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COMMUNICATION

Synthesis and Hetero-Diels–Alder Reactions of Enantiomerically Pure Dihydro-1*H*-azepines

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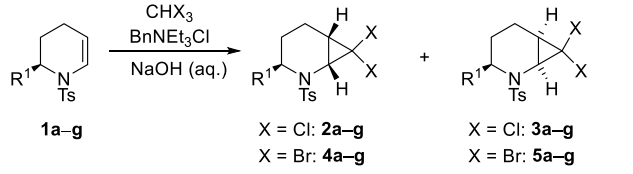
Thermolysis of enantiomerically pure 3-substituted 7,7-dihalo-2-azabicyclo[4.1.0]heptanes in the presence of K_2CO_3 gives in good yields 2-alkyl-6-halo-1-tosyl-2,3-dihydro-1*H*-azepines. These undergo highly stereoselective [4+2] cycloaddition reactions with heterodienophiles and arylation/alkenylation under Suzuki conditions.

Stereodefined azepine and azepane derivatives are valuable molecular scaffolds present in several bioactive natural products and pharmaceutically relevant molecules.[1] Species featuring these seven-membered heterocyclic cores and related compounds have received considerable attention because of their potential as glycosidase inhibitors[2] and anticancer,[3] anti-diabetic[4] and anti-viral agents.[5] Consequently, a number of methodologies have been developed for their preparation, with recent accounts detailing ring-expansion cascades,[6] cycloaddition approaches[7] and cyclisation strategies.[8]

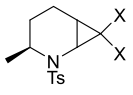
The importance of *gem*-dihalocyclopropanes in synthesis stems in large part from their ready accessibility and high reactivity in a range of transformations.[9] More specifically, a number of synthesis methodologies that have been developed exploit the reactivity of cyclopropanes bearing nitrogen substituents, most notably involving ring-opening and rearrangement processes.[10] Of particular interest to us were the relatively unexplored thermal ring-expansion reactions of *gem*-dihalocyclopropanes in which the three-membered ring was fused to an N-heterocycle. These often low-yielding processes required high temperatures or activation by silver(I) salts to generate the putative allylic cationic intermediates, which were typically intercepted by alcohols or hydride reagents to afford vinyl halides.[11] To date, there have been few reports of the successful isolation of diene products in the absence of a nucleophilic additive or solvent.[12]

Our laboratory has previously investigated the synthesis and chemistry of *N*-arylsulfonyl-1,2,3,4-tetrahydropyridines, in particular the utility of these for the stereoselective elaboration of more complex N-heterocycles.[13] It occurred to us that bicyclo[4.1.0] products of dihalocyclopropanation of enantiomerically pure *N*-arylsulfonyl-1,2,3,4-tetrahydropyridines would undergo electrocyclic ring-opening and deprotonation to give stereodefined dihydroazepines. In this work, we describe base-mediated thermal ring-expansion reactions of 3-substituted 7,7-dihalo-2-azabicyclo[4.1.0]-heptanes to give halogenated dihydro-1*H*-azepines, and present stereoselective [4+2] cycloaddition and Pd(0)-catalysed cross-coupling reactions of these novel scaffolds.

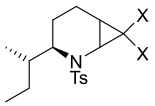
Table 1 Cyclopropanation of enantiomerically pure 1,2,3,4-tetrahydropyridines



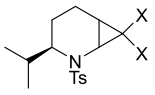
1a–g X = Cl: **2a–g** X = Br: **4a–g** X = Cl: **3a–g** X = Br: **5a–g**



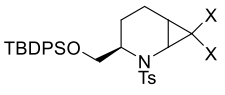
X = Cl: yield: 90%; 76:24 **2a**:**3a**
X = Br: yield: 78%; 60:40 **4a**:**5a**



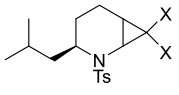
X = Cl: yield: 76%; 80:20 **2b**:**3b**
X = Br: yield: 62%; 65:35 **4b**:**5b**



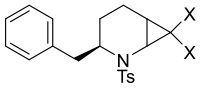
X = Cl: yield: 70%; 84:16 **2c**:**3c**
X = Br: yield: 64%; 63:37 **4c**:**5c**



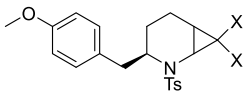
X = Cl: yield: 55%; 80:20 **2d**:**3d**
X = Br: yield: 53%; 65:35 **4d**:**5d**



X = Cl: yield: 81%; 77:23 **2e**:**3e**
X = Br: yield: 64%; 55:45 **4e**:**5e**



X = Cl: yield: 84%; 80:20 **2f**:**3f**
X = Br: yield: 74%; 60:40 **4f**:**5f**



X = Cl: yield: 77%; 75:25 **2g**:**3g**
X = Br: yield: 73%; 62:38 **4g**:**5g**

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Electronic Supplementary Information (ESI) available: full experimental procedures, spectroscopic and X-ray crystallographic data (for **2b/3b**, **15**, **23**, **37**

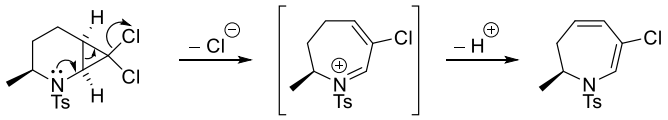
The enantiomerically pure 2-substituted 1,2,3,4-tetrahydropyridines **1a**–**g** used in this study were synthesised according to the procedure of Harrity and co-workers[14] from L-aminoacid-derived *N*-tosylaziridines.[15] Substrates **1a**–**g** were subjected to dihalocyclopropanation under conditions reported by Mąkosza,[16] giving dichloro- and dibromo-substituted 2-azabicyclo[4.1.0]heptanes **2a**–**g**, **3a**–**g** and **4a**–**g**, **5a**–**g**, respectively as *anti*/*syn* mixtures in good to excellent yields. For examples **a** (R^1 = Me), **d** (R^1 = $TBDPSOCH_2$), **f** (R^1 = Bn), and **g** (R^1 = 4-$MeOC_6H_4CH_2$), compounds **2**/**3** (X = Cl) and **4**/**5** (X = Br) were obtained as inseparable *anti*/*syn* mixtures (Table 1).

Moderate stereoselectivity for the *anti* diastereoisomers **2** and **4** was observed for all the substrates studied, as was indicated by ^{1}H NMR analysis and assigned unambiguously by X-ray crystallographic analysis of **2a** and **3a**. Similar facial selectivity in the dichlorocyclopropanation of cyclic enamides has been reported recently.[17] We postulate that the lower *anti*-selectivity observed in the dibromocarbene addition reactions is a consequence of the greater steric interaction of the carbene with the *N*-tosyl group, which adopts a conformation *anti* to the R substituent.[13]

Initial ring-expansion experiments involved exposure of the *ca*. 3:1 mixture of **2a** + **3a** to varying combinations of base and silver salts (see Supporting Information for optimisation conditions). Although no consumption of substrate was observed at ambient temperature, the use of microwave irradiation at 150 °C resulted in conversion of only the *syn* diastereoisomer **3a** into the desired dihydro-1*H*-azepine **6**. Further investigation revealed that Ag(I) additives were unnecessary and that the addition of one equivalent of potassium carbonate in toluene at 150 °C for 5 hours under microwave irradiation conditions resulted in improved yields of **6**, although the *anti* diastereoisomer **2a** still failed to react under these modified conditions. Several additional 7,7-dihalo-2-azabicyclo[4.1.0]heptanes were subjected to the optimised ring-expansion reaction conditions either as pure *syn* isomers **3** (**3b**, **3e**: R^1 = *s*-Bu, *i*-Bu) and **5** (**5b**, **5e**: R^1 = *s*-Bu, *i*-Pr) or as *anti*/*syn* mixtures of **2**/**3** (**2**/**3a**, **2**/**3f**: R^1 = Me, Bn) and **4**/**5** (**4**/**5a**, **4**/**5f**, **4**/**5g**: R^1 = Me, Bn, 4-$MeOC_6H_4CH_2$) to give dihydroazepines **6**–**14** in good to excellent yields based on the *syn* isomers **3** and **5** (Table 2). Dihydroazepines **9**, **13** and **14** were inseparable from the unreacted *anti* substrates **2f**, **4f** and **4g**, respectively.

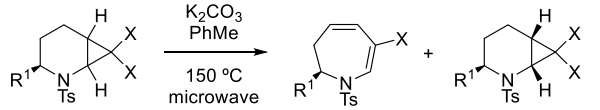
The difference in ring-expansion reactivity between the *syn* isomers **3**/**5** and the *anti* isomers **2**/**4** is striking. Inspection of the obtained crystal structures for **2a** and **3a** indicates a greater degree of nitrogen pyramidalisation in the *syn*-isomer **3a** than in the *anti*-isomer **2a** (see X-ray Supporting Information). We speculate that this increases the availability of the nitrogen lone pair in **3** to participate in cyclopropane ring opening (Scheme 1).

Scheme1 Proposed mechanism for ring-opening of **3a**

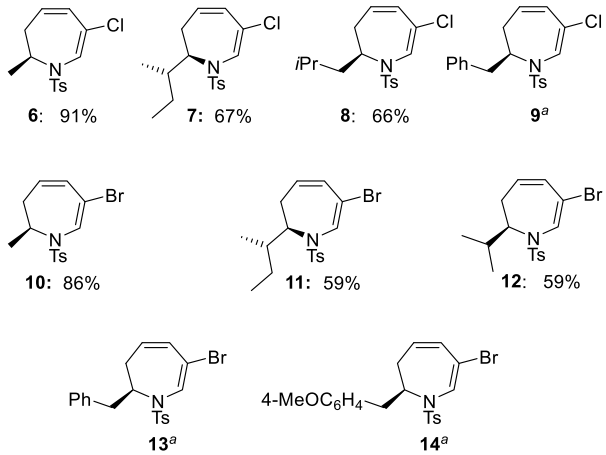


3a **6**

Table 2 Ring-expansion of 7,7-dihalo-2-azabicyclo[4.1.0]heptanes to give 2,3-dihydro-1*H*-azepines **6**–**14**[a]



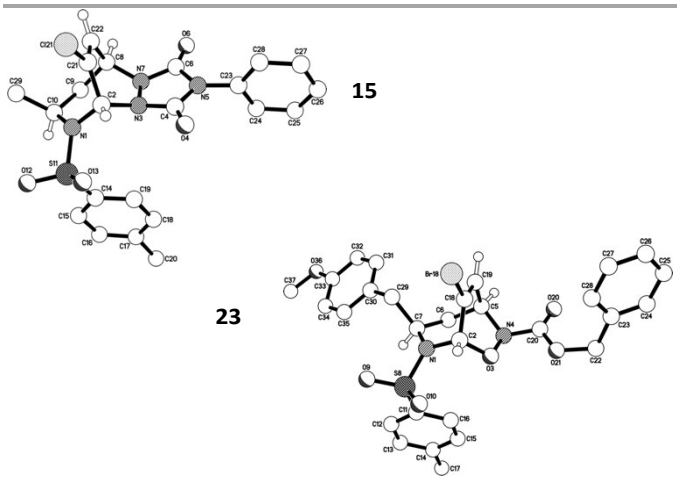
X = Cl: **2**/**3a**, **3b**, **3e**, **2**/**3f** X = Cl: **6**–**9** X = Cl: **2a**, **2f**
X = Br: **4**/**5a**, **5b**, **5c**, **4**/**5f**, **4**/**5g** X = Br: **10**–**14** X = Br: **4a**, **4f**, **4g**



[a]Compounds **9**, **13**, **14** were obtained as inseparable mixtures with unreacted *anti* substrates **2f**, **4f** and **4g**, respectively

The cycloaddition reactivity of the enantiomerically pure dihydroazepines was investigated next. Combination of analogues **6**, **9**, **13** and **14**[18] at ambient temperature with the highly reactive heterodienophiles 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione, and *tert*–butyl or benzyl nitrosoformate generated *in situ* by Bu_4NIO_4-mediated oxidation of the corresponding alkyl hydroxycarbamates gave in excellent yields the products of [4+2] heterocycloaddition, exclusively *anti* with respect to the R^1 substituent on the seven-membered ring (Table 3). The stereochemistry of the cycloadducts **15** and **23** was unequivocally established by X-ray crystallographic analysis (Figure 1), which demonstrated also the complete regioselectivity of formation of the benzyl nitrosoformate adduct **23**.

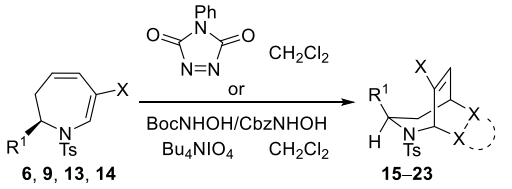
Figure 1 The molecular structures of **15** and **23**



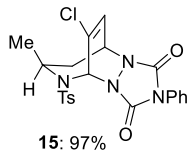
15

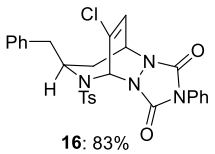
23

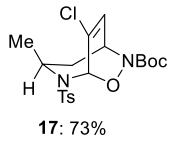
Table **3** Hetero-Diels–Alder reactions of 6-halo-2,3-dihydro-1*H*-azepines[a]

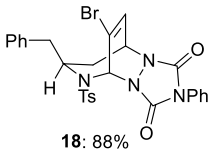


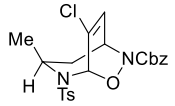
6, **9**, **13**, **14** → **15**–**23**

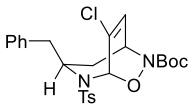

15: 97%

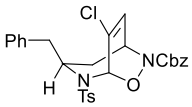

16: 83%

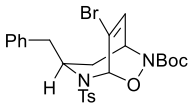

17: 73%

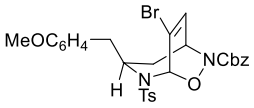

18: 88%


19: 58%


20: 58%

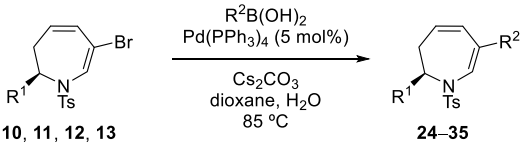

21: 52%


22: 68%

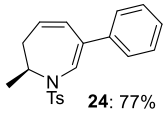

23: 77%

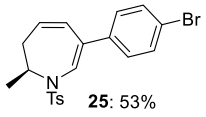
[a]Compounds **9**, **13**, **14** were used as inseparable mixtures with unreacted **2f**, **4f** and **4g**, respectively; yields of **16**, **18**, **20**–**23** are based on the calculated amount of the dihydroazepines in the mixtures (^{1}H NMR)

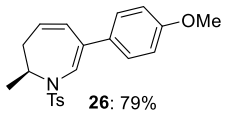
Table **4** Suzuki cross-coupling reactions of 6-bromo-2,3-dihydro-1*H*-azepines[a]

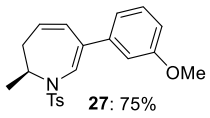


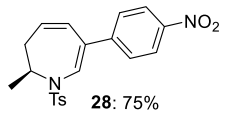
10, **11**, **12**, **13** → **24**–**35**

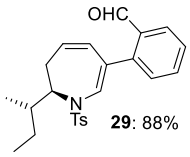

24: 77%

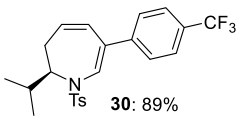

25: 53%

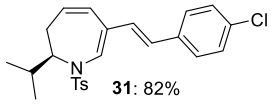

26: 79%

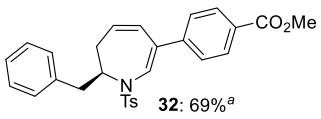

27: 75%

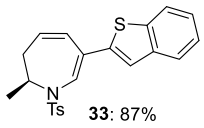

28: 75%

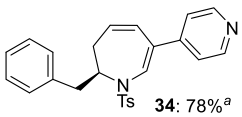

29: 88%

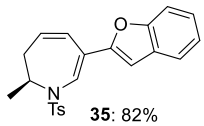

30: 89%


31: 82%


32: 69%[a]


33: 87%


34: 78%[a]


35: 82%

[a]2-Benzyl-6-bromo-1-tosyl-2,3-dihydro-1*H*-azepine **13** was used in these reactions as an inseparable mixture with unreacted **4f**; yields for products **32** and **34** are for the two steps from the **4f**/**5f** mixture based on the calculated amount of **5f** (^{1}H NMR)

The last part of this study looked at the functionalisation of bromo-substituted 6-bromo-2,3-dihydro-1*H*-azepines using Pd-catalysed cross-coupling reactions. Substrates **10**–**13** were coupled with a range of electron-rich and electron-poor arylboronic acids under Suzuki–Miyaura conditions to give the 6-arylated analogues in excellent yields (Table 4).[19] On combination with excess 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione in CH_2Cl_2 at ambient temperature, the triene product **31** entered into hetero-Diels–Alder reaction to give in 87% yield a chromatographically separable mixture of the mono- and bis-adducts **36** and **37** in a 1:2.5 ratio (Scheme 2). The stereochemistry of mono-adduct **36** was inferred from the stereoselectivity observed in the hetero-Diels–Alder reactions of **6**, **9**, **13** and **14**; that of the bis-adduct **37** was established by X-ray crystallographic analysis (Figure 2).

This selectivity demonstrated the expected greater intrinsic reactivity of the *s*-cis cyclic diene in **31** with respect to the conformationally more flexible styryl-containing endocyclic/exocyclic moiety.

Scheme 2 Formation of **36** and **37**

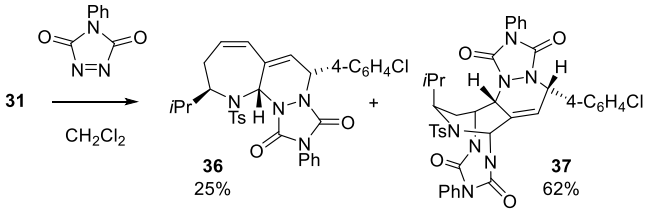


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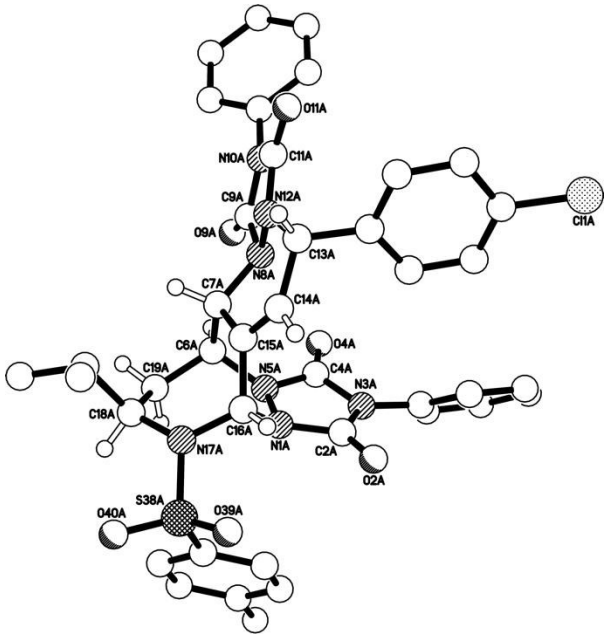
Figure 2 The molecular structure of **37**



In conclusion, we have developed an efficient ring-expansion sequence for the conversion of stereodefined 7,7-dihalo-2-azabicyclo[4.1.0]heptanes into enantiomerically pure 2,3-dihydro-1*H*-azepines. These molecular scaffolds undergo hetero-Diels–Alder cycloadditions with high stereoselectivity and complete regioselectivity. Additionally, these entities can be efficiently elaborated with a range of aromatic substituents using Suzuki coupling reactions. Further investigation into dihydroazepine derivatisation and application of this chemistry to natural and unnatural product synthesis is ongoing.

Conflicts of interest

The authors have no conflicts of interest to declare.

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18 In the hetero-Diels–Alder reactions 2,3-dihydro-1*H*-azepines **9**, **13** and **14** were used as inseparable mixtures with the unreacted *anti*-7,7-dihalo-2-azabicyclo[4.1.0]heptanes **2f**, **4f** and **4g**, respectively.

19 Bromo-substituted hetero-Diels–Alder adducts **18** and **22** also were found to be effective substrates in Suzuki reactions, giving arylated products in 75–98% yield. Full experimental and spectroscopic details are provided in the ESI.