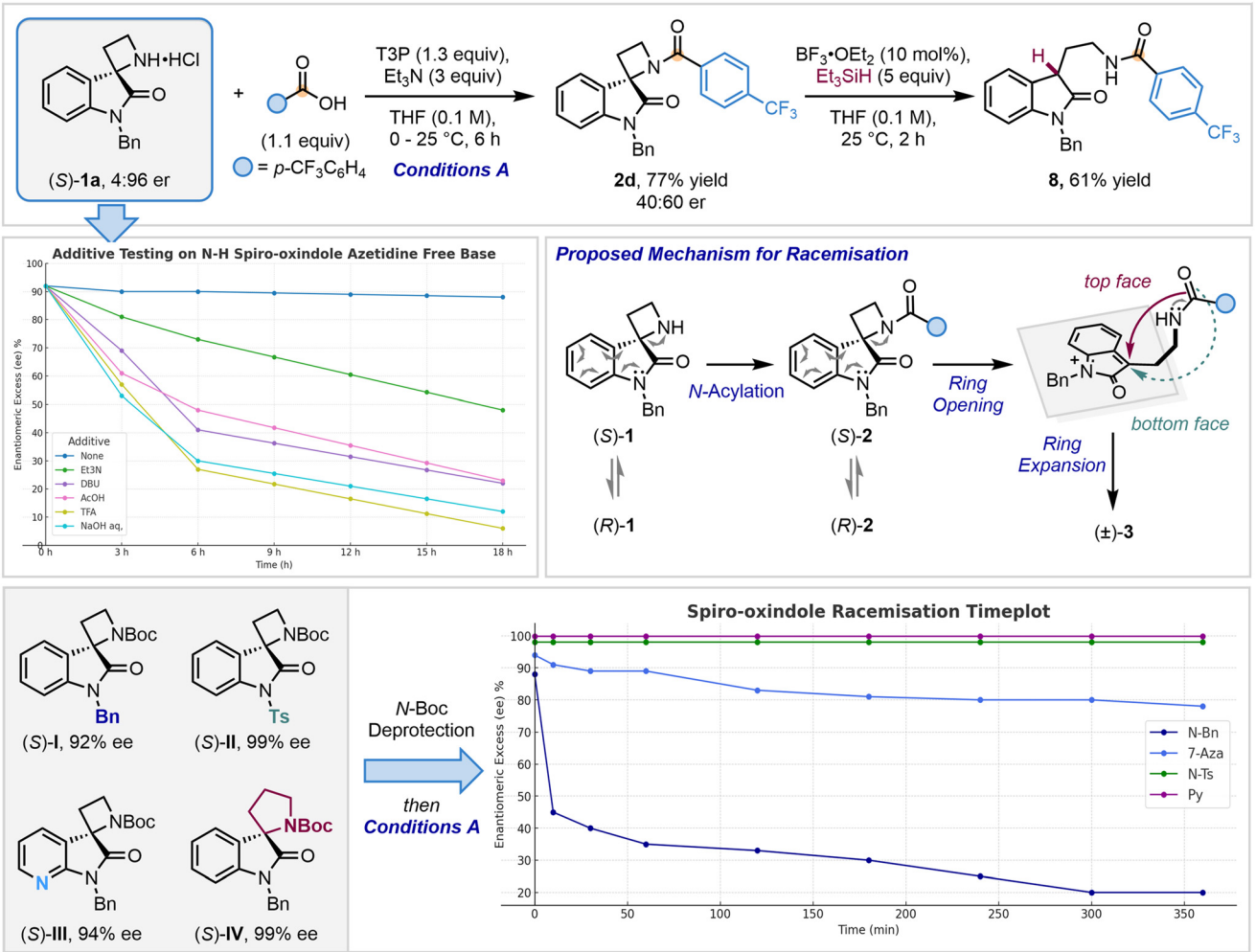


Scheme 3 Dihydro-1,3-oxazine formation from other 2,2-disubstituted azetidines.

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 ers (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 $BF_3{\cdot}Et_2O$ and Et_3SiH, 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 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 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.[16d,f] 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

†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 S_N2 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 SI).

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 enantioenriched oxindole derivatives through reaction sequences. However, rational modifications to the spiro-oxindole framework enables the synthesis of spiro-azetidine 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 ^{1}H 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

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