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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 largely 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 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.

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-amino acid-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 ESI† for optimisation conditions). Although no consumption of substrate was observed at ambient temperature,

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† Electronic supplementary information (ESI) available: Full experimental procedures, spectroscopic and X-ray crystallographic data (for **2b**/**3b**, **15**, **23**, **37**). CCDC 2011985–2011988. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0cc04413j

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

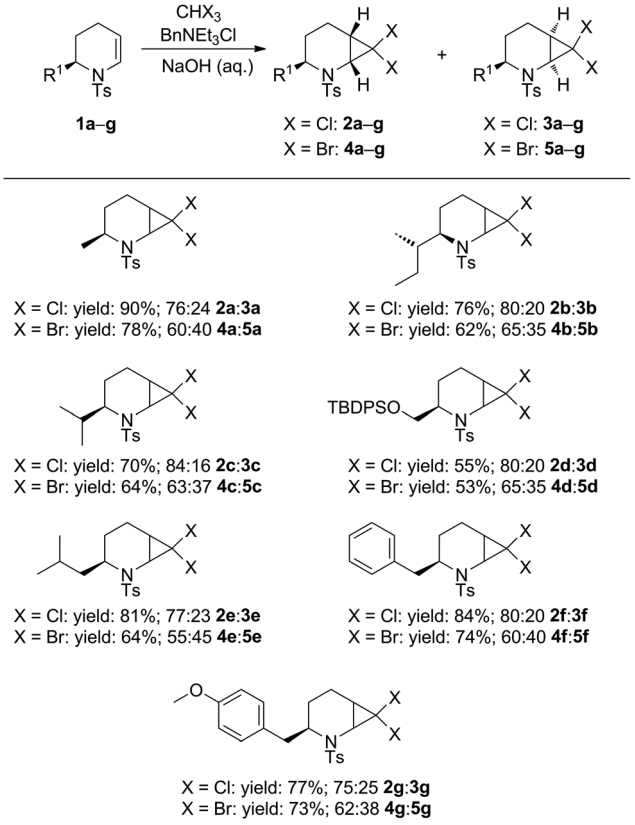
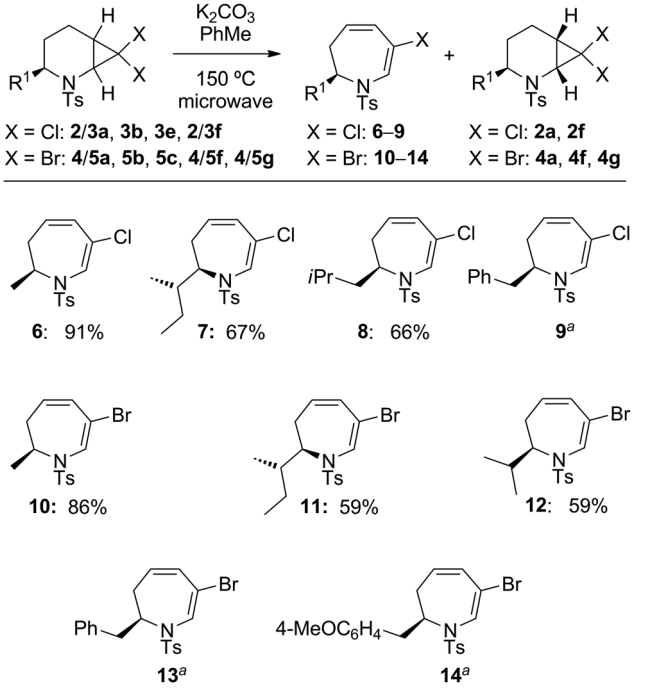


Table 2 Ring-expansion of 7,7-dihalo-2-azabicyclo[4.1.0]heptanes to give 2,3-dihydro-1*H*-azepines **6–14**[a]



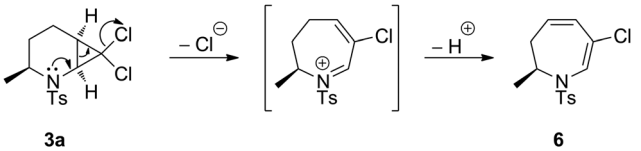
[a] Compounds **9**, **13**, **14** were obtained as inseparable mixtures with unreacted *anti* substrates **2f**, **4f** and **4g**, respectively.

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 ESI†). We speculate that this increases the availability of the nitrogen lone pair in **3** to participate in cyclopropane ring opening (Scheme 1).

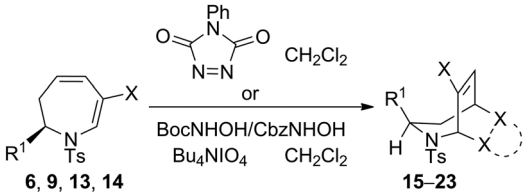
The cycloaddition reactivity of the enantiomerically pure dihydroazepines was investigated next. Combination of analogues **6**, **9**, **13** and **14**[18] at ambient temperature with the highly reactive heterodienophiles 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione, and *tert*-butyl or benzyl nitrosoformate 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 (Fig. 1), which demonstrated also the complete regioselectivity of formation of the benzyl nitrosoformate adduct **23**.

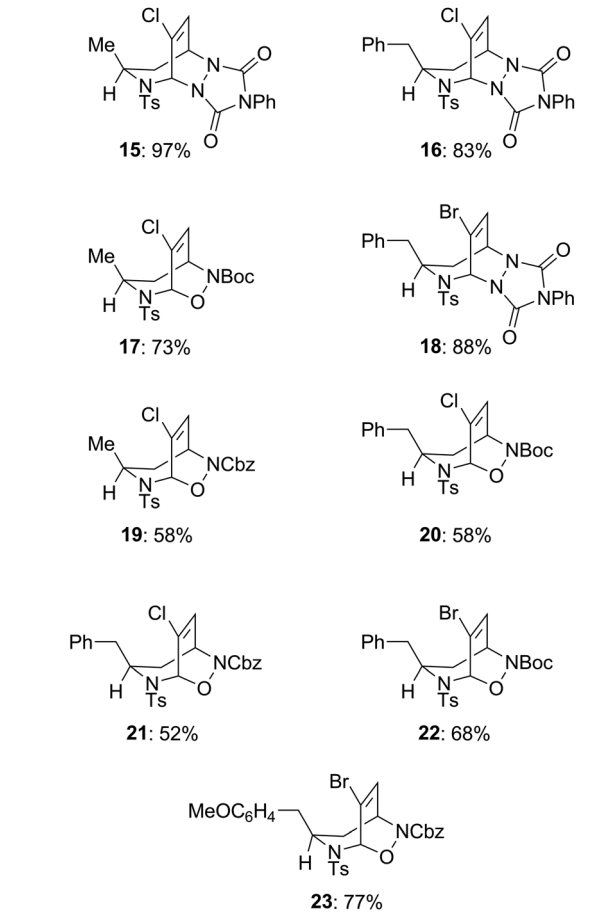
The last part of this study looked at the functionalisation of bromo-substituted 6-bromo-2,3-dihydro-1*H*-azepines using Pd-catalysed cross-coupling reactions. Substrates **10–13** were coupled with a range of electron-rich and electron-poor arylboronic acids under Suzuki–Miyaura conditions to give the 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



Scheme 1 Proposed mechanism for ring-opening of **3a**.

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





[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).

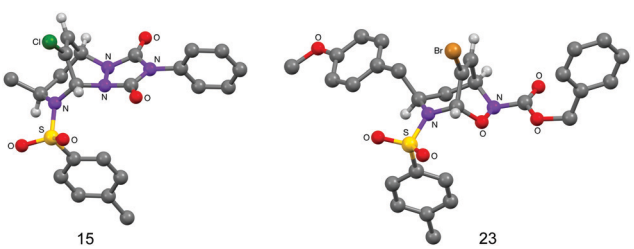
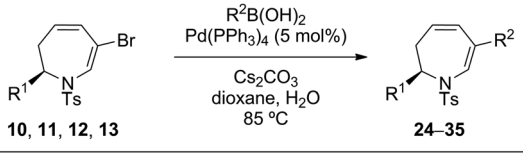
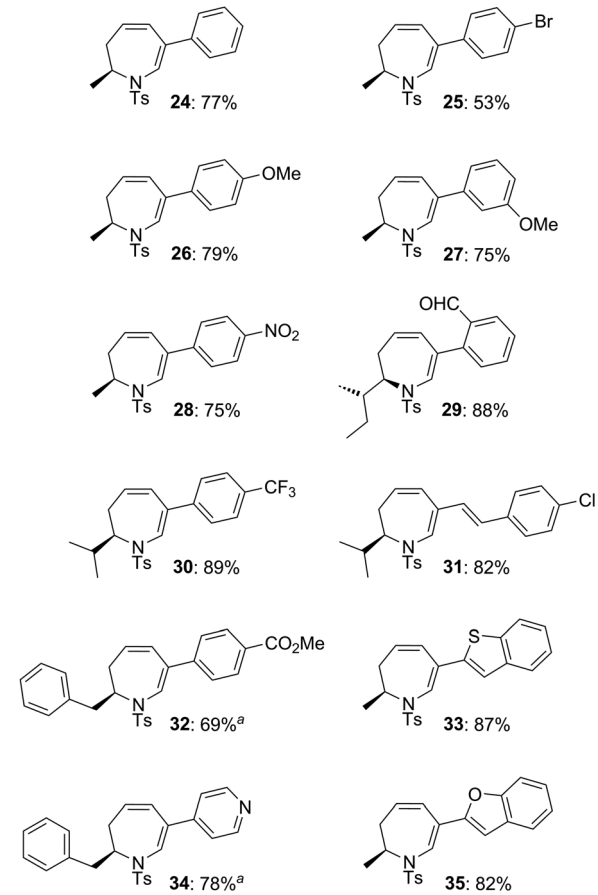


Fig. 1 The crystal structures of **15** and **23**.

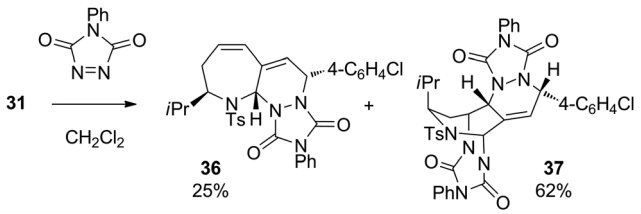
inferred from the stereoselectivity observed in the hetero-Diels–Alder reactions of **6**, **9**, **13** and **14**; that of the bis-adduct **37** was established by X-ray crystallographic analysis (Fig. 2).

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





[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).



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

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.

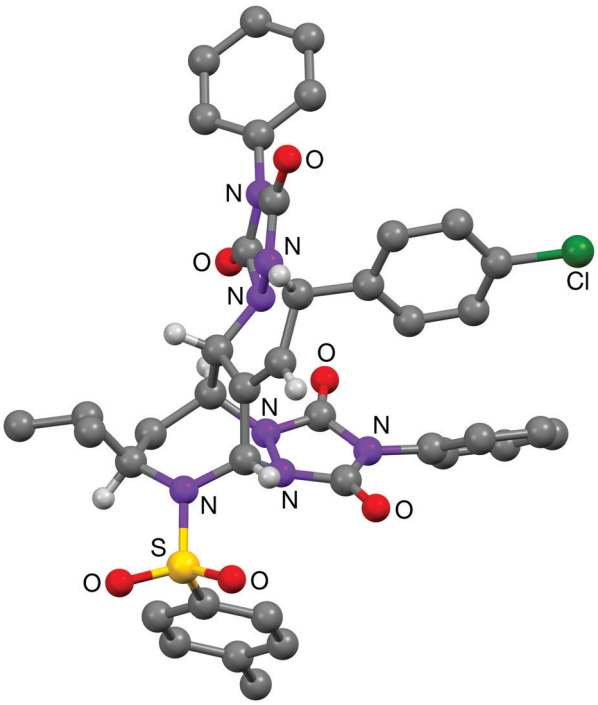


Fig. 2 The structure of **37-A**, one of the two independent molecules present in the crystal of **37**.

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.

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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†.

