Acid-Mediated Ring-Expansion of 2,2-Disubstituted Azetidine Carbamates to 6,6-Disubstituted 1,3-Oxazinan-2-ones

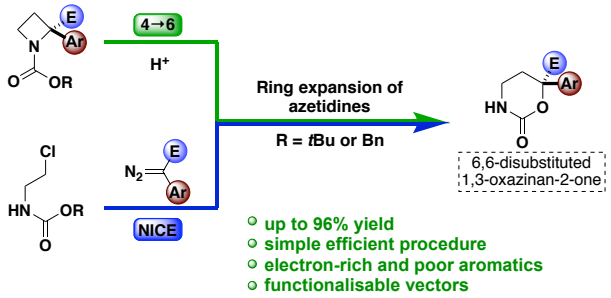
Alexander J. Boddy,[†] Christopher J. Cordier,[†] Kristin Goldberg,[‡] Andrew Madin,[§] Alan C. Spivey,[†] and James A. Bull*,[†]

† Department of Chemistry, Imperial College London, Molecular Sciences Research Hub, White City Campus, Wood Lane, London W12 0BZ, UK.

‡ Medicinal Chemistry, Oncology, IMED Biotech Unit, AstraZeneca, Cambridge CB4 0WG, UK.

§ Hit Discovery, Discovery Sciences, IMED Biotech Unit, AstraZeneca, Cambridge CB4 0WG, UK.

Supporting Information Placeholder



ABSTRACT: The ring expansion of 2-ester-2-aryl-azetidine carbamates can be achieved using Brønsted acids to form 6,6-disubstituted 1,3-oxazinan-2-ones. The reaction is rapid at room temperature with Boc or Cbz derivatives, and proceeds with excellent yield (up to 96%) and broad substrate scope. Derivatives of drug compounds and natural products are incorporated. The combination of this ring expansion in a 3-step N–H insertion/cyclization/expansion (NICE) sequence is applied to directly access medicinally relevant scaffolds from acyclic precursors.

Small, strained heterocycles, such as aziridines or epoxides, are often utilized in the synthesis of complex, larger heterocyclic frameworks.[1] The ring expansion of aziridines is particularly common to build molecular complexity.[2] For example, the ring expansion of carbamate protected aziridines yields 5-membered oxazolidine-2-ones as first developed by Tomasini (Figure 1A).[3] On the other hand, the use of 4-membered azetidines for ring opening and ring expansion is much less developed,[4,5] and there remains considerable potential for novel transformations. The strain of the azetidine ring is comparable to the strain of the aziridine ring (105 kJ mol^{-1} *vs*. 113 kJ mol^{-1}),[6] yet, the reactivity of an azetidinium ion to ring opening has been shown to be 1.7×10^4 times slower than aziridinium ions.[7] Azetidines therefore present highly tractable building blocks because of their predisposition to ring opening reactions yet relatively low reactivity, even when activated.[8]

While ring expansion of *N*-acyl aziridines and aziridine carbamates has been well-explored, the analogous ring expansion of azetidines remains unprecedented.[9,10] This process on azetidines would afford 1,3-oxazinan-2-ones, interesting scaffolds within natural products and pharmaceuticals (Figure 1B). They have been utilized as the core scaffold in anti-HIV,[11] antidiabetic,[12] anti-inflammatory[13] and anti-cancer[14] compounds.

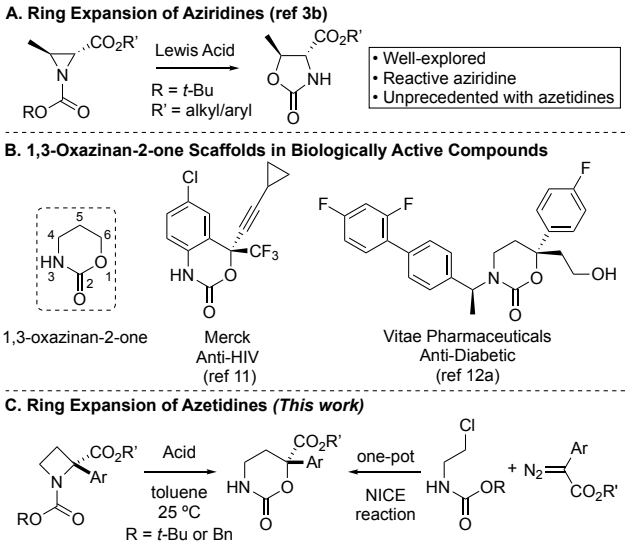


Figure 1. A) Ring expansion of aziridines. B) 1,3-Oxazinan-2-ones and their application in medicinal chemistry. C) Ring expansion of azetidines to oxazinan-2-ones. NICE = NH Insertion/Cyclization/Expansion.

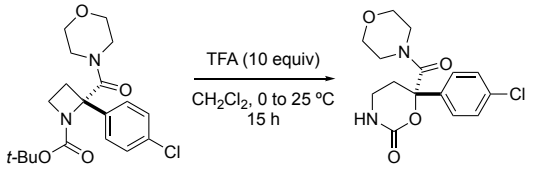
They are also used as intermediates in synthetic chemistry,[15] including in the synthesis of drug compounds and natural products.[16]

Numerous synthetic approaches have been used to access monosubstituted 1,3-oxazinan-2-ones.[17] However, general methods for the synthesis of disubstituted 1,3-oxazinan-2-ones remain limited. A notable exception is a formal [3+2+1] cycloaddition of α-isocyanoacetates with phenyl vinyl selenones and water to afford 4,4-disubstituted oxazinan-2-ones developed by Zhu.[18] In 2003, Yao and co-workers demonstrated a Lewis-acid promoted ring opening of an epoxide by a carbamate protected amine to form a 6,6-disubstituted 1,3-oxazinan-2-one, though this was limited to 6-methyl substitution and was not fully exemplified.[19] New general syntheses of disubstituted 1,3-oxazinan-2-ones, particularly, of 6,6-disubstituted examples, remain of high utility. During the preparation of this manuscript, Johnston developed the capture of CO_2 by dialkyl amines to form 6,6-disubstituted 1,3-oxazinan-2-ones.[20]

Here we report the ring expansion of azetidine carbamates to give 6,6-disubstituted 1,3-oxazinan-2-ones in high yields using Brønsted acids (Figure 1C). This is the first example of this type of ring expansion reaction with azetidine substrates. The products can be accessed either from the isolated azetidine or in a 3 step sequence from the diazo compound. Further elaboration of the 1,3-oxazinan-2-one scaffolds demonstrates their utility as fragments for medicinal chemistry.

We recently reported a one-pot N–H insertion/cyclization strategy for the synthesis of 2,2-disubstituted azetidines, pyrrolidines, piperidines and azepanes.[21] As part of this work compound **1** was prepared, aiming to Boc deprotect to afford a novel azetidine fragment compound (Scheme 1). However, treatment of **1** with TFA afforded oxazinanone **2** as the major product in 43% yield. Notably, the new ring system retains the densely functionalized fully substituted carbon center of the starting material.

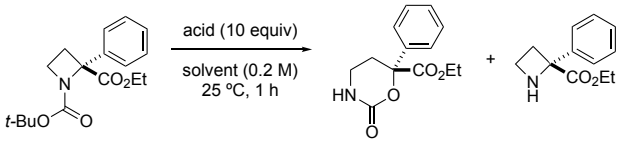
Scheme 1. Initial hit reaction for the ring expansion of azetidine 1.



1 **2**, 43%

Given the interest in this ring system, a range of acids and solvents were tested for the transformation of azetidine **3a** to oxazinanone **4a** (Table 1). TFA was the only acid which afforded exclusively the ring expanded product, and the reaction was complete in 1 h (Entry 1). Other acids (HCl, PTSA, CSA) gave a mixture of deprotection and ring expanded product, whereas, acetic acid gave no reaction (Entries 2 to 5).[22] Stronger acids (TfOH) or Lewis acids ($BF_3{\cdot}OEt_2$) gave lower yields of the desired product (Entries 6 and 7). Polar solvents (EtOAc) prevented any reaction and non-polar hexane afforded a 3.5:1 mixture of **4a**:**5a** (Entries 8 and 9). Toluene gave similar yields and selectivity to dichloromethane and was selected as a more environmentally benign solvent. Reducing the equivalents of TFA to five, the time from 1 h to 30 min, and increasing the concentration from 0.2 M to 1 M gave an optimized process with an 87% yield of **4a**, which was isolated in 76% yield.

Table 1. Selected optimization for 4 to 6 ring expansion of 2,2-disubstituted azetidine 3a.[a]



3a **4a** **5a**

entry	acid	solvent	yield (%)[b]			
			3a	**4a**	**5a**	**total**
1	TFA	CH_2Cl_2	0	89	0	89
2	4 M HCl[c]	CH_2Cl_2	0	22	65	87
3	PTSA[d]	CH_2Cl_2	14	23	52	89
4	CSA	CH_2Cl_2	65	4	16	85
5	CH_3CO_2H	CH_2Cl_2	95	0	0	95
6	TfOH	CH_2Cl_2	0	49	7	56
7	$BF_3{\cdot}Et_2O$[e]	CH_2Cl_2	0	58	0	58
8	TFA	EtOAc	97	0	0	97
9	TFA	hexane	0	77	22	99
10	TFA	toluene	0	93	0	93
11[f]	TFA	toluene	0	94	0	94
12[g]	TFA	toluene	40	53	0	93
13[h]	**TFA**	**toluene**	**0**	**87 (76)**	**0**	**87**

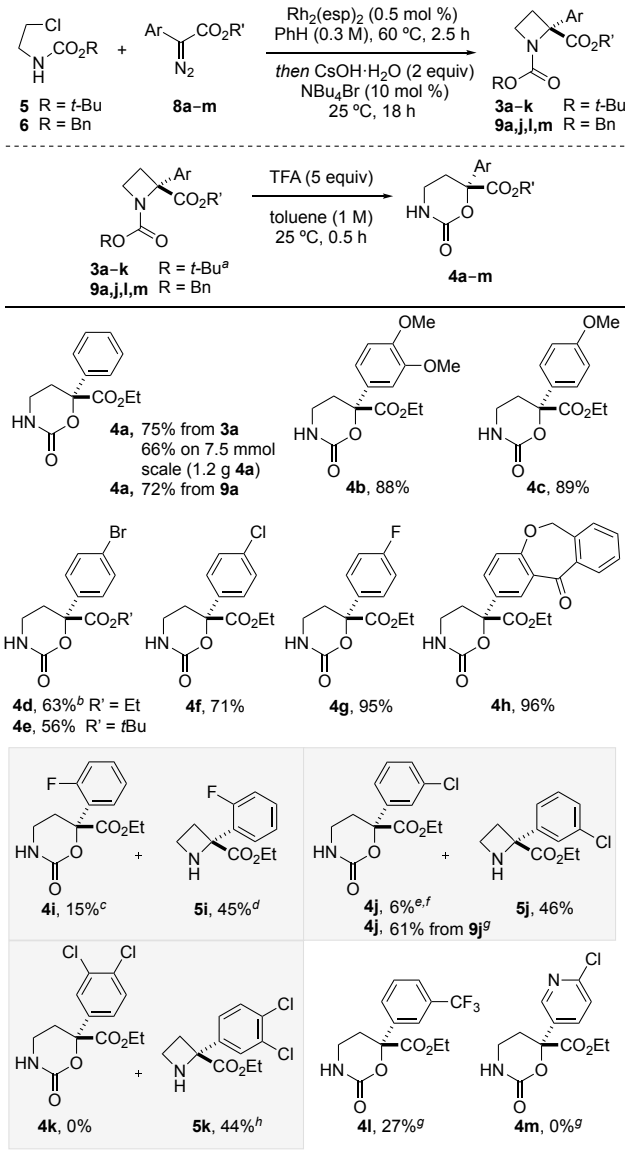
[a] Reactions on 0.2 mmol scale. [b] Yields determined by ^{1}H NMR spectroscopy relative to 1,3,5-trimethoxybenzene as an internal standard. [c] Used as solution in 1,4-dioxane. [d] Monohydrate. [e] 2 equiv. [f] 5 min. [g] TFA (5 equiv), 30 min. [h] TFA (5 equiv), 1 M concn, 0.5 h.

The scope of the ring expansion reaction was then explored by changing the azetidine substrates, which were prepared as previously reported by Rh-catalyzed NH insertion and base-mediated cyclization (Scheme 2).[21] Oxazinanone **4a** was formed in similar yields from the Boc or Cbz-protected azetidine. From azetidine **3a**, >1 g of oxazinanone **4a** was prepared in 66% yield. Electron donating aromatic rings gave high yields for the ring expansion reaction (**4b** and **c**). *tert*-Butyl esters were also tolerant of the acidic conditions and underwent exclusive ring expansion without significant deprotection. σ-Electron-withdrawing substituents on the aromatic ring were well-tolerated under these conditions when π-donation was also possible, i.e. 95% yield for oxazinanone **4g**. The ring expansion of azetidine **3h** derived from the anti-inflammatory agent isoxepac proceeded in 96% yield. When comparing oxazinanone **4g** and **4i**, moving the fluorine atom to the *ortho* position led to a significant reduction in conversion and reduced selectivity between ring expanded and deprotected product, likely due to an increased influence of σ-electron withdrawal from the fluoride. In the reactions to form oxazinanones **4j** and **4k** bearing more electron poor aromatic groups, very low yields were observed with much higher selectivity observed for the deprotected azetidine.

To avoid competitive deprotection on these more challenging substrates, the Cbz group was expected to be sufficiently stable to acid mediated deprotection to allow ring expansion to occur selectively. Gratifyingly, treating azetidine **9j** with TfOH promoted the ring expansion and afforded a 61% yield of **4j**. For

the *meta*-trifluoromethyl group (**9l**) a 27% yield of the oxazinanone product **4l** was obtained using TfOH. For azetidine **9m** with a pyridyl substituent only deprotection was observed.[23]

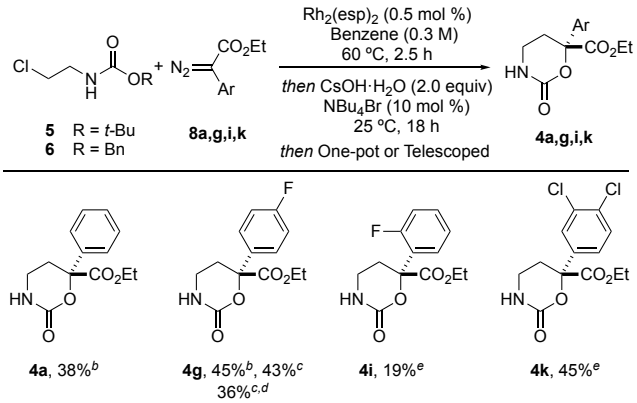
Scheme 2. Scope of 4 to 6 ring expansion of azetidines to 6,6-disubstituted 1,3-oxazinan-2-ones.



[a] Reactions on 0.1 to 0.5 mmol scale. [b] 10 equiv TFA for 1 h. [c] 76% conversion from **3i** to **4i**/**5i**. [d] Yield by ^{1}H NMR, not isolated. [e] 79% conversion from **3j** to **4j**/**5j**. [f] 2 h reaction time. [g] TfOH (10 equiv) and toluene (0.2 M) for 1 h. [h] 52% conversion from **3i** to **4i**/**5i**.

Next we combined the ring expansion with the synthesis of the azetidine substrates in one-pot to avoid isolation of the azetidine (Scheme 3). A Rh-catalyzed N–H insertion of aryl-ester diazo compounds followed by a base-mediated cyclization[21] and then direct treatment with acid in one-pot gave the ring expanded product directly. 1,3-Oxazinan-2-ones **4a** and **4g** were obtained through this NH insertion/cyclization/ring expansion (NICE) sequence in 38% and 45% yield respectively from the corresponding diazo compounds. Comparable yields were achieved in a telescoped process involving a simple filtration prior to ring expansion, and this protocol allowed for more facile purification. The reaction was suitable for scale-up to 3 mmol, generating 290 mg of oxazinanone **4g** from acyclic precursors over 3 steps. Using Cbz protected chloroamine **6**, oxazinanones **4i** and **4k** were afforded in 19% and 45% overall yield respectively. For the *ortho*-fluoro derivative, a greater yield was obtained for 1,3-oxazinan-2-one **4i** over 3 steps, using the TfOH acid conditions and the *N*-Cbz substrate, than compared to the yield obtained in a single step from the Boc-protected substrate with TFA.

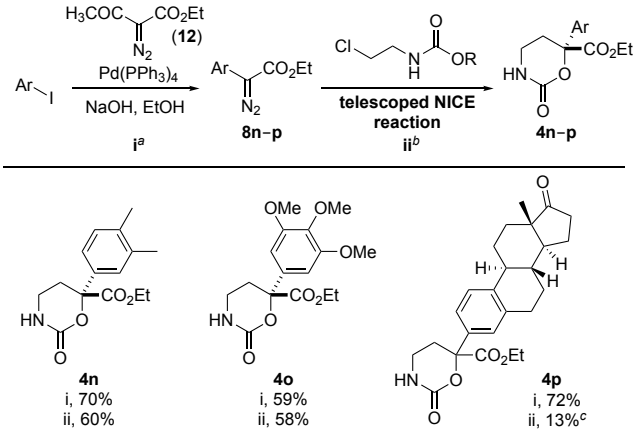
Scheme 3. N–H insertion/cyclization/ring-expansion (NICE) sequence to synthesize 6,6-disubstituted 1,3-oxazinan-2-ones.[a]



[a] Yields over 3 steps. [b] From **5** (0.5 mmol)**,** addition of TFA (10 equiv) in one-pot, 25 ºC, 1 h. [c] From **5** (0.5 mmol), filter through silica with CH_2Cl_2, concentrate, addition of TFA (5 equiv), toluene, 25 ºC, 0.5 h. [d] 3 mmol scale. [e] From **6** (0.5 mmol), addition of TfOH (10 equiv) in one-pot, 25 ºC, 0.5–1.5 h.

The combination of the NICE sequence with an initial cross-coupling to prepare the diazo reagent allowed further demonstration of both functional group compatibility of the reaction sequence and diversification (Scheme 4). Using a method adapted from a procedure developed by Wang for Pd-catalyzed coupling of aryliodides to prepare donor-acceptor diazo compounds, more elaborated aromatic substituents could be readily accommodated.[24] For example, oxazinanones **4n** and **4o** were prepared in 42% and 34% yield respectively over the 4 step sequence. Estrone derivative **4p** was also prepared, albeit in just 9% yield over 4 steps.

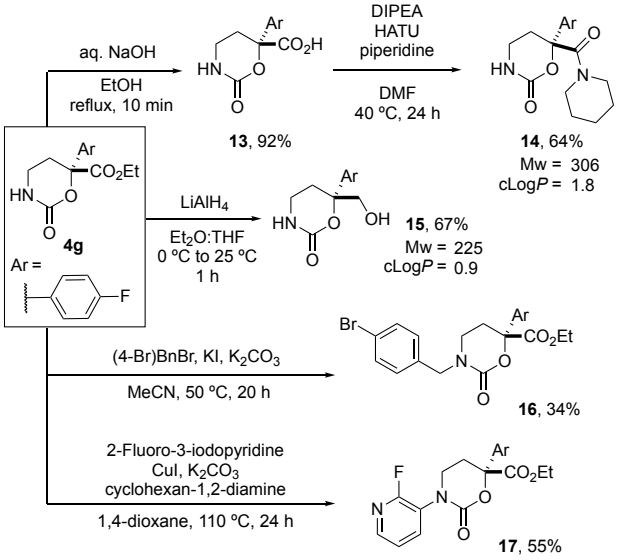
Scheme 4. Synthesis of 6,6-disubstituted 1,3-oxazinanones through a 4-step Pd-catalyzed cross-coupling/NICE reaction sequence.



[a] 2.0 mmol scale. For conditions used in steps i and ii see Supporting Information. [b] 0.5 mmol scale. [c] 0.2 mmol scale. **4p** is assumed to be a 1:1 mixture of diastereoisomers.

These 6,6-disubstituted 1,3-oxazinan-2-one products provide different functionalizable vectors for modification in an analysis of structural affinity for a biological target. From oxazinanone **4g**, ester hydrolysis to afford carboxylic acid **13** and subsequent amide bond formation gave **14** in good yields (Scheme 5). Reduction of the ester with $LiAlH_4$ in the presence of the cyclic carbamate successfully afforded alcohol **15**, which is an attractive fragment for screening. Alkylation of the nitrogen yielded **16** in moderate yield which is a functionalizable analogue of a biologically active scaffold (*cf* Figure 1B).[12] Copper catalyzed Ullmann coupling of an iodopyridine installed the aryl group on nitrogen to afford **17**.

Scheme 5. Functionalization of 6,6-disubstituted 1,3-oxazinanon-2-one scaffold 4g.



We propose a mechanism for the ring-expansion reaction involving protonation of the azetidine nitrogen, then C–N bond cleavage to ring-open the azetidine and form a carbocation intermediate. This intermediate would be trapped by the oxygen from the carbamate group, prior to loss of the carbamate R-group (*t*-Bu or Bn carbocations).[25] This is supported by the improved yields for the derivatives containing electron-rich aryl groups, which can stabilize the carbocation. To further probe this, a sample of enantioenriched Boc-protected azetidine **3a** (>99% ee) was subjected to the reaction conditions which gave partial racemization in the product oxazinanone (53–65% ee, presumably proceeding with retention at the stereogenic center; see Supporting Information for further details). Resubjecting the product to the reaction conditions showed that it was stable to racemization. From these observations we propose significant carbocation formation, where bond rotation of this intermediate competes with ring closure. This is likely to be dependent on the exact substrate structure, with the electronics of the aryl moiety and the protecting group employed influencing the lifetime of the carbocation.

In conclusion, we have developed a novel ring expansion of azetidine carbamates to afford 1,3-oxazinan-2-ones. The reaction is promoted by acid to form an intermediate carbocation upon azetidine ring-opening. Both electron-donating and electron-withdrawing aryl substituents were tolerated in this transformation to form a wide variety of 6,6-disubstituted 1,3-oxazinan-2-ones. We have developed an efficient 3 step NICE process for the synthesis of these scaffolds from acyclic precursors. A simple 4 step sequence to rapidly form functionalizable oxazinanone scaffolds from aryl iodides in 2 reaction-pots has also been demonstrated.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data, HPLC traces, and copies of ^{1}H and ^{13}C NMR spectra. (PDF)

All characterization data for synthesized compounds can be found at https://doi.org/10.14469/hpc/4982.

AUTHOR INFORMATION

Corresponding Author

*E-mail: j.bull@imperial.ac.uk.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

For financial support, we gratefully acknowledge The Royal Society [University Research Fellowships (to J.A.B and C.C.) and Research Grants (RG150444 and RGF\EA\180031)], the EPSRC and AstraZeneca for an iCASE studentship and Imperial College London. We acknowledge the EPSRC UK National Mass Spectrometry Facility at Swansea University.

REFERENCES

(1) (a) Mack, D. J.; Njardarson, J. T. *ACS Catal.* **2013**, *3*, 272–286; (b) Huang, C.-Y.; Doyle, A. G. *Chem. Rev.* **2014**, *114*, 8153–8198; (c) Ilardi, E. A.; Njardarson, J. T. *J. Org. Chem.* **2013**, *78*, 9533–9540; (d) Bull, J. A.; Croft, R. A.; Davis, O. A.; Doran, R.; Morgan, K. F. *Chem. Rev.* **2016**, *116*, 12150–12233.

(2) For reviews on ring opening/expansion of aziridines see: (a) McCoull, W.; Davis, F. A. *Synthesis* **2000**, *2000*, 1347–1365; (b) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247–258; (c) Stanković, S.; D'hooghe, M.; Catak, S.; Eum, H.; Waroquier, M.; Van Speybroeck, V.; De Kimpe, N.; Ha, H.-J. *Chem. Soc. Rev.* **2012**, *41*, 643–665.

(3) (a) Cardillo, G.; Gentilucci, L.; Tolomelli, A.; Tomasini, C. *Tetrahedron Lett.* **1997**, *38*, 6953–6956; (b) Tomasini, C.; Vecchione, A. *Org. Lett.* **1999**, *1*, 2153–2156; (c) C. S. Park, M. S. Kim, T. B. Sim, D. K. Pyun, C. H. Lee, D. Choi, W. K. Lee, J.-W. Chang, H.-J. Ha, *J. Org. Chem.* **2003**, *68*, 43–49; (d) T. B. Sim, S. H. Kang, K. S. Lee, W. K. Lee, H. Yun, Y. Dong, H.-J. Ha, *J. Org. Chem.* **2003**, *68*, 104–108; (e) Morán-Ramallal, R.; Liz, R.; Gotor, V. *Org. Lett.* **2008**, *10*, 1935–1938.

(4) For ring expansion of azetidines *via* bicyclic azetidinium ions: For reviews see (a) Couty, F.; Evano, G. *Synlett* **2009**, *2009*, 3053–3064. (b) Dolfen, J.; Yadav, N. N.; De Kimpe, N.; D'hooghe, M.; Ha, H.-J. *Adv. Synth. Catal.* **2016**, *358*, 3485–3511. For selected examples, see: (c) Outurquin, F.; Pannecoucke, X.; Berthe, B.; Paulmier, C. *Eur. J. Org. Chem.* **2002**, *2002*, 1007–1014; (d) Couty, F.; Durrat, F.; Prim, D. *Tetrahedron Lett.* **2003**, *44*, 5209–5212; (e) Van Brabandt, W.; Van Landeghem, R.; De Kimpe, N. *Org. Lett.* **2006**, *8*, 1105–1108; (f) Feula, A.; Male, L.; Fossey, J. S. *Org. Lett.* **2010**, *12*, 5044–5047; (g) Drouillat, B.; Dorogan, I. V.; Kletskii, M.; Burov, O. N.; Couty, F. *J. Org. Chem.* **2016**, *81*, 6677–6685. (h) *Via* ammonium ylides: Couty, F.; Durrat, F.; Evano, G.; Marrot, J. *Eur. J. Org. Chem.* **2006**, *2006*, 4214–4223; (i) Bott, T. M.; Vanecko, J. A.; West, F. G. *J. Org. Chem.* **2009**, *74*, 2832–2836. (j) *Via* ring-opening/closing cascade: Nocquet, P.-A.; Hazelard, D.; Compain, P. *Eur. J. Org. Chem.* **2011**, *2011*, 6619–6623. (k) [3,3]-sigmatropic rearrangement: Shimizu, T.; Koya, S.; Yamasaki, R.; Mutoh, Y.; Azumaya, I.; Katagiri, K.; Saito, S. *J. Org. Chem.* **2014**, *79*, 4367–4377. (l) Cu-catalyzed ring expansion: Ghorai, M. K.; Shukla, D.; Bhattacharyya, A. *J. Org. Chem.* **2012**, *77*, 3740–3753.

(5) (a) Drouillat, B.; Wright, K.; David, O.; Couty, F. *Eur. J. Org. Chem.* **2012**, *2012*, 6005–6012; (b) Wang, Z.; Sheong, F. K.; Sung, H. H. Y.; Williams, I. D.; Lin, Z.; Sun, J. *J. Am. Chem. Soc.* **2015**, *137*, 5895–5898; (c) Lugiņina, J.; Uzuleņa, J.; Posevins, D.; Turks, M. *Eur. J. Org. Chem.* **2016**, *2016*, 1760–1771; (d) Wright, K.; Drouillat, B.; Menguy, L.; Marrot, J.; Couty, F. *Eur. J. Org. Chem.* **2017**, *2017*, 7195–7201; (e) Cai, W.; Wang, S.; Jalani, H. B.; Wu, J.; Lu, H.; Li, G. *Org. Lett.* **2018**, *20*, 3833–3837; (f) Qian, D.; Chen, M.; Bissember, A. C.; Sun, J. *Angew. Chem. Int. Ed.* **2018**, *57*, 3763–3766.

(6) Banks, H. D. *J. Org. Chem.* **2006**, *71*, 8089–8097.

(7) De Rycke, N.; David, O.; Couty, F. *Org. Lett.* **2011**, *13*, 1836–1839.

(8) For reviews see: (a) Bott, T. M.; West, F. G. *Heterocycles* **2012**, *84*, 223–264; (b) Couty, F.; Drouillat, B.; Evano, G.; David, O. *Eur. J. Org. Chem.* **2013**, *2013*, 2045–2056; (c) Mehra, V.; Lumb, I.; Anand, A.; Kumar, V. *RSC Adv.* **2017**, *7*, 45763–45783.

(9) For an example of conversion of azetidines to oxazinanones in a 2-step process, *via* ring opening of an azetidine to an alkyl chloride intermediate, see: Ma, S.; Yoon, D. H.; Ha, H.-J.; Lee, W. K. *Tetrahedron Lett.* **2007**, *48*, 269–271.

(10) (a) See Ref 3 for relevant ring expansion of aziridines; (b) For recent single example of an acid catalyzed ring expansion from an amide bound azetidine to a piperidin-2-one: King, F. D.; Aliev, A.; Caddick, S.; Tocher, D. *Tetrahedron* **2015**, *71*, 3411–3416; (c) For electrocyclic expansion of benzofused azetidines, see: Rocaboy, R.; Dailler, D.; Zellweger, F.; Neuburger, M.; Salomé, C.; Clot, E.; Baudoin, O. *Angew. Chem. Int. Ed.* **2018**, *57*, 12131–12135.

(11) Young, S. D.; Britcher, S. F.; Tran, L. O.; Payne, L. S.; Lumma, W. C.; Lyle, T. A.; Huff, J. R.; Anderson, P. S.; Olsen, D. B.; Carroll, S. S.; Pettibone, D. J.; Brien, J. A. O.; Ball, R. G.; Balani, S. K.; Lin, J. H.; Chen, I.; Schleif, W. A.; Sardana, V. V.; Long, W. J.; Byrnes, V. W.; Emini, E. A. *Antimicrob. Agents Chemother.* **1995**, *39*, 2602–2605.

(12) (a) Xu, Z.; Tice, C. M.; Zhao, W.; Cacatian, S.; Ye, Y.-J.; Singh, S. B.; Lindblom, P.; McKeever, B. M.; Krosky, P. M.; Kruk, B. A.; Berbaum, J.; Harrison, R. K.; Johnson, J. A.; Bukhtiyarov, Y.; Panemangalore, R.; Scott, B. B.; Zhao, Y.; Bruno, J. G.; Togias, J.; Guo, J.; Guo, R.; Carroll, P. J.; McGeehan, G. M.; Zhuang, L.; He, W.; Claremon, D. A. *J. Med. Chem.* **2011**, *54*, 6050–6062; (b) Zhuang, L.; Tice, C. M.; Xu, Z.; Zhao, W.; Cacatian, S.; Ye, Y.-J.; Singh, S. B.; Lindblom, P.; Mckeever, B. M.; Krosky, P. M.; Zhao, Y.; Lala, D.; Kruk, B. A.; Meng, S.; Howard, L.; Johnson, J. A.; Bukhtiyarov, Y.; Panemangalore, R.; Guo, J.; Guo, R.; Himmelsbach, F.; Hamilton, B.; Schuler-Metz, A.; Schauerte, H.; Gregg, R.; Mcgeehan, G. M.; Leftheris, K.; Claremon, D. A. *Bioorg. Med. Chem.* **2017**, *25*, 3649–3657.

(13) (a) Ullrich, T.; Baumann, K.; Welzenbach, K.; Schmutz, S.; Camenisch, G.; Meingassner, J. G.; Weitz-Schmidt, G. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2483–2487; (b) Ina, S.; Kenjirou, Y; Kyoji, N. Nikken Chemicals Co Ltd, US6251897 (B1), 2001.

(14) Cassady, J. M.; Chan, K. K.; Floss, H. G.; Leistner, E. *Chem. Pharm. Bull.* **2004**, *52*, 1–26.

(15) Schmid, S. C.; Guzei, I. A.; Schomaker, J. M. *Angew. Chem. Int. Ed.* **2017**, *56*, 12229–12233.

(16) (a) Hilborn, J. W.; Lu, Z.-H.; Jurgens, A. R.; Fang, Q. K.; Byers, P.; Wald, S. A.; Senanayake, C. H. *Tetrahedron Lett.* **2001**, *42*, 8919–8921; (b) Wang, Y.-F.; Izawa, T.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1982**, *104*, 6465–6466.

(17) For use of CDI, chloroformates, isocyanates or strong base see ref 9 and selected examples: (a) Dao Thi, H; Decuyper, L.; Mollet, K; Kenis, S.; De Kimpe, N.; Van Nguyen, T.; D'hooghe, M. *Synlett* **2016**, *27*, 1100–1105; (b) Dao Thi, H.; Le Nhat Thuy, G.; Catak, S.; Van Speybroeck, V.; Van Nguyen, T.; D'hooghe, M. *Synthesis* **2018**, *50*, 1439–1456; (c) Caggiano, L.; Fox, D. J.; Warren, S. *Chem. Commun.* **2002**, 2528–2529; (d) Mayol-Llinàs, J.; Farnaby, W.; Nelson, A. *Chem. Commun.* **2017**, *53*, 12345–12348. (e) Iodocyclization of a γ,δ-vinyl carbamate: Fujita, M.; Kitagawa, O.; Suzuki, T.; Taguchi, T. *J. Org. Chem.* **1997**, 62, 7330–7335. (f) Gold-catalyzed 6-*exo-dig* cyclization: Robles-Machín, R.; Adrio, J.; Carretero, J. C. *J. Org. Chem.* **2006**, 71, 5023–5026. (g) Intramolecular Michael addition of carbamates to α,β-unsaturated esters: Hirama, M.; Shigemoto, T.; Yamazaki, Y.; Itô, S. *J. Am. Chem. Soc.* **1985**, *107*, 1797–1798. (h) CH amination: Donohoe, T. J.; Bataille, C. J. R.; Gattrell, W.; Kloesges, J.; Rossignol, E. *Org. Lett.* **2007**, *9*, 1725–1728. (i) Aminohydroxylation of olefins: Jakob, U.; Bannwarth, W. *Tetrahedron Lett.* **2015**, *56*, 6340–6344. (j) Cu-catalyzed ring closure of ureas: Jakob, U.; Bannwarth, W. *Tetrahedron Lett.* **2015**, *56*, 6340–6344. Others: (k) Takeda, Y.; Okumura, S.; Tone, S.; Sasaki, I.; Minakata, S. *Org. Lett.* **2012**, *14*, 4874–4877; (l) Ella-Menye, J.-R.; Sharma, V.; Wang, G. *J. Org. Chem.* **2005**, *70*, 463–469; (m) Rigoli, J. W.; Weatherly, C. D.; Vo, B. T.; Neale, S.; Meis, A. R.; Schomaker, J. M. *Org. Lett.* **2013**, *15*, 290–293.

(18) Buyck, T.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2014**, *136*, 11524–11528.

(19) Shen, J.-W.; Qin, D.-G.; Zhang, H.-W.; Yao, Z.-J. *J. Org. Chem.* **2003**, *68*, 7479–7484.

(20) Yousefi, R.; Struble, T. J.; Payne, J. L.; Vishe, M.; Schley, N. D.; Johnston, J. N. *J. Am. Chem. Soc.* **2018**,141, 618–625.

(21) Boddy, A. J.; Affron, D. P.; Cordier, C. J.; Rivers, E. L.; Spivey, A. C.; Bull, J. A. *Angew. Chem. Int. Ed.* **2019**, *58*, 1458-1462

(22) In the case where the free azetidine is desired, 4 M HCl in 1,4-dioxane shows orthogonal reactivity to TFA (See Supporting Information for reaction to synthesise **5a** in 71% yield).

(23) Reaction of Cbz protected ethyl 2-phenylpyrrolidine-2-carboxylate **10** under the same conditions gave only deprotected product (ethyl 2-phenylpyrrolidine-2-carboxylate **11**, see Supporting Information for further details).

(24) Ye, F.; Wang, C.; Zhang, Y.; Wang, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 11625–11628.

(25) The successful rearrangement of Cbz-protected azetidines with TFA, supports that the mechanism did not involve trapping of an intermediate carbamic acid. Treating Cbz-protected pyrrolidine **10** with TFA afforded no deprotected product.