A detailed investigation of the aza-Prins reaction†

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The development of a Lewis acid-promoted aza-Prins reaction to form piperidines and pyrrolidines is described. Indium trichloride has been found to be a highly successful and mild Lewis acid for promoting this reaction. A thorough mechanistic investigation is described, including the factors that influence the formation of the 5- or 6-membered ring product(s).

1. Introduction

The Prins reaction[1–3] has become one of the cornerstone reactions of organic synthesis over the last 15 years, being employed in the key stages of many natural product total syntheses. Its particular strength is in the synthesis of heterocycles, and especially pyrans and related compounds. Piperidines are even more widespread in natural products and also pharmaceuticals.[4] Despite the fact that there are now many routes by which to prepare piperidines,[4] it has long been a target of many research groups to develop a viable nitrogen-based version of the Prins reaction, in order to prepare piperidines—the so-called aza-Prins reaction.

Moderate success has started to be achieved towards this goal by various research groups. Historically, Overman has performed pioneering work in the area of Brønsted acid-catalysed iminium ion cyclisations,[5–12] and this has been further studied by Tanner;[13] from this, we have developed the Lewis acid-promoted aza-silyl-Prins reaction to form tetrahydropyridines.[14–17] Padwa has also performed related reactions involving *N*-acyliminium ions.[18–20] Several groups have used aza-Prins-type cyclisations in total syntheses, without always making specific reference to the key Prins-type step: Frank and Aubé[21] reported a titanium tetrachloride-promoted aza-Prins-type reaction in their synthesis of the core tricycle of the martinellines; Hanessian *et al.*[22] used tin tetrabromide to promote the *N*-acyloxyiminium ion aza-Prins cyclisation to form octahydroindoles; Hsung *et al.*[23] employed a formic acid-promoted aza-Prins reaction (followed by Wharton rearrangement) in their synthesis of the (+)-cylindricines, and Shair *et al.* used an aza-Prins bicyclisation in their approach to the endothelial cell proliferation inhibitor (+)-Cortistatin.[24] In 2005, Armstrong *et al.* reported an aza-Prins-pinacol approach to 7-azabicyclo[2.2.1]heptanes[25,26] but it was not until 2006 that Martín *et al.*[27,28] reported the first study devoted specifically to developing an aza-Prins reaction, in the conventional sense of a Prins reaction, and followed this with a catalytic version in 2009.[29] More recently, Yadav *et al.* have also reported that $BiCl_3$,[30] GaI_3/I_2[31] and heteropoly acids[32] (such as phosphomolybdic acid) will also promote aza-Prins type reactions. In 2007, Shimizu *et al.* reported that olefins and acetylenes, in the presence of titanium tetraiodide and iodine, underwent an aza-Prins-type reaction to yield 1,3-iodoamines.[33] Finally, both Fuchigama *et al.*[34] and ourselves[35] have utilised fluorine in Prins-type reactions to piperidines, Fuchigami by using hydrogen fluoride salts in ionic liquids, and we incorporated fluorine in the cyclisation precursors.

However, many of these methods have distinct drawbacks, primarily either low yield or a lack of stereocontrol between substituents during the cyclisation. What is clear from the literature, however, is a lack of a detailed survey and study of potential conditions for a Lewis acid-promoted aza-Prins reaction, and a detailed study on the effects of conditions and of substituents on the outcome of any successful aza-Prins reaction. Herein, we attempt to fill this void and report our findings on developing a Lewis acid-promoted aza-Prins cyclisation reaction.

2. Results and discussion

2.1. Initial studies and Lewis acid screening

Initially, we simply wished to screen a variety of reaction conditions for the formation of 1,2,4-tri- and 1,2,4,6-tetra-substituted piperidines from appropriately substituted homoallylic amines and an aldehyde. Two methods were employed for the preparation of the corresponding amines: tosylation of but-3-en-1-ol followed by displacement with an amine, or an iodine-catalysed one-pot multi-component reaction between an aldehyde, benzyl carbamate and allyltrimethylsilane (Scheme 1).[36]

Employing our previously optimised conditions for the related silicon-modified aza-silyl-Prins reaction (*N*-protected silylated homoallylic amine, aldehyde and Lewis acid in a 1 : 1 : 1 ratio in acetonitrile at reflux for 3–36 h) as a starting point, we proceeded to screen a range of conditions for the aza-Prins cyclisation (Scheme 2). This was then extended to a wide variety of conditions

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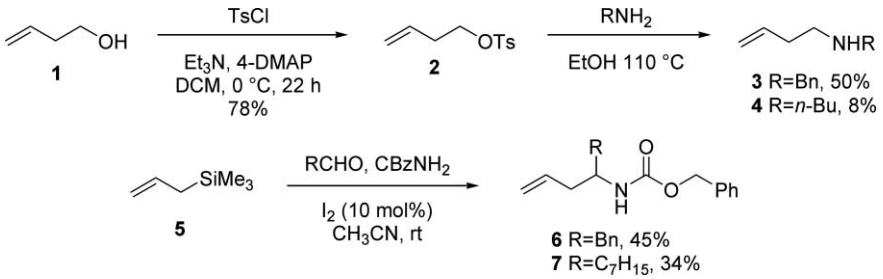
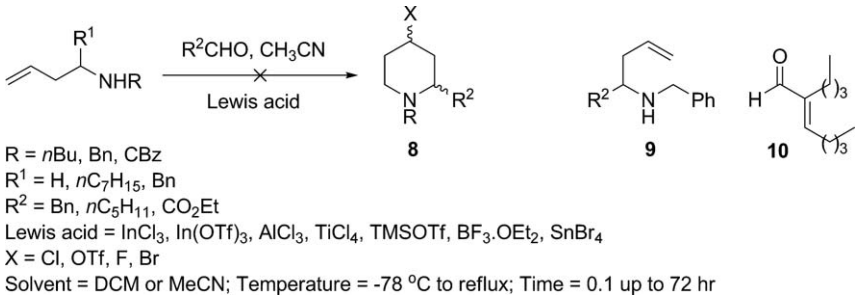
† Electronic supplementary information (ESI) available: The preparation of, and characterisation data for, the precursor alcohols, their tosyl derivatives, and for the *N*-tosyl amines, and full details concerning the unsuccessful Lewis acid screening conditions. CCDC reference numbers 748949–748951. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b915797b



Scheme 1 Synthesis of homoallylic amines.



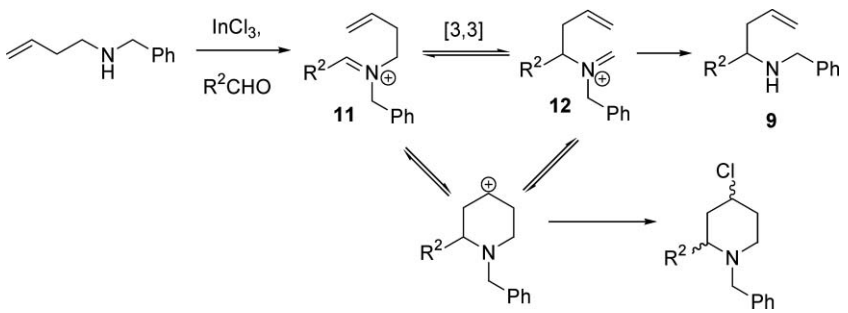
Scheme 2 Lewis acid screening.

and Lewis acids; however, all failed to give any piperidine **8**, with quantitative recovery of starting material in almost every case. Even the use of the more reactive ethyl glyoxylate, which only required much milder conditions in the aza-silyl-Prins reaction, failed to yield any product. The full range of conditions and exact variables explored is presented in the ESI.†

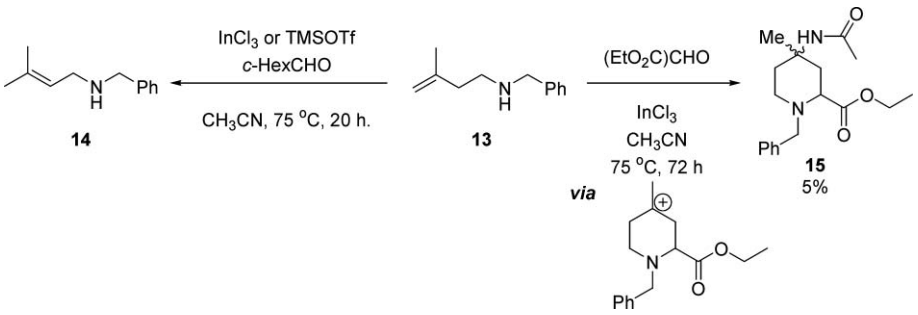
Two reactions did not lead either to recovered starting material or decomposition. The first involved the use of indium triflate, which with any substrate or substituent gave the aza-Cope hydrolysis product **9**. It is thought that this arises from initial iminium ion **11** formation, followed either by direct aza-Cope rearrangement, or by cyclisation and subsequent ring opening, to give a new iminium ion **12**, which was then hydrolysed under the reaction conditions to the secondary amine isolated (Scheme 3). While not useful, this product does at least imply that initial iminium ion formation was taking place under the reaction conditions, even if not going on to give the desired product. The second product, which was only observed on one occasion when using indium trichloride with hexanal, was the aldol product **10** in 45% yield. The most probable reason for the lack of cyclised product being obtained is an instability of the cyclic carbocation formed during this reaction, preferring to exist as an open-form iminium ion, with the cyclic carbocation not being sufficiently stable or long lived to allow trapping to the desired piperidine.

The use of the *N*-carbamate-protected amine similarly failed to give any cyclised product; not unsurprising given the extent of delocalisation of the lone pair of electrons on the nitrogen atom.

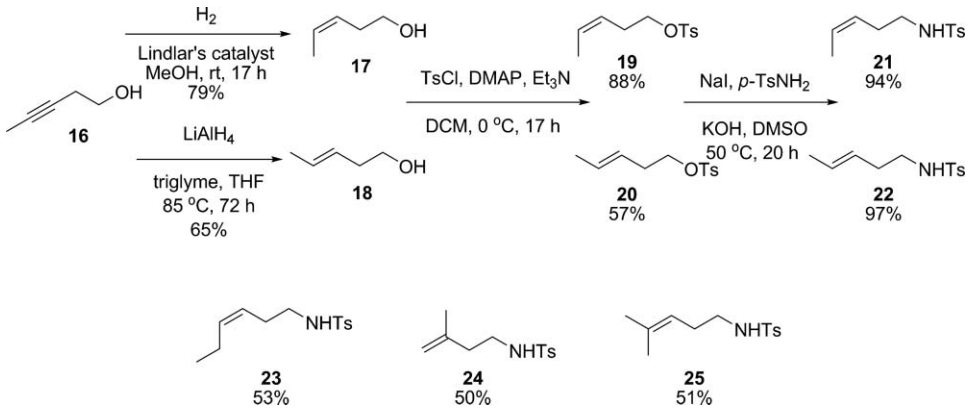
Given the relative ease of cyclisation in the aza-silyl-Prins reaction, compared with the lack of observed cyclisation in these examples, the only difference between the two reactions was the presence of a stabilising trimethylsilyl moiety in the aza-silyl-Prins reaction, which stabilises the intermediate, cyclised carbocation by the β-effect. Therefore, it was decided to try to impart some extra stabilisation in the carbocation intermediate in the aza-Prins reaction by the introduction of an electron donating methyl group on the alkene in the homoallylic amine, as the corresponding



Scheme 3 Aza-Cope rearrangement leading to the hydrolysis product.



Scheme 4 Unsuccessful aza-Prins reactions of *N*-benzyl-3-methylbut-3-enylamine.



Scheme 5 Preparation of (*E*)- and (*Z*)-alkenyl *N*-tosylamines.

alcohol was commercially available. The *N*-benzylamine **13** was prepared as before, *via* tosylation and reaction with benzylamine. After coupling of this amine with cyclohexanecarboxaldehyde in the presence of either indium trichloride or TMSOTf, the only product obtained was the isomerised amine **14** (Scheme 4). On reaction with ethyl glyoxylate in the presence of indium trichloride after 3 d at reflux, TLC showed complete consumption of the amine substrate and GC-MS showed presence of the molecular ion for the acetonitrile-trapped piperidine **15** (Scheme 4). However, after flash chromatography, this product was only obtained pure in a disappointing 5% yield, with no other identifiable products.

Concurrent with our research, Martín *et al.* have reported the use of iron(III) halides in an aza-Prins and an alkyne-aza-Prins type reaction, and employing *N*-tosyl amines.[27,29] Surprisingly, iron(III) halides have been quite unsuccessful in our previous work.[14,15,17,37] Further, it is known that the nitrogen atom in a sulfonamide is of similar nucleophilicity to that of the oxygen atom in an alcohol moiety, which is perhaps why this demonstrated success for Martín, by enhancement of the electrophilicity of the iminium ion and so aiding the cyclisation step. Therefore, we decided to repeat our failed cyclisations with our preferred Lewis acid, indium trichloride (owing to it being cheaper, easier to use/manipulate and more moisture tolerant/resistant to moisture in the atmosphere), with a *N*-tosylamine.

Starting with pent-3-yn-1-ol, we first prepared both the *E*- and *Z*-alkenyl tosylamines **21** and **22** *via* hydrogenation (*Z*, **17**) or $LiAlH_4$ reduction (*E*, **18**), tosylation (**19** and **20**) and reaction with 4-methylbenzenesulfonamide in the presence of catalytic quantities of sodium iodide (Scheme 5). Additional homoallylic amines **23**, **24** and **25** were also prepared by this method.

2.2. Aza-Prins cyclisations: use of (*Z*)-alkenes

The use of the (*Z*)-alkenyl homoallylic tosylamine **21** in an aza-Prins reaction promoted by indium trichloride was successful, giving piperidines in reasonable yields. Scandium triflate was also found to give piperidines, albeit in consistently 10–15% lower yields, although having the advantage that the scandium triflate was recyclable after an aqueous work up. A number of aldehydes were successfully employed (Table 1), with the optimum reaction conditions being amine : indium trichloride : aldehyde 1 : 1.5 : 1.5.

We were surprised to observe a second cyclised product in these reactions, in addition to the piperidine: 3-(1-chloroethyl)pyrrolidines. All the reactions showed complete consumption of starting materials. GCMS also suggested traces of minor diastereoisomers, which could have been formed in the reaction, or more probably from the very low traces of the inseparable minor (*E*)-geometric isomer (that had been formed in the reduction step earlier in the synthesis of the *N*-tosyl amine). However, these trace isomers could not be isolated nor their relative stereochemistry determined. Particularly low yields of 4-chloropiperidines were observed with benzaldehyde and ethyl glyoxylate (Table 1, entries 2 and 5) and without any pyrrolidine or other product. This is not unsurprising with benzaldehyde, which has consistently given low yields in indium trichloride-mediated Prins-type reactions,[14,37] but was unexpected for ethyl

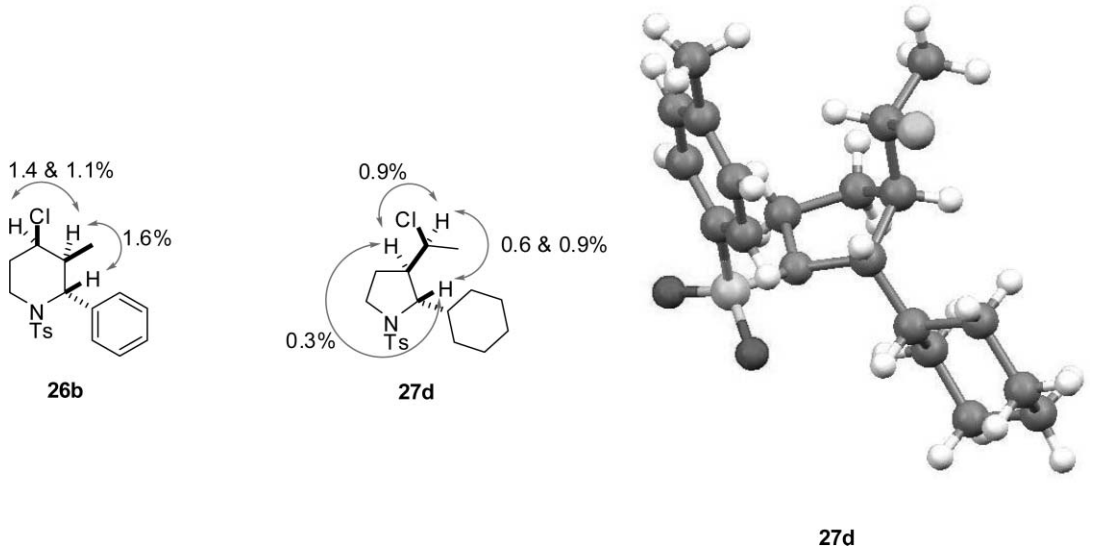


Fig. 1 NOE data and X-ray structure for 4-chloro-3-methyl-2-phenyl-1-tosylpiperidine (**26b**) and 3-(1-chloroethyl)-2-cyclohexyl-1-tosylpyrrolidine (**27d**)

Table 1 Aza-Prins reactions of (*Z*)-homoallyl tosylamine

Entry	R	Time/h	Yield **26** (%)	Yield **27** (%)
1a	n-C_7H_{15}	17	35	35
2b	Ph	144	15	0
3c	$Ph(CH_2)_2$	17	40	36
4d	*c*-Hex	144	26	50
5e	CO_2Et	1	20	0

glyoxylate. High overall yields of cyclised material were obtained for the three aliphatic aldehydes (Table 1, entries 1, 3 and 4). The relative stereochemistry of both the 6- and 5-membered heterocycles were determined both by NOESY experiments and X-ray crystallography (Fig. 1).

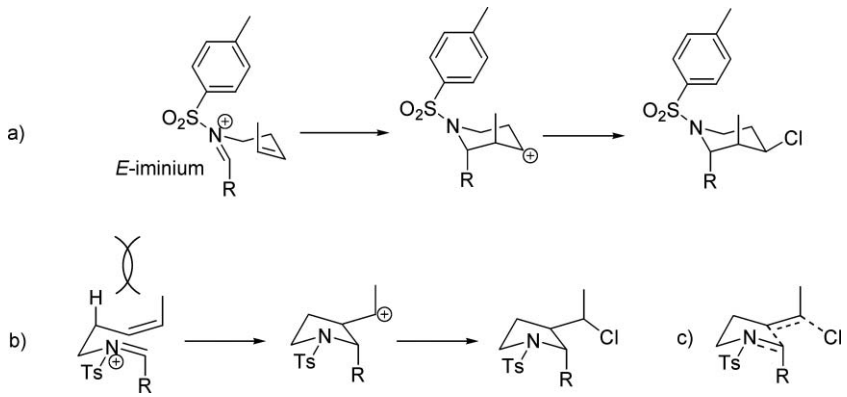
The X-ray structure of 3-(1-chloroethyl)-2-cyclohexyl-1-tosylpyrrolidine **27d** clearly supported the NOE data: the cyclohexyl substituent adopts an axial conformation and the 1-chloroethyl substituent also adopts an axial conformation on the opposite face (assuming that there is no conformational averaging on the NMR timescale). Perhaps surprisingly, in the solid state, the *N*-tosyl group is *endo* over the pyrrolidine ring, orientated rather like a "sunshade" over the molecule.

Li *et al.*[38] have previously reported a mixture of tetrahydropyran and tetrahydrofuran products when employing internal olefins in oxa-Prins reactions, and it is believed that a similar system is in operation here. We postulate that the formation of the pyrrolidines is based upon unfavourable 1,3-diaxial interactions. *Ab initio* calculations have shown the intermediate (*E*)-iminium ions are more stable than the corresponding (*Z*)-iminium ions,[27,39] and thus we assume that our system formed the (*E*)-iminium ion. (However, the authors made no comment on the Curtin–Hammett principle, which dictates that the product ratio depends only on the difference in the activation energy of the transition state going to each product, and not on the equilibrium constant between the intermediates, in this case between the *E*- and *Z*-iminium ion intermediates.) Therefore, as the iminium ion then folds around in order to cyclise, the (*E*)-iminium ion and methyl group from the olefin repel on steric grounds. This forces both substituents to adopt a pseudo-axial conformation, with the consequence that the intermediate secondary carbocation is trapped by a chloride anion from the least hindered opposite face to the ring C2 substituent (Scheme 6a).

A similar argument can be applied to the formation of 3-(1-chloroethyl)pyrrolidine (Scheme 6b): the (*E*)-iminium ion again forces the C2 substituent axial. Based on a chair-like transition state, the ethyl side chain becomes pseudo-equatorial as the 5-membered ring is formed and the sp^2–sp^2 olefin character is lost. It is not entirely clear, however, what controls the configuration of the third stereocenter. Assuming the carbocation to be trigonal planar, then chloride could trap from either face, yet only one diastereoisomer was observed. It appears unlikely that the neighbouring groups would hinder the approach of the chloride from one direction. The only alternative would be a transition state where the chloride ion attacks the sp^2 alkene carbon at the point of cyclisation and so the geometry of the olefin is important (Scheme 6c).

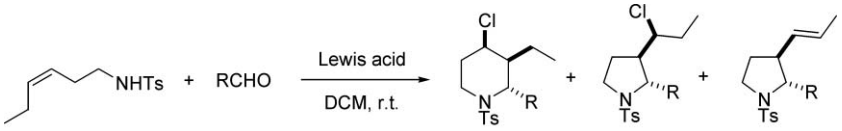
In order to investigate further if disfavoured 1,3-diaxial interactions during the cyclisation process were responsible for the formation of the pyrrolidine products, the chain length of the olefin substituent was increased, by preparing (*Z*)-*N*-(hex-3-enyl)-4-methylbenzenesulfonamide **23** from (*Z*)-hex-3-en-1-ol using the identical tosylation/displacement with tosylamine route (53% over 2 steps). The indium trichloride aza-Prins reaction was again performed using three different aldehydes, and three different products were now obtained (Table 2).

Each aliphatic aldehyde again gave a mixture of a 2-substituted 4-chloropiperidine **28** and a 2-substituted 3-(1-chloropropyl)pyrrolidine **29**, together with a previously unobserved



Scheme 6 Effect of (*E*)-iminium geometry on stereochemistry in 3-(1-chloroethyl)pyrrolidine.

Table 2 Further aza-Prins reactions of (*Z*)-homoallyl tosylamines



23 **28** **29** **30**

Entry	R	Time/h	Yield **28** (%)	Yield **29** (%)	Yield **30** (%)	Ratio 6-ring : 5-ring[a]	Ratio 6-ring : 5-ring from Table 1[b]
$InCl_3$:							
1	*n*-C_7H_{15}	17	34	43	7	17 : 25	1 : 1
2	$(CH_2)_2$ Ph	17	31	49	10	31 : 59	10 : 9
3	*c*-Hex	72	14	62	10	7 : 36	13 : 25
$FeCl_3$:							
4	*n*-C_7H_{15}	<1	28	47	5	35 : 65	40 : 60
5	$(CH_2)_2$ Ph	10	0	0	0	N/A	34 : 66
6	*c*-Hex	5	9	63	11	11 : 89	16 : 84

[a] Ratio of 6-membered product to 5-membered products. [b] Previous example using (*Z*)-4-methyl-*N*-(pent-3-enyl)benzenesulfonamide.

side chain-eliminated pyrrolidine **30**. The total yield of cyclised material increased in each case based on comparison to the reactions performed with (*Z*)-4-methyl-*N*-(pent-3-enyl)benzenesulfonamide (**21**). The starting amine was completely consumed in under 24 h for the reactions with octanal or hydrocinnamaldehyde (Table 2, entries 1 and 2) but again required longer reaction times for cyclohexanecarboxaldehyde (Table 2, entry 3), although all three were significantly shorter times compared to the reactions with (*Z*)-4-methyl-*N*-(pent-3-enyl)benzenesulfonamide. The major difference in these reactions was the appearance of an unsaturated pyrrolidine, assumed to be formed either by E1-type elimination from the intermediate carbocation after cyclisation or by direct E2 elimination of chloride from the trapped product. The eliminated product was always the minor reaction product, and was the (*E*)-isomer, as judged by NOE experiment and confirmed by the X-ray structure. If the sum of the two 5-membered ring products is considered, the quantity of 5-membered product has been enhanced compared to 6-membered product as a result of chain elongation. It is assumed that increased disfavoured pseudo-1,3-diaxial interactions in the chair transition state were more prominent with the ethyl group and so the yield of 5-membered product increased (Fig. 2c). The relative stereochemistry of the substituents was again determined by a combination of NOESY experiments (with each compound showing very similar enhancements between corresponding protons) and X-ray crystallography (Fig. 2a and b). Finally, we repeated these reactions with iron(III) chloride following the conditions of Martín, in order to see how the results compared with those from indium trichloride (Table 2, entries 4–6). The overall conversions to product were better with indium trichloride, although with the iron trichloride perhaps showing slightly better selectivity for the 5-ring over the 6-ring.

Interestingly, in these piperidines the tosyl group is no longer orientated over the piperidine ring, but now points away, presumably minimising interaction with the ethyl group (Fig. 2c). Particularly pleasing was that X-ray structures could be obtained from the adducts with cyclohexanecarboxaldehyde for both the eliminated pyrrolidine product (confirming both its formation and existence as the (*E*)-isomer) and the chlorine-containing pyrrolidine (Fig. 3).

2.3. Aza-Prins cyclisations: use of (*E*)-alkenes

The same studies were repeated, now employing the corresponding (*E*)-alkene: the indium trichloride-promoted reaction of *N*-(pent-3-(*E*)-enyl)-4-methylbenzenesulfonamide **22** with different aldehydes (Table 3).

The results were quite different from those observed from the (*Z*)-alkene. In all except one case, the 4-chloropiperidine product was formed exclusively; in the other example, the

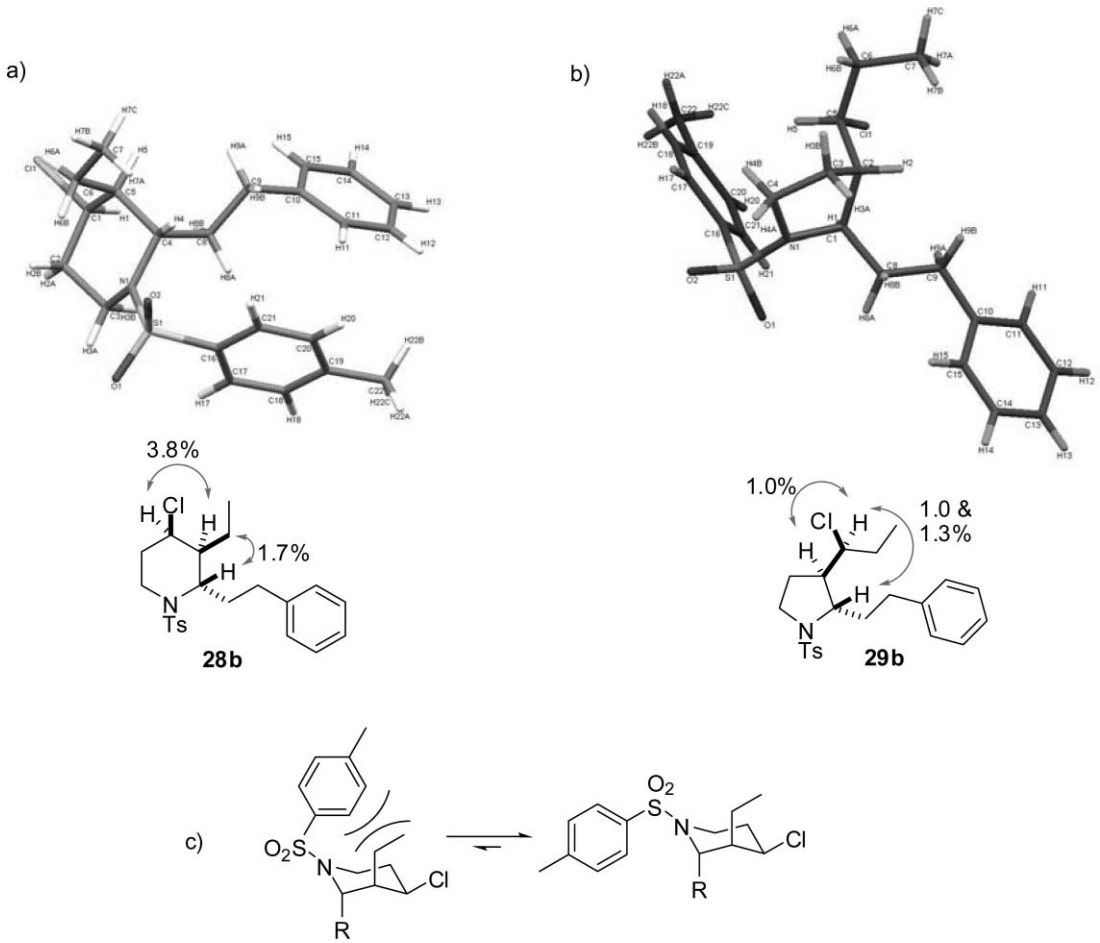


Fig. 2 NOEs and X-ray structures of 2,3,4-trisubstituted piperidines.

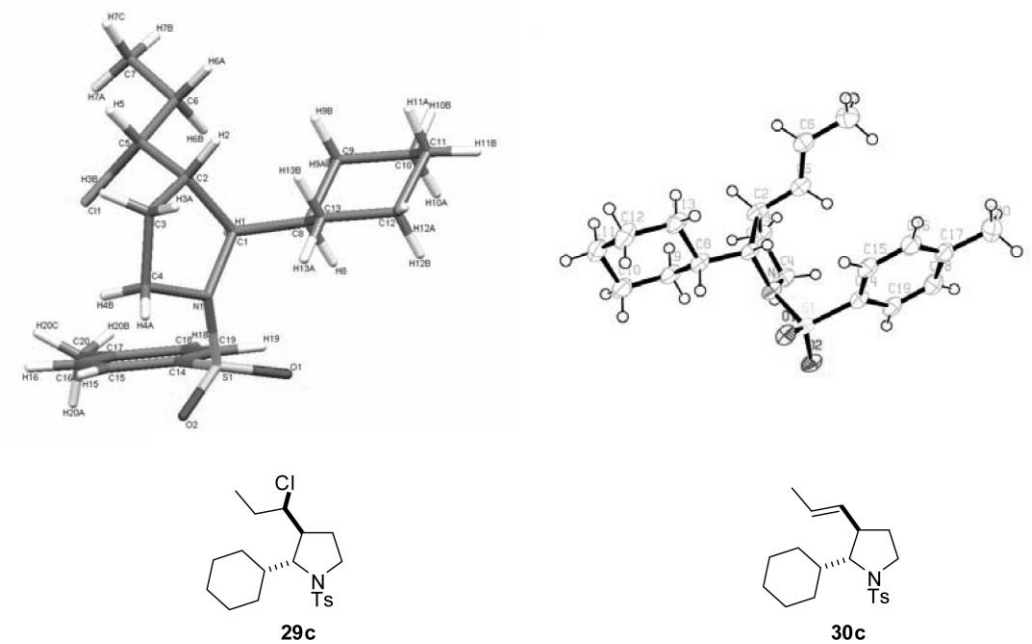
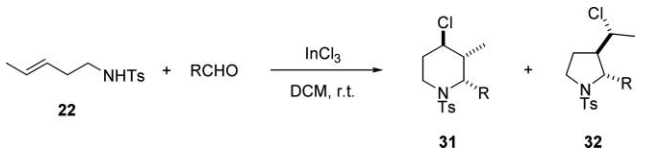


Fig. 3 X-Ray structure of 3-(1-chloropropyl)-2-cyclohexyl-1-tosylpyrrolidine and 2-cyclohexyl-3-(*E*-prop-1′-enyl)-1-tosylpyrrolidine.

Table 3 Aza-Prins reactions of (*E*)-homoallyl tosylamine



Entry	R	Time/h	Yield **31** (%)	Yield **32** (%)
1a	n-C_7H_{15}	17	66	0
2b	$(CH_2)_2Ph$	17	64	0
3c	*c*-Hex	240	0	70
4d	CO_2Et	1	21	0

3-(1-chloroethyl)pyrrolidine was formed exclusively. As before, the aliphatic aldehydes produced good yields of piperidines in reasonably short reaction times (Table 3, entries 1 and 2) with a slight depreciation in yield compared with the overall (combined) yield of cyclised product from the (*Z*)-amine precursor. No other products could be isolated or identified, and certainly no 2-substituted 3-(1-chloroethyl)pyrrolidine product. The use of ethyl glyoxylate (Table 3, entry 4) is highly comparable with the example involving the (*Z*)-amine precursor, with a very short reaction time and consumption of all the starting materials, but a disappointingly low yield. The conformation of the products were again determined by NOE experiments, with similar enhancements being observed for each of the piperidine compounds and confirmed for 4-chloro-2-phenethyl-3-methyl-1-tosylpiperidine and 3-(1-chloroethyl)-2-cyclohexyl-1-tosylpyrrolidine by X-ray crystallography (Fig. 4).

A similar argument to before could be used to explain the selectivity within the products. Once again, it was assumed that the (*E*)-iminium ion was formed preferentially and that this sets the axial conformation of the C2 substituent in all products. The major difference is that the (*E*)-alkene allows the C3 methyl group to adopt a pseudo-equatorial conformation, and then the chloride adds to the carbocation from the least hindered face, also ending up equatorial (Scheme 7).

The only difference for the pyrrolidine product is that the third stereocenter is the opposite configuration to that observed in examples taken from the (*Z*)-amine precursor. This could be a result of the geometry of the olefin in the starting material, although if the mechanism proceeds *via* a planar carbocation, this is debatable. Alternatively, the difference may point to an alternative mechanism that does not proceed through a planar carbocation. As before, in both cases, the *N*-tosyl group is *endo* over the ring.

2.4. Effects of additional substituents

Having investigated the effects of an (*E*)- or (*Z*)-alkene on the outcome of the aza-Prins reaction, we now examined the outcome when using either an alkene with an internal substituent, 4-methyl-*N*-(3-methylbut-3-enyl)benzenesulfonamide (**24**) or a trisubstituted alkene, 4-methyl-*N*-(4-methylpent-3-enyl)-benzenesulfonamide (**25**). Both homoallylic amines were again

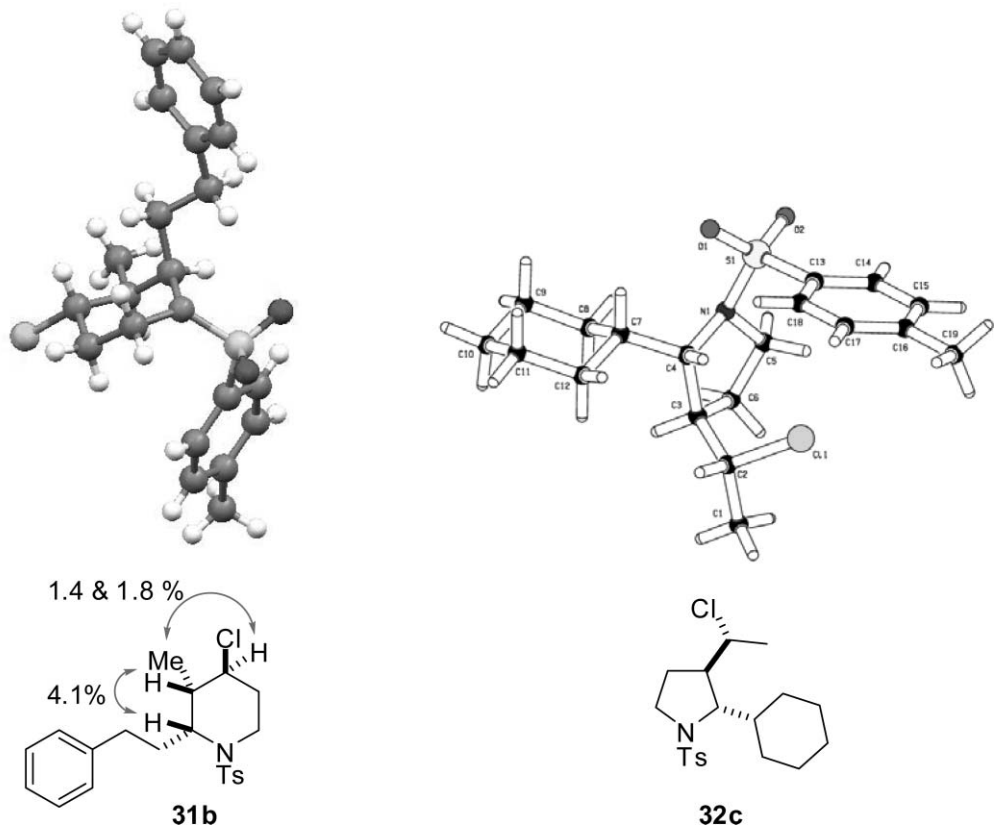
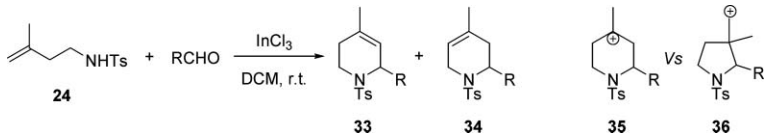


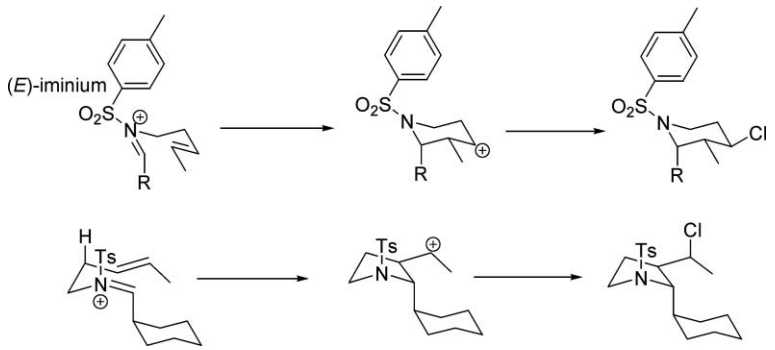
Fig. 4 NOE data and X-Ray structure of 4-chloro-2-phenethyl-3-methyl-1-tosylpiperidine (**31b**) and 3-(1-chloroethyl)-2-cyclohexyl-1-tosylpyrrolidine (**32c**).

Table 4 Aza-Prins reactions of 4-methyl-*N*-(3-methylbut-3-enyl)benzenesulfonamide (**24**)



Entry	R	Time/h	Total yield (%)	Ratio[a]
1	$(CH_2)_2Ph$	2	90	53 : 47
2	*n*-C_7H_{15}	2	73	53 : 47
3	CO_2Et	1	0	N/A

[a] Inseparable by chromatography—ratio obtained by analysis of ^{1}H NMR integration.



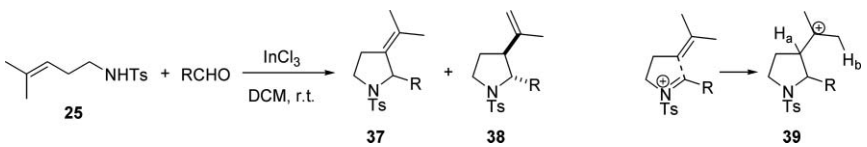
Scheme 7 Iminium ion and olefin geometry effects in 4-chloropiperidine formation.

prepared from the corresponding available alcohols *via* the same 2-step process used previously (Scheme 5).

The most surprising feature when using 4-methyl-*N*-(3-methylbut-3-enyl)benzenesulfonamide under identical reaction conditions to the previous studies was the rapidity of the reaction, with the reaction complete in under 2 h (Table 4). The most striking feature was the formation of two isomeric 4-methyltetrahydropyridines, in a near 1 : 1 ratio, and no chlorine-containing products nor pyrrolidine(s). The two isomers were inseparable by chromatography (flash, GC or HPLC) and the ratios were obtained by analysis of the ^{1}H NMR integration values of the olefinic proton signals, which were separate. It is believed that both the rapidity and exclusivity of the 6-membered ring can be explained by considering the carbocation that is formed upon cyclisation. In forming the 6-membered ring, extra stability is gained by forming a tertiary carbocation **35**, compared with a primary carbocation **36** in forming a 5-membered ring; then there is an equal chance of elimination from either side of the carbocation to give the two isomeric products.

Finally, as far as studying substituents around the alkene, a trisubstituted alkene, 4-methyl-*N*-(4-methylpent-3-enyl)benzenesulfonamide (**25**), was employed and once again the results were slightly different from any of the previous examples (Table 5). In each of the successful reactions, only eliminated pyrrolidine products were obtained, but this time as a mixture of two different alkene regioisomers (which were inseparable by chromatography). Once again, we believe that the explanation lies with the driving force for forming a tertiary carbocation: this is possible if the pyrrolidine carbocation **39** is formed, but not if forming a piperidine. Furthermore, there is a much greater chance of unfavourable 1,3-diaxial interactions between the two methyl groups and the other substituents if a 6-membered ring is formed (as in Sections 2.2 and 2.3), which cannot happen when forming a pyrrolidine. It was slightly surprising that the two eliminated

Table 5 Further aza-Prins reactions involving trisubstituted olefin

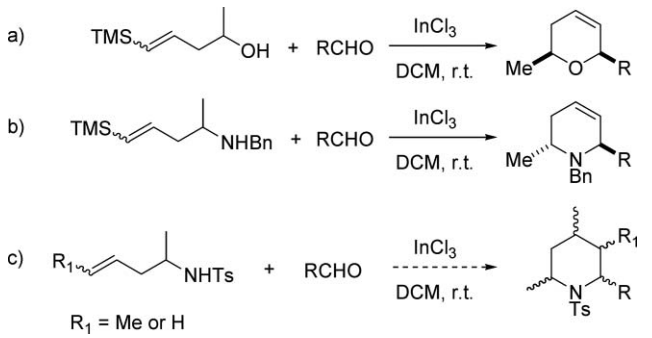


Entry	R	Time/h	Total yield (%)	Ratio
1	$(CH_2)_2Ph$	6	75	52 : 48
2	*n*-C_7H_{15}	6	60	58 : 42
3	*c*-Hex	144	trace	50 : 50

products were formed in equal amounts. Statistically, there are six methyl H_b protons compared with one H_a proton. This suggests that the loss of H_b to give **38** (the kinetic product) would be sterically and statistically favoured. However, the loss of H_a to give **37** generates the more substituted (and presumably more stable) double bond, and thus this would be the thermodynamic product. Therefore, it is assumed that the transition state for forming the internal double bond is lower in energy and that this balances out the statistical effect.

Finally, we investigated the formation of tetrasubstituted piperidines, and in particular the effect of using an α-substituted sulfonamide to generate a tetrasubstituted piperidine. It has been reported (Scheme 8) that in the Prins and silyl-Prins reactions with alcohols, very high *cis* selectivity is observed across the oxygen atom in the ring,[14,35,37] and for the aza-silyl-Prins reaction that this is reversed and a *trans* selectivity observed[14–17] (presumably through the presence of the extra substituent on the nitrogen atom and A strain).

The target cyclisation material, 4-methyl-*N*-(pent-4-en-2-yl)benzenesulfonamide **41**, was prepared in two steps from the commercially available pent-4-en-2-ol. On this occasion, the tosylation/amination procedure was unsuccessful (failing at the second amination step), and instead the Mitsunobu reaction was employed between pent-4-en-2-ol and *t*-butyl tosylcarbamate to form the homoallylic tertiary amine in 69% yield (Scheme 9). The carbamate function was then cleaved with TFA in DCM to give the required homoallylic tosylamine in quantitative yield. In order to investigate the effects of a substituent on the alkene

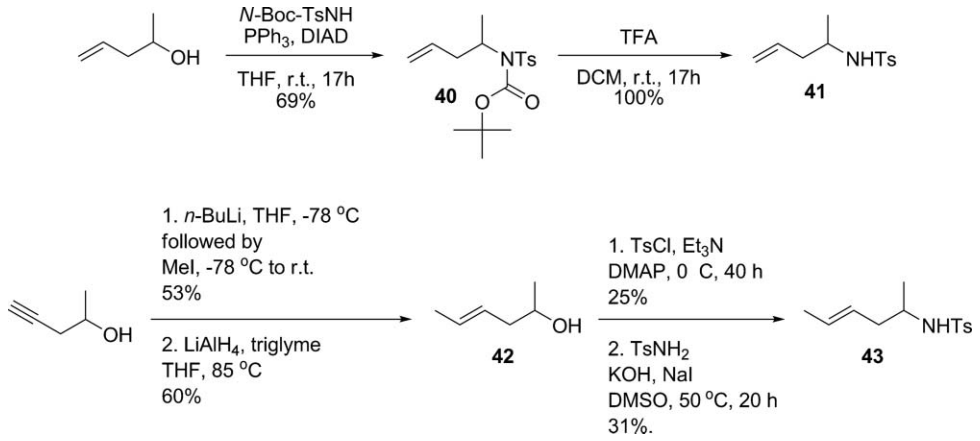


Scheme 8 Selectivity in the (a) silyl-Prins and (b) aza-silyl-Prins reactions.

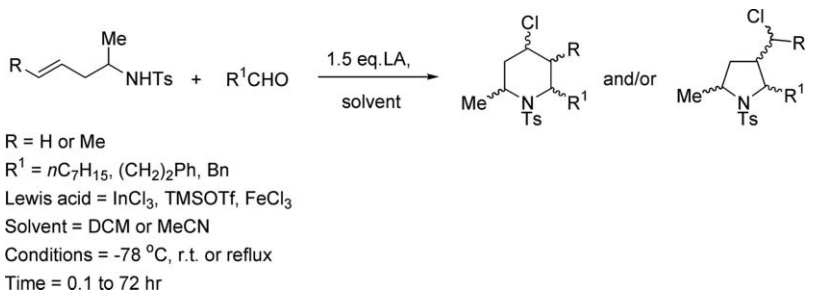
(as before), (*E*)-*N*-(hex-4-en-2-yl)-4-methylbenzenesulfonamide **43** was also prepared in four steps, using our more conventional approach. Unfortunately, despite repeated efforts, we were unable to prepare the corresponding (*Z*)-*N*-(hex-4-en-2-yl)-4-methylbenzenesulfonamide, with the amination step repeatedly proving unsuccessful.

Aza-Prins reactions were now attempted under a variety of conditions (Scheme 10).

When the three aliphatic aldehydes that brought the most success in previous examples were screened in the presence of indium trichloride and DCM or acetonitrile under a variety of conditions (full details in the ESI†), no reaction was observed when using **41**. Even when more forcing conditions were attempted with DCM or acetonitrile at reflux, still only starting material



Scheme 9 Synthesis of C1-substituted *N*-tosylamines.



Scheme 10 Aza-Prins reactions involving C1-substituted tosylamines.

remained. The same outcome was observed with TMSOTf. Finally we decided to screen iron(III) chloride and after 70 h at room temperature all the starting material was consumed by TLC. However, only trace quantities (*ca.* 5%) of product were detected on analysis by GCMS and could not be isolated; the rest of the crude mass was unidentifiable. The desired product could not be obtained by chromatography. A similar trend emerged when using (*E*)-*N*-(hex-4-en-2-yl)-4-methylbenzenesulfonamide **43**, with all conditions giving, at best, only a trace of product.

3. Conclusions

In summary, we have demonstrated a general aza-Prins reaction of *N*-tosylhomoallylic amines promoted by Lewis acids, and indium trichloride in particular. Further, we have shown that this may give rise to both piperidine and pyrrolidine products, and that the stereochemistry of the products depends on the conformation of the starting material alkene. We are currently looking at the application of the reaction in the synthesis of various natural products and will report our results in due course.

4. Experimental details

4.1. General

Diethyl ether and tetrahydrofuran were predried over sodium wire and distilled from sodium under nitrogen, with benzophenone ketyl as indicator directly in the reaction vessel. Dichloromethane was distilled over calcium hydride and kept under nitrogen. All reactions were carried out under anhydrous conditions and in an atmosphere of nitrogen unless otherwise stated, using flame-dried glassware and standard vacuum/nitrogen manifold techniques, with all transfers performed using plastic syringes and needles. Reactions were mixed by internal magnetic follower. All chemicals were purified by distillation, recrystallisation or chromatography where appropriate; commercially available compounds were generally used without further purification. All reactions were followed by TLC. Plates were visualised by ultraviolet light (254 nm) and aqueous potassium permanganate spray ($KMnO_4$: K_2CO_3 : water 6 : 1 : 100, w/w/v). Purification was by flash column chromatography or the use of Mass-Directed-Auto-Prep (MDAP), a form of preparative HPLC, performed in the laboratories at GlaxoSmithKline, Harlow, UK. Infrared spectra were recorded in the range 4000–600 cm^{-1} with internal calibration. Spectra were recorded as thin films between NaCl plates, as KBr disks or as Nujol pastes. Proton (^1H) NMR spectra were recorded at 270, 300 or 400 MHz and carbon (^{13}C) NMR spectra at 75.5 or 100.6 MHz, respectively, in deuterated solvents. NMR chemical shift values (δ_H and δ_C) are quoted in parts per million (ppm) relative to an internal standard ($CDCl_3$), or from the residual protic solvent peaks. Coupling constants, *J*, are quoted as experimentally observed.

The preparation of, and characterisation data for, the alcohol precursors and their tosyl derivatives, for the *N*-tosyl amines, and details concerning the unsuccessful Lewis acid screening conditions are given in the ESI.† All X-ray structure determination was performed at the EPSRC National Crystallographic Service (University of Southampton). Crystallographic data has been deposited with the Cambridge Crystallographic Data Centre (CCDC).

4.1 General procedure for alcohol tosylation

A round-bottomed flask was charged with a homoallylic alcohol (69.73 mmol, 1.00 eq.) and dichloromethane (140 mL). The resulting solution was cooled to 0 °C before adding portionwise and sequentially 4-dimethylaminopyridine (5.08 g, 41.84 mmol, 0.60 eq.), *p*-toluenesulfonyl chloride (15.96 g, 83.68 mmol, 1.20 eq.) and triethylamine (dropwise, 9.82 mL, 69.73 mmol, 1.00 eq.). The resulting solution was stirred at 0 °C until TLC showed complete consumption of starting material. The resulting suspension was diluted with diethyl ether (150 mL), stirred for a further 30 min and the precipitate removed by filtration. The solution was then washed sequentially with 10% aqueous copper sulfate (2 × 75 mL), 10% aqueous sodium hydrogen carbonate (2 × 75 mL) and a saturated aqueous sodium chloride solution (60 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*.

Characterisation data for compounds **2**, **19**, **20** and **42** is presented in the ESI.†

4.2. General procedure for tosyl displacement by primary amine

A round-bottomed flask equipped with a condenser was charged with ethanol (18 mL), followed by a primary amine (90 mmol, 5.00 eq.) and finally a tosylated alcohol (18 mmol, 1.00 eq.). The resulting solution was heated to reflux temperature and stirred at this temperature until TLC showed complete consumption of starting material. The solution was cooled to room temperature, the ethanol removed *in vacuo* and the excess of primary amine carefully distilled under reduced pressure. The resulting residue was partitioned between dichloromethane (60 mL) and 1.0 M aqueous sodium hydroxide solution (40 mL). The organic layer was separated, the aqueous layer extracted with dichloromethane (3 × 10 mL), and the combined organic layers dried over magnesium sulfate, filtered and concentrated *in vacuo*.

Characterisation data for compounds **3** and **13** is in the ESI.†

4.3. General procedure for the iodine-catalysed synthesis of homoallylic amines

To a solution of an aldehyde (15.00 mmol, 1 eq.) in acetonitrile (15 ml) at room temperature was added sequentially iodine (0.38 g, 1.5 mmol, 0.10 eq., in one portion), benzyl carbamate (2.38 g, 15.75 mmol, 1.05 eq., portionwise), and allyltrimethylsilane (2.38 mL, 15 mmol, 1.00 eq., dropwise). The resulting suspension was stirred at room temperature until TLC showed complete consumption of starting material. To the solution was added sodium thiosulfate (0.90 g) and distilled water (10 mL), and the reaction mixture stirred for a further 20 min. The biphasic solution was diluted with diethyl ether (30 mL), the organic layer washed with saturated aqueous sodium chloride (2 × 25 mL) and the combined aqueous layers extracted with diethyl ether (2 × 25 mL). The combined organic layers were dried over sodium thiosulfate, filtered, and concentrated *in vacuo*.

Data for compounds **6** and **7** is in the ESI.†

4.4. General procedure for tosyl displacement with 4-methylbenzenesulfonamide, catalysed by sodium iodide

A round-bottomed flask fitted with a reflux condenser was charged with dimethylsulfoxide (87 mL), 4-methylbenzenesulfonamide (27.98 g, 160.38 mmol, 2.30 eq.) and finely powdered potassium hydroxide (5.06 g, 90.65 mmol, 1.30 eq.). The resulting suspension was heated to 50 °C and stirred for 2 h. The resulting solution was cooled to room temperature and an alcohol-derived tosylate derivative (69.73 mmol, 1.00 eq.) in dimethylsulfoxide (10 mL) added dropwise, followed by sodium iodide (3.15 g, 20.92 mmol, 0.30 eq.) in one portion. The mixture was heated to 50 °C and stirred until TLC showed full consumption of starting material. The mixture was cooled to room temperature, ice cold water (100 mL) added, the organic layer separated, and the aqueous layer extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with a 15% aqueous solution of potassium hydroxide (100 mL), water (100 mL) and a saturated aqueous solution of sodium chloride (100 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*.

Data for compounds **21**, **22**, **24**, **25**, **40** and **41** is in the ESI.†

4.5. General procedure for the aza-Prins reaction

A round-bottomed flask was charged with indium trichloride (642 mg, 2.96 mmol, 1.50 eq.) and dichloromethane (5 mL). To the resulting suspension was added an aldehyde (2.96 mmol, 1.50 eq.) in dichloromethane (1.5 mL). After stirring the mixture for 15 min at room temperature, a *N*-tosyl homoallylicamine derivative (1.97 mmol, 1.00 eq.) in dichloromethane (1.5 mL) was added and the resulting mixture stirred until TLC showed complete consumption of starting material. The mixture was diluted with dichloromethane (10 mL) and water (10 mL), and stirred for 30 min. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*, and purified by chromatography.

4.5.1 (2*R*,3*R*,4*S*)-4-Chloro-2-heptyl-3-methyl-1-tosylpiperidine/(2*S*,3*S*,4*R*)-4-chloro-2-heptyl-3-methyl-1-tosylpiperidine and (2*S*,3*R*)-3-((*S*)-1-chloroethyl)-2-heptyl-1-tosylpyrrolidine/(2*R*,3*S*)-3-((*R*)-1-chloroethyl)-2-heptyl-1-tosylpyrrolidine. Following the general procedure for the aza-Prins reaction, (*Z*)-4-methyl-*N*-(pent-3-enyl)benzenesulfonamide (150 mg, 0.62 mmol), and octanal (120 mg, 0.94 mmol), were consumed based on analysis by TLC after 17 h of stirring at room temperature. The work up afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the two *title compounds*.

*(2*R*,3*R*,4*S*)-4-Chloro-2-heptyl-3-methyl-1-tosylpiperidine/(2*S*,3*S*,4*R*)-4-chloro-2-heptyl-3-methyl-1-tosylpiperidine* ***26a*** *(Table 1 entry 1).* 84 mg (0.22 mmol, 35%) as a colourless oil. ν_{max}(neat)/cm^{-1} 2928, 1729, 1598; δ_H (300 MHz, $CDCl_3$) 7.67 (2H, d, *J* 8.2, H-C15), 7.27 (2H, d, *J* 8.2, H-C16), 4.31 (1H, td, *J* 12.6, 4.6, H-C4), 3.96-3.88 (1H, m, H-C2), 3.78-3.69 (1H, m, H-C6), 2.94 (1H, td, *J* 13.6, 3.2, H-C6), 2.41 (3H, s, H-C18) 2.16-2.05 (1H, m, H-C3), 2.01-1.84 (1H, m, H-C5), 1.84-1.74 (1H, m, H-C5), 1.66-1.33 (2H, m, H-C7), 1.32-1.11 (10H, m, H-C8 to H-C12), 1.08 (3H, d, *J* 6.9, H-C19), 0.87 (3H, t, *J* 6.8, H-C13); δ_C (75.5 MHz; $CDCl_3$) 143.1 (C17), 138.1 (C14), 129.5 (C16), 126.9 (C15), 60.1 (C2), 57.4 (C4), 40.6 (C6), 37.3 (C3), 31.7 (C11), 30.0 (C5), 29.4 (C9 and C10), 26.8 (C12), 22.6 (C8), 21.5 (C18), 14.1 (C13), 12.7 (C19); *m/z* (CI) 386 (MH^+, 100), 350 (60), 286 (42); HRMS (ES) found $[M + H]^+$ 386.1910, $C_{20}H_{33}ClNO_2S$ requires 386.1915.

*(2*S*,3*R*)-3-((*S*)-1-Chloroethyl)-2-heptyl-1-tosylpyrrolidine/(2*R*,3*S*)-3-((*R*)-1-chloroethyl)-2-heptyl-1-tosylpyrrolidine* ***27a*** *(Table 1 Entry 1).* Further elution (90% hexane, 10% ethyl acetate) provided the other *title compound* (84 mg, 0.22 mmol, 35%) as a colourless oil. ν_{max}(neat)/cm^{-1} 2927, 1598; δ_H (300 MHz; $CDCl_3$) 7.75 (2H, d, *J* 8.3, H-C15), 7.32 (2H, d, *J* 8.3, H-C16), 3.80 (1H, ddd, *J* 7.6, 4.9, 2.9, H-C2), 3.36 (1H, ddd, *J* 10.7, 7.3, 5.7, H-C5), 3.25 (1H, td, *J* 10.7, 7.3, H-C5), 3.09 (1H, qd, *J* 8.8, 6.5, H-C6), 2.43 (3H, s, H-C18), 2.13-2.01 (1H, m, H-C3), 1.93 (1H, dt, *J* 14.6, 7.3, H-C4), 1.79-1.66 (1H, m, H-C7), 1.66-1.51 (1H, m, H-C7), 1.48-1.31 (1H, m, H-C4), 1.27 (3H, d, *J* 6.5, H-C19), 1.33-1.19 (10H, m, H-C8 to H-C12), 0.88 (3H, t, *J* 6.6, H-C13); δ_C (75.5 MHz; $CDCl_3$) 143.4 (C17), 135.0 (C14), 129.6 (C16), 127.5 (C15), 63.7 (C1), 59.2 (C6), 52.5 (C3), 47.3 (C5), 37.0 (C7), 31.8 (C11), 29.4 (C9 and C10), 27.8 (C4), 25.8 (C8), 23.1 (C19), 22.6 (C12), 21.5 (C18), 14.1 (C13); *m/z* (CI) 386 (MH^+, 100), 350 (25), 286 (27); HRMS (ES) found $[M + NH_4]^+$ 403.2185, $C_{20}H_{36}ClN_2O_2S$ requires 403.2181.

(2*S*,3*R*,4*S*)-4-Chloro-3-methyl-2-phenyl-1-tosylpiperidine/(2*R*,3*S*,4*R*)-4-chloro-3-methyl-2-phenyl-1-tosylpiperidine 26b (Table 1 Entry 2). Following the general procedure, (*Z*)-4-methyl-*N*-(pent-3-enyl)benzenesulfonamide (150 mg, 0.62 mmol) in the presence of benzaldehyde (99 mg, 0.94 mmol), was consumed based on analysis by TLC after 144 h of stirring at room temperature. The work up afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the *title compound* (34 mg, 0.09 mmol, 15%) as a white solid. M.p. 112–114 °C; ν_{max}(neat)/cm^{-1} 3029, 2940, 2344, 1596; δ_H (300 MHz; $CDCl_3$) 7.70 (2H, d, *J* 7.8, H-C8), 7.45-7.27 (5H, m, Ar–H), 7.21 (2H, d, *J* 7.8, H-C9), 5.19 (1H, s, H-C2), 4.09 (1H, td, *J* 11.8, 4.1, H-C4), 3.97-3.80 (1H, m, H-C6), 3.27 (1H, ddd, *J* 13.9, 11.8, 3.5, H-C6), 2.88-2.72 (1H, m, H-C3), 2.47 (3H, s, H-C11), 2.07-1.91 (1H, m, H-C5) 1.85-1.78 (1H, m, H-C5), 1.16 (3H, d, *J* 6.9, H-C12); δ_C (75.5 MHz; $CDCl_3$) 143.8 (C10), 137.8 (C7), 137.7 (ArC), 129.6 (ArC), 128.7 (ArC), 127.2 (ArC), 127.1 (C8), 126.8 (C9), 62.5 (C2), 57.5 (C4), 41.8 (C6), 39.3 (C3), 29.8 (C5), 21.5 (C11), 13.0 (C12); *m/z* (CI) 364 (MH^+, 64), 328 (30), 210 (55); HRMS (ES) Found $[M + H]^+$ 364.1135, $C_{19}H_{23}ClNO_2S$ requires 364.1133.

(2*R*,3*R*,4*S*)-4-Chloro-3-methyl-2-phenethyl-1-tosylpiperidine, (2*S*,3*S*,4*R*)-4-chloro-3-methyl-2-phenethyl-1-tosylpiperidine, (2*S*,3*R*)-3-((*S*)-1-chloroethyl)-2-phenethyl-1-tosylpyrrolidine and (2*R*,3*S*)-3-((*R*)-1-chloroethyl)-2-phenethyl-1-tosylpyrrolidine. Following the general procedure, (*Z*)-4-methyl-*N*-(pent-3-enyl)-benzenesulfonamide (150 mg, 0.62 mmol) in the presence of 3-phenylpropanal (126 mg, 0.94 mmol), was consumed based on analysis by TLC after 17 h of stirring at room temperature. The work up afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the two *title compounds*.

(2R,3R,4S)-4-Chloro-3-methyl-2-phenethyl-1-tosylpiperidine/(2S,3S,4R)-4-chloro-3-methyl-2-phenethyl-1-tosylpiperidine ***26c*** *(Table 1 Entry 3).* (98 mg, 0.25 mmol, 40%) as a colourless oil. ν_{max}(neat)/cm^{-1} 3063, 2938, 1598; δ_H (300 MHz; $CDCl_3$) 7.66 (2H, d, *J* 8.3, H-C10), 7.34-7.13 (5H, m, Ar–H), 7.08 (2H, d, *J* 8.3, H-C11), 4.32 (1H, td, *J* 12.3, 4.6, H-C4), 4.01 (1H, m, H-C2), 3.80 (1H, dd, *J* 13.3, 4.5, H-C6), 2.99 (1H, td, *J* 13.3, 3.3, H-C6), 2.66-2.47 (2H, m, H-C8), 2.42 (3H, s, H-C13), 2.22-2.13 (1H, m, H-C3), 2.02-1.88 (1H, m, H-C5), 1.89-1.77 (1H, m, H-C5), 1.78-1.52 (2H, m, H-C7), 1.07 (3H, d, *J* 6.9, H-C14); δ_C (75.5 MHz; $CDCl_3$) 143.2 (C12), 140.9 (ArC), 138.0 (C9), 129.7 (C11), 128.5 (ArC), 128.2 (ArC), 126.9 (C10), 126.1 (ArC), 59.6 (C2), 57.2 (C4), 40.7 (C6), 37.4 (C3), 33.1 (C8), 31.8 (C5 or C7), 30.0 (C5 or C7), 21.5 (C13), 12.7 (C14); *m/z* (CI) 392 (MH^+, 100), 356 (18), 238 (48); HRMS (ES) found $[M + NH_4]^+$ 409.1716, $C_{21}H_{30}ClN_2O_2S$ requires 409.1711.

(2S,3R)-3-((S)-1-Chloroethyl)-2-phenethyl-1-tosylpyrrolidine/(2R,3S)-3-((R)-1-chloroethyl)-2-phenethyl-1-tosylpyrrolidine ***27c*** *(Table 1 Entry 3).* Further elution (90% hexane, 10% ethyl acetate) provided the other *title compound* (88 mg, 0.22 mmol, 36%) as a white solid. M.p. 122–123 °C; ν_{max}(KBr)/cm^{-1} 3062, 2955, 1664, 1594; δ_H (300 MHz; $CDCl_3$) 7.81 (2H, d, *J* 8.3, H-C10), 7.39 (2H, d, *J* 8.3, H-C11), 7.36-7.24 (5H, m, Ar–H), 3.94 (1H, dt, *J* 6.7, 3.2, H-C2), 3.55-3.31 (2H, m, H-C5), 3.18 (1H, qd, *J* 9.1, 6.6, H-C6), 2.82 (2H, t, *J* 8.3, H-C8), 2.50 (3H, s, H-C13), 2.25-2.17 (1H, m, H-C3), 2.18-2.08 (2H, m, H-C7), 2.19-1.95 (1H, m, H-C4), 1.45 (1H, dt, *J* 13.0, 6.2, H-C4), 1.34 (3H, d, *J* 6.6, H-C14); δ_C (75.5 MHz; $CDCl_3$) 143.6 (C12), 141.6 (ArC), 134.8 (C9), 129.6 (C11), 128.4 (ArC), 128.3 (ArC), 127.5 (C10), 125.7 (ArC), 63.4 (C2), 59.2 (C6), 52.9 (C3), 47.6 (C5), 38.6 (C7), 32.1 (C8), 27.9 (C4), 23.1 (C14), 21.5 (C13); *m/z* (CI) 392 (MH^+, 100), 356 (12), 238 (58); Anal. Calcd. for $C_{21}H_{26}ClNO_2S$ requires C, 64.35; H, 6.69; N, 3.57%. Found: C, 64.47; H, 6.58; N, 3.54%.

(2*R*,3*R*,4*S*)-4-Chloro-2-cyclohexyl-3-methyl-1-tosylpiperidine/(2*S*,3*S*,4*R*)-4-chloro-2-cyclohexyl-3-methyl-1-tosylpiperidine and (2*S*,3*R*)-3-((*S*)-1-chloroethyl)-2-cyclohexyl-1-tosylpyrrolidine/(2*R*,3*S*)-3-((*R*)-1-chloroethyl)-2-cyclohexyl-1-tosylpyrrolidine. Following the general procedure, (*Z*)-4-methyl-*N*-(pent-3-enyl)benzenesulfonamide (150 mg, 0.62 mmol) in the presence of cyclohexanecarbaldehyde (105 mg, 0.94 mmol), was consumed based on analysis by TLC after 144 h of stirring at room temperature. The work up afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the two *title compounds*.

(2R,3R,4S)-4-Chloro-2-cyclohexyl-3-methyl-1-tosylpiperidine/(2S,3S,4R)-4-chloro-2-cyclohexyl-3-methyl-1-tosylpiperidine ***26d*** *(Table 1 Entry 4).* (60 mg, 0.16 mmol, 26%) as a white solid. M.p. 89–91 °C; ν_{max}(KBr)/cm^{-1} 3044, 2923, 1597; δ_H (300 MHz; $CDCl_3$) 7.70 (2H, d, *J* 8.4, H-C12), 7.27 (2H, d, *J* 8.4, H-C13), 4.34-4.24 (1H, m, H-C4), 3.76-3.64 (2H, m, H-C2 and H-C6), 2.98-2.83 (1H, m, H-C6), 2.42 (3H, s, H-C15), 2.39-2.28 (1H, m, H-C3), 1.85-1.71 (2H, m, H-C5), 1.77-1.53 (5H, m, H-C7 and H-C8), 1.27-0.99 (6H, m, H-C9 and H-C10), 0.95 (3H, d, *J* 6.9, H-C16); δ_C (75.5 MHz; $CDCl_3$) 142.9 (C14), 138.3 (C11), 129.4 (C13), 127.1 (C12), 65.8 (C2), 57.6 (C4), 41.0 (C6), 36.1 (C3), 34.7 (C7), 31.0 (C8), 30.2 (C8), 29.5 (C5), 26.3 (C10), 26.2 (C9), 26.1 (C9), 21.5 (C15), 13.2 (C16); *m/z* (CI) 370 (MH^+, 100), 334 (12), 286 (10); Anal. Calcd. for $C_{19}H_{28}ClNO_2S$ requires C, 61.68; H, 7.63; N, 3.79%. Found: C, 61.44; H, 7.72; N, 3.76%.

(2S,3R)-3-((S)-1-Chloroethyl)-2-cyclohexyl-1-tosylpyrrolidine/(2R,3S)-3-((R)-1-chloroethyl)-2-cyclohexyl-1-tosylpyrrolidine ***27d*** *(Table 1 Entry 4).* Further elution (90% hexane, 10% ethyl acetate) provided the other *title compound* (115 mg, 0.31 mmol, 50%) as a white solid. M.p. 109–112 °C; ν_{max}(KBr)/cm^{-1} 2918, 1670, 1597; δ_H (300 MHz; $CDCl_3$) 7.74 (2H, d, *J* 8.1, H-C12), 7.30 (2H, d, *J* 8.1, H-C13), 3.69 (1H, dd, *J* 4.3, 2.5, H-C2), 3.38-3.30 (1H, m, H-C5), 3.28-3.19 (1H, m, H-C5), 3.02 (1H, qd, *J* 8.8, 6.5, H-C6), 2.41 (3H, s, H-C15), 2.17-2.09 (1H, m, H-C3), 1.98-1.83 (1H, m, H-C4), 1.78-1.58 (5H, m, H-C7 and H-C8), 1.38 (1H, ddd, *J* 16.8, 8.1, 4.8, H-C4), 1.16 (3H, d, *J* 6.5, H-C16), 1.22-0.76 (6H, m, H-C9 and H-C10); δ_C (75.5 MHz; $CDCl_3$) 143.4 (C14), 134.8 (C11), 129.5 (C13), 127.6 (C12), 68.1 (C2), 59.5 (C6), 49.6 (C3), 48.0 (C5), 43.3 (C7), 29.8 (C8), 28.5 (C8), 27.9 (C4), 26.4 (C10), 26.3 (C9), 26.2 (C9), 22.7 (C16), 21.5 (C15); *m/z* (CI) 370 (MH^+, 100), 334 (28), 286 (20); Anal. Calcd. for $C_{19}H_{28}ClNO_2S$ requires C, 61.69; H, 7.63; N, 3.79%. Found: C, 61.65; H, 7.84; N, 3.66%; HRMS (ES) Found $[M + H]^+$ 370.1602, $C_{19}H_{29}ClNO_2S$ requires 370.1599.

Crystal data. $C_{19}H_{28}ClNO_2S$; $M = 369.93$; Orthorhombic; space group $P2_12_12_1$; $a = 9.5924(3)$, $b = 12.9905(3)$, $c = 15.0218(4)$ Å; volume 1871.87(9) Å^3; $T = 120$ K; Z 4; 16 779 reflections measured, 4283 unique [$R_{int} = 0.0484$]. The final R values $R_1 = 0.0376$, w$R_2 = 0.0826$ (observed) and $R_1 = 0.0516$, w$R_2 = 0.0886$ (all).

(2*S*,3*R*,4*S*)-Ethyl-4-chloro-3-methyl-1-tosylpiperidine-2-carboxylate/(2*R*,3*S*,4*R*)-ethyl-4-chloro-3-methyl-1-tosylpiperidine-2-carboxylate 26e (Table 1 Entry 5). Following the general procedure, (*Z*)-4-methyl-*N*-(pent-3-enyl)benzenesulfonamide (40 mg, 0.17 mmol), in the presence of a pre-heated 33% solution of ethyl 2-oxoacetate in toluene (76 mg, 0.25 mmol, 1.50 eq.), was consumed based on analysis by TLC after 1 h of stirring at room temperature. The work up afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the *title compound* (12 mg, 0.03 mmol, 20%) as a pale yellow oil.

ν_{max}(neat)/cm^{-1} 2927, 1736, 1598; δ_H (300 MHz; $CDCl_3$) 7.66 (2H, d, *J* 8.3, H-C8), 7.29 (2H, d, *J* 8.3, H-C9), 4.54 (1H, d, *J* 1.2, H-C2), 4.13-4.02 (1H, m, H-C4), 4.04-3.94 (2H, m, H-C13), 3.79-3.70 (1H, m, H-C6), 3.31 (1H, td, *J* 12.4, 3.4, H-C6), 2.69-2.58 (1H, m, H-C3), 2.42 (3H, s, H-C11), 2.13-1.97 (1H, m, H-C5), 1.94-1.82 (1H, m, H-C5), 1.25 (3H, d, *J* 6.9, H-C15), 1.16 (3H, t, *J* 7.1, H-C14); δ_C (75.5 MHz; $CDCl_3$) 169.9 (C12), 143.4 (C10), 136.3 (C7), 129.4 (C9), 127.2 (C8), 61.6 (C13), 61.0 (C2), 57.2 (C4), 42.3 (C6), 37.2 (C3), 29.3 (C5), 21.5 (C11), 13.9 (C14), 11.9 (C15); *m/z* (CI) 360 (MH^+, 90), 286 (45), 206 (100); HRMS (ES) found $[M + H]^+$ 360.1027, $C_{16}H_{23}ClNO_4S$ requires 360.1031.

(2*R*,3*R*,4*S*)-4-Chloro-3-ethyl-2-heptyl-1-tosylpiperidine/(2*S*,3*S*,4*R*)-4-chloro-3-ethyl-2-heptyl-1-tosylpiperidine and (2*S*,3*R*)-3-((*S*)-1-chloropropyl)-2-heptyl-1-tosylpyrrolidine/(2*R*,3*S*)-3-((*R*)-1-chloropropyl)-2-heptyl-1-tosylpyrrolidine. Following the general procedure, (*Z*)-*N*-(hex-3-enyl)-4-methylbenzenesulfonamide (500 mg, 1.97 mmol), in the presence of octanal (379 mg, 2.96 mmol), was consumed based on analysis by TLC after 17 h of stirring at room temperature. The work up afforded a yellow oil,

which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give two *title compounds*.

*(2*R*,3*R*,4*S*)-4-Chloro-3-ethyl-2-heptyl-1-tosylpiperidine/(2*S*,3*S*,4*R*)-4-chloro-3-ethyl-2-heptyl-1-tosylpiperidine* ***28a*** *(Table 2 Entry 1).* 323 mg, (0.81 mmol, 41%) as a colourless oil. ν_{max}(neat)/cm^{-1} 2957, 1729, 1598; δ_H (300 MHz; $CDCl_3$) 7.66 (2H, d, *J* 8.4, H-C15), 7.26 (2H, d, *J* 8.4, H-C16), 4.37-4.28 (1H, m, H-C4), 4.11-4.03 (1H, m, H-C2), 3.79-3.69 (1H, m, H-C6), 3.01-2.87 (1H, m, H-C6), 2.40 (3H, s, H-C18), 1.91-1.74 (2H, m, H-C5), 1.75-1.63 (1H, m, H-C3), 1.59-1.29 (2H, m, H-C7), 1.32-1.23 (8H, m, H-C8 to H-C11), 1.23-1.16 (4H, m, H-C19 and H-C12), 0.94 (3H, t, *J* 7.3, H-C20), 0.87 (3H, t, *J* 6.8, H-C13); δ_C (75.5 MHz; $CDCl_3$) 143.0 (C17), 138.1 (C14), 129.5 (C16), 126.8 (C15), 58.1 (C4), 55.8 (C2), 44.7 (C3), 40.6 (C6), 31.7 (C11), 30.9 (C5), 29.1 (C9 and C10), 26.7 (C8), 22.6 (C12), 22.6 (C7), 21.4 (C18), 17.4 (C19), 14.0 (C13), 12.3 (C20); *m/z* (CI) 400 (MH^+, 100), 364 (78), 300 (42); HRMS (ES) found $[M + H]^+$ 400.2073, $C_{21}H_{35}ClNO_2S$ requires 400.2072.

*(2*S*,3*R*)-3-((*S*)-1-Chloropropyl)-2-heptyl-1-tosylpyrrolidine/(2*R*,3*S*)-3-((*R*)-1-chloropropyl)-2-heptyl-1-tosylpyrrolidine* ***29a*** *(Table 2 Entry 1).* Further elution (90% hexane 10% ethyl acetate) provided the other *title compound* (339 mg, 0.85 mmol, 43%) as a colourless oil. ν_{max}(neat)/cm^{-1} 2954, 1597, δ_H (300 MHz; $CDCl_3$) 7.73 (2H, d, *J* 8.3, H-C15), 7.30 (2H, d, *J* 8.3, H-C16), 3.83-3.77 (1H, m, H-C2), 3.39-3.20 (2H, m, H-C5), 2.78 (1H, td, *J* 9.1, 2.8, H-C6), 2.41 (3H, s, H-C18), 2.16-2.05 (1H, m, H-C3), 1.96-1.82 (1H, m, H-C4), 1.73-1.54 (2H, m, H-C7), 1.60-1.39 (2H, m, H-C19), 1.43-1.29 (1H, m, H-C4), 1.31-1.19 (10H, m, H-C8 to H-C12), 0.86 (3H, t, *J* 6.5, H-C13), 0.83 (3H, t, *J* 7.2, H-C20); δ_C (75.5 MHz; $CDCl_3$) 143.4 (C17), 135.0 (C14), 129.5 (C16), 127.5 (C15), 66.7 (C6), 63.7 (C2), 50.7 (C3), 47.4 (C5), 36.9 (C7), 31.8 (C11), 29.3 (C9 and C10), 28.5 (C19), 27.8 (C4), 25.8 (C8), 22.6 (C12), 21.4 (C18), 14.0 (C20), 10.5 (C13); *m/z* (CI) 400 (MH^+, 100), 364 (40), 300 (25); Anal. calcd. for $C_{21}H_{34}ClNO_2S$ requires C, 63.05; H, 8.57; N, 3.50%. Found: C, 62.99; H, 8.83; N, 3.50%.

(2*R*,3*R*,4*S*)-4-Chloro-3-ethyl-2-phenethyl-1-tosylpiperidine/(2*S*,3*S*,4*R*)-4-chloro-3-ethyl-2-phenethyl-1-tosylpiperidine, (2*S*,3*R*)-3-((*S*)-1-chloropropyl)-2-phenethyl-1-tosylpyrrolidine and (2*R*,3*S*)-3-((*R*)-1-chloropropyl)-2-phenethyl-1-tosylpyrrolidine. Following the general procedure, (*Z*)-*N*-(hex-3-enyl)-4-methylbenzenesulfonamide (500 mg, 1.97 mmol), in the presence of 3-phenylpropanal (398 mg, 2.96 mmol), was consumed based on analysis by TLC after 17 h of stirring at room temperature. The work up afforded a pale yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the two *title compounds*.

*(2*R*,3*R*,4*S*)-4-Chloro-3-ethyl-2-phenethyl-1-tosylpiperidine/(2*S*,3*S*,4*R*)-4-chloro-3-ethyl-2-phenethyl-1-tosylpiperidine* ***28b*** *(Table 2 Entry 2).* 328 mg (0.81 mmol, 41%) as a white solid. M.p. 95–97 °C; ν_{max}(neat)/cm^{-1} 3032, 1941, 1598; δ_H (300 MHz; $CDCl_3$) 7.58 (2H, d, *J* 8.3, H-C10), 7.29-7.11 (5H, m, Ar–H), 7.04 (2H, d, *J* 8.3, H-C11), 4.35-4.25 (1H, m, H-C4), 4.11-4.04 (1H, m, H-C2), 3.81-3.70 (1H, m, H-C6), 2.99-2.85 (1H, m, H-C6), 2.64-2.39 (2H, m, H-C8), 2.37 (3H, s, H-C13), 1.88-1.73 (2H, m, H-C5), 1.73-1.62 (1H, m, H-C3), 1.73-1.50 (2H, m, H-C7), 1.30-1.11 (1H, m, H-C14), 0.84 (3H, t, *J* 7.3, H-C15); δ_C (75.5 MHz; $CDCl_3$) 143.2 (C12), 140.6 (ArC), 137.9 (C9), 129.6 (C11), 128.4 (ArC), 128.3 (ArC), 126.8 (C10), 126.1 (ArC), 57.9 (C4), 55.2 (C2), 44.8 (C3), 40.7 (C6), 33.0 (C8), 31.2 (C5 or C7), 30.9 (C7 or C5), 21.4 (C13), 17.4 (C14), 12.2 (C15); *m/z* (CI) 406 (MH^+, 20), 216 (90), 111 (100); HRMS (ES) found $[M + H]^+$ 406.1606, $C_{22}H_{29}ClNO_2S$ requires 406.1602.

Crystal data. $C_{22}H_{28}ClNO_2S$; *M* = 405.96; Monoclinic; *a* = 8.9411(3), *b* = 11.0719(3), *c* = 10.9373(4) Å; volume 1066.91(6) Å^3; *T* = 120 K; *Z* 2, 13 213 reflections measured, 4663 unique [R_{int} = 0.0367]. The final *R* values R_1 = 0.0404, wR_2 = 0.1043 (observed) and R_1 = 0.0470, wR_2 = 0.1078 (all data). Flack parameter 0.44(6).

*(2*S*,3*R*)-3-((*S*)-1-Chloropropyl)-2-phenethyl-1-tosylpyrrolidine and (2*R*,3*S*)-3-((*R*)-1-chloropropyl)-2-phenethyl-1-tosylpyrrolidine* ***29b*** *(Table 2 Entry 2).* Further elution (90% hexane 10% ethyl acetate) provided the other *title compound* (392 mg, 0.97 mmol, 49%) as a white solid. M.p. 69–71 °C; ν_{max}(neat)/cm^{-1} 3088, 2936, 1598; δ_H (300 MHz; $CDCl_3$) 7.75 (2H, d, *J* 8.3, H-C10), 7.35-7.16 (5H, m, Ar–H), 7.23 (2H, d, *J* 8.3, H-C11), 3.89 (1H, dt, *J* 6.2, 3.1, H-C2), 3.45-3.30 (2H, m, H-C5), 2.84 (1H, dt, *J* 9.1, 2.9, H-C6), 2.80-2.71 (2H, m, H-C8), 2.43 (3H, s, H-C13), 2.24-2.14 (1H, m, H-C3), 2.09-1.84 (2H, m, H-C7), 1.97-1.85 (1H, m, H-C4), 1.59-1.44 (1H, m, H-C14), 1.44-1.29 (2H, m, H-C14 and H-C4), 0.85 (3H, t, *J* 7.2, H-C15); δ_C (75.5 MHz; $CDCl_3$) 143.6 (C12), 141.7 (ArC), 135.0 (C9), 129.6 (C11), 128.4 (ArC), 128.3 (ArC), 127.6 (C10), 125.8 (ArC), 66.7 (C6), 63.6 (C2), 51.2 (C3), 47.7 (C5), 38.6 (C7), 32.2 (C8), 28.6 (C14), 28.0 (C4), 21.5 (C13), 10.6 (C15); *m/z* (CI) 406 (MH^+, 92), 252 (52), 216 (100); HRMS (ES) found $[M + H]^+$ 406.1602, $C_{22}H_{29}ClNO_2S$ requires 406.1606.

Crystal Data. $C_{22}H_{28}ClNO_2S$; *M* = 405.96; Orthorhombic; *a* = 14.7643(7), *b* = 13.3490(6), *c* = 10.3953(3) Å; volume 2048.80(15) Å^3; space group *Pna*2$_1$; *T* = 120 K; *Z* 4, 16 800 reflections measured, 4515 unique [R_{int} = 0.0836]. The final *R* values R_1 = 0.0504, wR_2 = 0.1017 (observed) and R_1 = 0.0832, wR_2 = 0.1143 (all data). Flack parameter 0.10(8).

(2*R*,3*R*,4*S*)-4-Chloro-2-cyclohexyl-3-ethyl-1-tosylpiperidine/(2*S*,3*S*,4*R*)-4-chloro-2-cyclohexyl-3-ethyl-1-tosylpiperidine, (2*S*,3*R*)-3-((*S*)-1-chloropropyl)-2-cyclohexyl-1-tosylpyrrolidine/(2*R*,3*S*)-3-((*R*)-1-chloropropyl)-2-cyclohexyl-1-tosylpyrrolidine and (2*S*,3*S*,*E*)-2-cyclohexyl-3-(prop-1-enyl)-1-tosylpyrrolidine/(2*S*,3*S*,*E*)-2-cyclohexyl-3-(prop-1-enyl)-1-tosylpyrrolidine. Following the general procedure, (*Z*)-*N*-(hex-3-enyl)-4-methylbenzenesulfonamide (500 mg, 1.97 mmol), in the presence of cyclohexanecarbaldehyde (332 mg, 2.96 mmol), was consumed based on analysis by TLC after 72 h of stirring at room temperature. The work up afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the three *title compounds*.

*(2*R*,3*R*,4*S*)-4-Chloro-2-cyclohexyl-3-ethyl-1-tosylpiperidine/(2*S*,3*S*,4*R*)-4-chloro-2-cyclohexyl-3-ethyl-1-tosylpiperidine* ***28c*** *(Table 2 Entry 3).* 182 mg (0.47 mmol, 24%) as a white solid. M.p. 151–153 °C (mixture); ν_{max}(neat)/cm^{-1} 3035, 2928, 1815 (mixture); δ_H (300 MHz; $CDCl_3$) 7.68 (2H, d, *J* 8.3, H-C12), 7.27 (2H, d, *J* 8.3, H-C13), 4.37-4.28 (1H, m, H-C4), 3.84 (1H, d, *J* 10.5, H-C2), 3.76-3.65 (1H, m, H-C6), 2.99-2.85 (1H, m, H-C6), 2.42 (3H, s, H-C15), 1.94-1.84 (1H, m, H-C3), 1.85-1.51 (5H, m, H-C7 and H-C8), 1.75-1.54 (2H, m, H-C5), 1.29-0.88 (6H, m, H-C9 and H-C10), 1.09-0.82 (2H, m, H-C16), 0.97-0.92 (3H, m,

H-C17); δ_C (75.5 MHz; $CDCl_3$) 142.9 (C14), 138.4 (C11), 129.4 (C13), 126.9 (C12), 61.4 (C2), 58.5 (C4), 43.8 (C3), 41.1 (C6), 35.9 (C7), 31.0 (C8), 30.4 (C8), 28.3 (C5), 26.5 (C10), 26.4 (C9), 26.2 (C9), 21.5 (C15), 17.2 (C16), 12.2 (C17); *m/z* (CI) 384 (MH^+, 100), 348 (78), 300 (22); Anal. calcd. for $C_{20}H_{30}ClNO_2S$ requires C, 62.56; H, 7.88; N, 3.65%. Found: C, 62.66; H, 8.01; N, 3.69%.

(2S,3S,E)-2-Cyclohexyl-3-(prop-1-enyl)-1-tosylpyrrolidine/(2S,3S,E)-2-cyclohexyl-3-(prop-1-enyl)-1-tosylpyrrolidine (only partially separable from piperidine product) ***30c*** *(Table 2 Entry 3).* δ_H (300 MHz; $CDCl_3$) 7.73 (2H, d, *J* 8.2, H-C12), 7.31 (2H, d, *J* 8.2, H-C13), 5.25-5.11 (1H, m, H-C16), 4.66-4.55 (1H, m, H-C6), 3.40-3.30 (1H, m, H-C5), 3.31-3.25 (1H, m, H-C5), 3.27-3.21 (1H, m, H-C2), 2.62-2.51 (1H, m, H-C3), 2.43 (3H, s, H-C15), 1.84-1.68 (5H, m, H-C7 and H-C8), 1.69-1.56 (2H, m, H-C4), 1.41 (3H, dd, *J* 6.4, 1.3, H-C17), 1.29-1.03 (6H, m, H-C9 and H-C10); δ_C (75.5 MHz; $CDCl_3$) 143.2 (C14), 135.1 (C6), 133.0 (C11), 129.5 (C13), 127.7 (C12), 124.7 (C16), 70.7 (C2), 48.5 (C5), 43.4 (C3), 42.0 (C7), 31.7 (C8), 30.2 (C8), 26.6 (C4), 26.4 (C10), 26.3 (C10), 26.1 (C9), 21.5 (C15), 17.7 (C17); *m/z* (CI) 348 (MH^+, 100), 264 (10), 194 (35).

Crystal data. $C_{20}H_{29}NO_2S$; M = 347.50; Monoclinic; a = 7.7257(2), b = 21.1223(7), c = 11.5315(2) Å; volume 1869.09(9) Å^3; space group $P2_1/c$; T = 120 K; Z 4; 20 906 reflections measured, 4239 unique [R_{int} = 0.0585]. The final R values R_1 = 0.0678, wR_2 = 0.1531 (observed) and R_1 = 0.0950, wR_2 = 0.1737 (all data).

(2S,3R)-3-((S)-1-Chloropropyl)-2-cyclohexyl-1-tosylpyrrolidine/(2R,3S)-3-((R)-1-chloropropyl)-2-cyclohexyl-1-tosylpyrrolidine ***29c*** *(Table 2 Entry 3).* Further elution (90% hexane, 10% ethyl acetate) provided the *title compound* (470 mg, 1.22 mmol, 62%) as a white solid. M.p. 102–103 °C; ν_{max}(neat)/cm^{-1} 3034, 2927, 1597; δ_H (300 MHz; $CDCl_3$) 7.75 (2H, d, *J* 8.3, H-C12), 7.31 (2H, d, *J* 8.3, H-C13), 3.70 (1H, dd, *J* 4.8, 2.3, H-C2), 3.40-3.20 (2H, m, H-C5), 2.67 (1H, dt, *J* 9.2, 2.6, H-C6), 2.42 (3H, s, H-C15), 2.29-2.19 (1H, m, H-C3), 1.96-1.82 (1H, m, H-C4), 1.83-1.71 (4H, m, H-C8), 1.71-1.60 (1H, m, H-C7), 1.54-1.37 (2H, m, H-C4 and H-C16), 1.37-1.24 (1H, m, H-C16), 1.28-0.96 (6H, m, H-C9 and H-C10), 0.81 (3H, t, *J* 7.2, H-C17); δ_C (75.5 MHz; $CDCl_3$) 143.4 (C14), 135.0 (C11), 129.5 (C13), 127.6 (C12), 68.4 (C2), 67.1 (C6), 48.1 (C3), 48.0 (C5), 43.4 (C7), 29.7 (C8), 28.9 (C8), 28.2 (C16), 27.9 (C4), 26.4 (C10), 26.3 (C9), 26.3 (C9), 21.4 (C15), 10.7 (C17); *m/z* (CI) 384 (MH^+, 100), 348 (45), 300 (25); HRMS (ES) found [M + NH_4]$^+$ 401.2021, $C_{20}H_{34}ClN_2O_2S$ requires 401.2024.

Crystal data. $C_{20}H_{30}ClNO_2S$; M = 383.96; Orthorhombic; a = 13.0538(3), b = 15.5288(3), c = 19.1088(4) Å; volume 3873.54(14) Å^3; space group *Pbca*; T = 120 K; Z 8, 31 418 reflections measured, 4422 unique [R_{int} = 0.0516]. The final R values R_1 = 0.0406, wR_2 = 0.1017 (observed) and R_1 = 0.0550, wR_2 = 0.1096 (all data).

(2*R*,3*S*,4*S*)-4-Chloro-2-heptyl-3-methyl-1-tosylpiperidine/(2*S*,3*R*,4*R*)-4-chloro-2-heptyl-3-methyl-1-tosylpiperidine 31a (Table 3 Entry 1). Following the general procedure, (*E*)-4-methyl-*N*-(pent-3-enyl)benzenesulfonamide (150 mg, 0.62 mmol)), in the presence of octanal (120 mg, 0.94 mmol), was consumed based on analysis by TLC after 17 h of stirring at room temperature. The work up afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the *title compound* (159 mg, 0.41 mmol, 66%) as a white solid.

M.p. 56–57 °C; ν_{max}(neat)/cm^{-1} 2925, 1712, 1461; δ_H (300 MHz; $CDCl_3$) 7.69 (2H, d, *J* 8.4, H-C15), 7.27 (2H, d, *J* 8.4, H-C16), 3.98 (1H, td, *J* 9.7, 4.4, H-C2), 3.84-3.82 (1H, m, H-C4), 3.81-3.75 (1H, m, H-C6), 2.99 (1H, td, *J* 15.1, 2.7, H-C6), 2.40 (3H, s, H-C18), 2.03-1.93 (1H, m, H-C5), 1.83-1.69 (1H, m, H-C3), 1.67-1.50 (1H, m, H-C5), 1.47-1.34 (2H, m, H-C7), 1.33-1.10 (10H, m, H-C8 to H-C12), 1.01 (3H, d, *J* 6.9, H-C19), 0.86 (3H, t, *J* 6.8, H-C13); δ_C (75.5 MHz; $CDCl_3$) 143.1 (C17), 138.4 (C14), 129.7 (C16), 126.8 (C15), 60.6 (C4), 58.8 (C2), 42.1 (C3), 39.9 (C6), 35.9 (C5), 31.7 (C11), 29.2 (C9 and C10), 26.2 (C8), 24.4 (C7), 22.6 (C12), 21.4 (C18), 16.4 (C19), 14.0 (C13); *m/z* (CI) 386 (MH^+, 100), 350 (42), 286 (40); HRMS (ES) Found [M+NH_4]$^+$ 403.2176, $C_{20}H_{36}ClN_2O_2S$ requires 403.2181.

(2*R*,3*S*,4*S*)-4-Chloro-3-methyl-2-phenethyl-1-tosylpiperidine/(2*S*,3*R*,4*R*)-4-chloro-3-methyl-2-phenethyl-1-tosylpiperidine 31b (Table 3 Entry 2). Following the general procedure, (*E*)-4-methyl-*N*-(pent-3-enyl)benzenesulfonamide (150 mg, 0.62 mmol) in the presence of 3-phenylpropanal (126 mg, 0.94 mmol), was consumed based on analysis by TLC after 17 h of stirring at room temperature. The work up afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the *title compound* (157 mg, 0.40 mmol, 64%) as a white solid.

M.p. 105–106 °C; ν_{max}(KBr)/cm^{-1} 3030, 2955, 1596; δ_H (300 MHz; $CDCl_3$) 7.83 (2H, d, *J* 8.1, H-C10), 7.39 (2H, d, *J* 8.1, H-C11), 7.36-7.18 (5H, m, Ar–H), 4.26-4.15 (1H, m, H-C2), 3.97 (1H, dd, *J* 15.0, 4.9, H-C6), 3.85 (1H, td, *J* 11.6, 4.5, H-C4), 3.25-3.11 (1H, m, H-C6), 2.79-2.66 (1H, m, H-C8), 2.65-2.52 (1H, m, H-C8), 2.51 (3H, s, H-C13), 2.13-2.00 (1H, m, H-C5), 1.95-1.71 (1H, m, H-C3), 1.87-1.63 (2H, m, H-C7), 1.74-1.56 (1H, m, H-C5), 1.09 (3H, d, *J* 6.8, H-C14); δ_C (75.5 MHz; $CDCl_3$) 143.4 (C12), 141.6 (ArC), 138.3 (C9), 129.9 (C11), 128.4 (ArC), 128.3 (ArC), 126.9 (C10), 125.9 (ArC), 60.4 (C4), 58.8 (C2), 41.9 (C3), 40.1 (C6), 35.7 (C5), 32.7 (C8), 26.9 (C7), 21.5 (C13), 16.4 (C14); *m/z* (CI) 392 (MH^+, 40), 238 (20), 202 (74); Anal. calcd. for $C_{21}H_{26}ClNO_2S$ requires C, 64.35; H, 7.08; N, 3.57%. Found: C, 64.15; H, 6.70; N, 3.50%; HRMS (ES) found [M + H]$^+$ 392.1446, $C_{21}H_{27}ClNO_2S$ requires 392.1444.

Crystal data. $C_{21}H_{26}ClNO_2S$; M = 391.94; Monoclinic; a = 24.2931(8), b = 11.7455(3), c = 14.3281(4) Å; volume 3937.7(2) Å^3; space group $C12/c1$; T = 120 K; Z 8; 22 425 reflections measured, 4514 unique [R_{int} = 0.0566]. The final R values R_1 = 0.0494, wR_2 = 0.1195 (observed) and R_1 = 0.0830, wR_2 = 0.1356 (all data).

(2*S*,3*R*)-3-((*S*)-1-Chloroethyl)-2-cyclohexyl-1-tosylpyrrolidine/(2*R*,3*S*)-3-((*R*)-1-chloroethyl)-2-cyclohexyl-1-tosylpyrrolidine 32c (Table 3 Entry 3). Following the general procedure, (*E*)-4-methyl-*N*-(pent-3-enyl)benzenesulfonamide (150 mg, 0.62 mmol) in the presence of cyclohexanecarbaldehyde (105 mg, 0.94 mmol), was consumed based on analysis by TLC after 240 h of stirring at room temperature. The work up afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the *title compound* (162 mg, 0.44 mmol, 70%) as a white solid.

M.p. 116–118 °C; ν_{max}(neat)/cm^{-1} 2927, 1669, 1599; δ_H (300 MHz; $CDCl_3$) 7.73 (2H, d, *J* 8.4, H-C12), 7.31 (2H, d, *J* 8.4, H-C13), 3.45-3.41 (1H, m, H-C2), 3.38-3.28 (3H, m, H-C6 and H-C5), 2.43 (3H, s, H-C15), 2.23-2.14 (1H, m, H-C3), 1.91-1.63 (7H, m, H-C4, H-C7 and H-C8), 1.32 (3H, d, *J* 6.6, H-C16),

1.28-0.81 (6H, m, H-C9 and H-C10); δ_C (75.5 MHz; $CDCl_3$) 143.5 (C14), 134.9 (C11), 129.5 (C13), 127.7 (C12), 67.2 (C2), 59.4 (C6), 49.1 (C3), 48.1 (C5), 43.3 (C7), 30.1 (C8), 28.0 (C8), 27.3 (C4), 26.5 (C10), 26.3 (C9), 26.2 (C9), 23.9 (C16), 21.5 (C15); *m/z* (CI) 370 (MH^+, 100), 334 (55), 286 (62); HRMS (ES) found $[M + NH_4]^+$ 387.1871, $C_{19}H_{32}ClN_2O_2S$ requires 387.1868.

Crystal data. $C_{19}H_{28}ClNO_2S$; $M = 369.93$; Orthorhombic; $a = 15.4076(3)$, $b = 12.9924(4)$, $c = 9.3800(3)$ Å; volume 1877.70(9) Å^3; space group $Pna2_1$; $T = 120$ K; Z 4; 10 624 reflections measured, 4506 unique [$R_{int} = 0.0506$]. The final R values $R_1 = 0.0699$, w$R_2 = 0.1726$ (observed) and $R_1 = 0.0743$, w$R_2 = 0.1761$ (all data). Flack parameter 0.40(12).

(2*S*,3*S*,4*S*)-Ethyl-4-chloro-3-methyl-1-tosylpiperidine-2-carboxylate/(2*R*,3*R*,4*R*)-ethyl-4-chloro-3-methyl-1-tosylpiperidine-2-carboxylate 31d (Table 3 Entry 4). Following the general procedure, (*E*)-4-methyl-*N*-(pent-3-enyl)benzenesulfonamide (150 mg, 0.62 mmol), in the presence of a pre-heated 33% solution of ethyl 2-oxoacetate in toluene (287 mg, 0.94 mmol, 1.50 eq.), was consumed based on analysis by TLC after 1 h of stirring at room temperature. The work up afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the *title compound* (47 mg, 0.13 mmol, 21%) as a pale yellow oil.

ν_{max}(neat)/cm^{-1} 2980, 1733, 1598; δ_H (300 MHz; $CDCl_3$) 7.62 (2H, d, *J* 8.4, H-C8), 7.27 (2H, d, *J* 8.4, H-C9), 4.59 (1H, d, *J* 5.8, H-C2), 4.01 (1H, td, *J* 11.6, 4.4, H-C4), 3.93-3.81 (1H, m, H-C6), 3.81-3.66 (2H, m, H-C13), 3.49 (1H, td, *J* 12.8, 2.8, H-C6), 2.41 (3H, s, H-C10), 2.26 (1H, tdd, *J* 9.5, 5.1, 2.8, H-C5), 2.14-2.01 (1H, m, H-C3), 2.01-1.85 (1H, m, H-C5), 1.14 (3H, t, *J* 7.2, H-C14), 1.08 (3H, d, *J* 6.9, H-C15); δ_C (75.5 MHz; $CDCl_3$) 168.9 (C12), 143.7 (C10), 135.6 (C7), 129.5 (C9), 127.1 (C8), 60.8 (C13), 59.6 (C2), 59.2 (C4), 42.1 (C6), 41.0 (C3), 36.0 (C5), 21.5 (C11), 15.2 (C15), 13.9 (C14); *m/z* (CI) 360 (MH^+, 100), 286 (65), 206 (87); HRMS (ES) found $[M + H]^+$ 360.1029, $C_{16}H_{23}ClNO_4S$ requires 360.1031.

(2*S*,3*S*)-2-Phenethyl-3-(prop-1-en-2-yl)-1-tosylpyrrolidine/(2*R*,3*R*)-2-Phenethyl-3-(prop-1-en-2-yl)-1-tosylpyrrolidine and (±)-2-phenethyl-3-(propan-2-ylidene)-1-tosylpyrrolidine (Table 5 Entry 1). Following the general procedure, 4-methyl-*N*-(4-methylpent-3-enyl)benzenesulfonamide (100 mg, 0.39 mmol), in the presence of 3-phenylpropanal (80 mg, 0.59 mmol), was consumed based on analysis by TLC after 6 h of stirring at room temperature. The work up afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the two regioisomer *title compounds* as only a partially separable mixture (108 mg, 0.29 mmol, 75%) as a colourless oil.

(2S,3S)-2-Phenethyl-3-(prop-1-en-2-yl)-1-tosylpyrrolidine/(2R,3R)-2-phenethyl-3-(prop-1-en-2-yl)-1-tosylpyrrolidine (major regioisomer) ***38a***. ν_{max}(neat)/cm^{-1} 3026, 2925, 1644, 1599 (mixture); δ_H (300 MHz; $CDCl_3$) 7.69-7.61 (2H, m, H-C10), 7.30-7.24 (2H, m, H-C11), 7.27-7.13 (5H, m, Ar–H), 4.46-4.40 (1H, m, H-C2), 3.47-3.32 (2H, m, H-C5), 2.71-2.58 (2H, m, H-C8), 2.40 (3H, s, H-C13), 2.28-2.10 (1H, m, H-C4), 2.09-1.94 (1H, m, H-C4), 1.95-1.81 (2H, m, H-C7), 1.39 (3H, s, H-C15), 1.37 (3H, s, H-C14); δ_C (75.5 MHz; $CDCl_3$) 143.2 (C12), 142.1 (ArC), 135.2 (C9), 132.2 (C3), 129.3 (C11), 128.4 (ArC), 128.2 (ArC), 127.4 (C10), 125.6 (ArC), 123.8 (C6), 62.0 (C2), 48.7 (C5), 37.2 (C4), 36.4 (C7), 31.7 (C8), 21.4 (C13), 21.0 (C15), 19.9 (C15); *m/z* (CI) 370 (MH^+, 100), 264 (18), 216 (35); HRMS (ES) found $[M + H]^+$ (mixture) 370.1837, $C_{22}H_{28}NO_2S$ requires 370.1835.

(±)-2-Phenethyl-3-(propan-2-ylidene)-1-tosylpyrrolidine (minor regioisomer) ***37a***. δ_H (300 MHz; $CDCl_3$) 7.69-7.61 (2H, m, H-C10), 7.30-7.24 (2H, m, H-C11), 7.30-7.24 (5H, m, Ar–H), 4.59-4.56 (1H, m, H-C14), 4.41-4.39 (1H, m, H-C14), 3.51-3.41 (1H, m, H-C2), 3.54-3.38 (2H, m, H-C5), 2.83-2.65 (2H, m, H-C8), 2.66-2.50 (1H, m, H-C3), 2.40 (3H, s, H-C13), 2.28-2.10 (1H, m, H-C4), 2.09-1.94 (1H, m, H-C4), 1.87-1.70 (2H, m, H-C7), 1.51 (3H, s, H-C15); δ_C (75.5 MHz; $CDCl_3$) 143.9 (C6), 143.3 (C12), 141.7 (ArC), 134.9 (C9), 129.5 (C11), 128.5 (ArC), 128.2 (ArC), 127.5 (C10), 125.7 (ArC), 111.9 (C14), 62.3 (C2), 51.7 (C3), 46.8 (C5), 31.4 (C8), 29.7 (C7), 28.2 (C4), 21.4 (C13), 20.9 (C15); *m/z* (CI) 370 (MH^+, 100), 264 (15), 216 (40).

(2*S*,3*S*)-2-Heptyl-3-(prop-1-en-2-yl)-1-tosylpyrrolidine/(2*R*,3*R*)-2-Heptyl-3-(prop-1-en-2-yl)-1-tosylpyrrolidine and (±)-2-heptyl-3-(propan-2-ylidene)-1-tosylpyrrolidine (Table 5 Entry 2). Following the general procedure, 4-methyl-*N*-(4-methylpent-3-enyl)benzenesulfonamide (100 mg, 0.39 mmol), in the presence of octanal (76 mg, 0.59 mmol), was consumed based on analysis by TLC after 6 h of stirring at room temperature. The work up afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the two *title compounds* as a partially separable mixture (85 mg, 0.23 mmol, 60%) as a colourless oil.

(2S,3S)-2-Heptyl-3-(prop-1-en-2-yl)-1-tosylpyrrolidine/(2R,3R)-2-heptyl-3-(prop-1-en-2-yl)-1-tosylpyrrolidine (major regioisomer) ***38b***. ν_{max}(neat)/cm^{-1} 2926, 1735, 1645, 1598 (mixture); δ_H (300 MHz; $CDCl_3$) 7.72 (2H, d, *J* 8.3, H-C15), 7.29 (2H, d, *J* 8.3, H-C16), 4.39-4.33 (1H, m, H-C2), 3.52-3.37 (2H, m, H-C5), 2.42 (3H, s, H-C18), 1.86-1.70 (2H, m, H-C4), 1.70-1.57 (2H, m, H-C7), 1.43 (3H, s, H-C20), 1.39 (3H, s, H-C19), 1.37-1.17 (10H, m, H-C8 to H-C12), 0.91-0.84 (3H, m, H-C13); δ_C (75.5 MHz; $CDCl_3$) 143.0 (C17), 135.5 (C14), 132.5 (C3), 129.2 (C16), 127.4 (C15), 123.3 (C6), 62.3 (C2), 46.6 (C5), 34.7 (C4), 31.8 (C11), 29.6 (C7), 29.4 (C9 and C10), 25.4 (C8), 22.6 (C12), 21.5 (C18), 21.0 (C20), 20.2 (C19), 14.1 (C13); *m/z* (CI) 364 (MH^+, 100), 264 (40), 210 (38); HRMS (ES) found $[M + NH_4]^+$ (mixture) 381.2569, $C_{21}H_{37}N_2O_2S$ requires 381.2570.

(±)-2-Heptyl-3-(propan-2-ylidene)-1-tosylpyrrolidine (minor regioisomer) ***37b***. δ_H (300 MHz; $CDCl_3$) 7.65 (2H, d, *J* 8.4, H-C15), 7.24 (2H, d, *J* 8.4, H-C16), 4.56-4.52 (1H, m, H-C19), 4.43-4.37 (1H, m, H-C19), 3.52-3.39 (1H, m, H-C2), 3.40-3.25 (2H, m, H-C5), 2.49 (1H, dd, *J* 13.2, 6.8, H-C3), 2.40 (3H, s, H-C18), 2.27-2.12 (1H, m, H-C4), 2.08-1.94 (1H, m, H-C4), 1.55 (3H, s, H-C20), 1.54-1.43 (2H, m, H-C7), 1.37-1.17 (10H, m, H-C8 to H-C12), 0.91-0.84 (3H, m, H-C13); δ_C (75.5 MHz; $CDCl_3$) 144.2 (C6), 143.2 (C17), 135.4 (C14), 129.5 (C16), 127.5 (C15), 111.4 (C19), 63.2 (C2), 51.2 (C3), 48.5 (C5), 35.8 (C4), 31.8 (C11), 29.7 (C7), 29.3 (C9), 28.2 (C10), 25.1 (C8), 22.6 (C12), 21.5 (C18), 21.0 (C20), 14.1 (C13); *m/z* (CI) 364 (MH^+, 100), 264 (30), 210 (44).

(±)-4-Methyl-2-phenethyl-1-tosyl-1,2,3,6-tetrahydropyridine and (±)-4-methyl-2-phenethyl-1-tosyl-1,2,5,6-tetrahydropyridine (Table 4 Entry 1). Following the general procedure, 4-methyl-*N*-(3-methylbut-3-enyl)benzenesulfonamide (250 mg, 1.04 mmol), in the presence of 3-phenylpropanal (210 mg, 1.56 mmol), was

consumed based on analysis by TLC after 2 h of stirring at room temperature. The work up afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the *title compounds* as an inseparable mixture (331 mg, 0.93 mmol, 90%) as a pale yellow oil.

(±)-4-Methyl-2-phenethyl-1-tosyl-1,2,3,6-tetrahydropyridine. ν_{max}(neat)/cm^{-1} 3026, 2929, 1736, 1598 (mixture); δ_H (300 MHz; $CDCl_3$) 7.82-7.79 (2H, m, H-C10), 7.44-7.39 (2H, m, H-C11), 7.39-7.23 (5H, m, Ar–H), 5.48-5.42 (1H, m, H-C3), 4.50-4.37 (1H, m, H-C2), 3.98 (1H, dd, *J* 14.6, 6.1, H-C6), 3.28 (1H, ddd, *J* 14.6, 11.8, 4.8, H-C6), 3.07 (1H, t, *J* 7.5, H-C8), 2.95-2.86 (1H, m, H-C8), 2.51 (3H, s, H-C13), 2.00-1.89 (2H, m, H-C7), 1.87-1.72 (2H, m, H-C5), 1.64 (3H, s, H-C14); δ_C (75.5 MHz; $CDCl_3$) 142.9 (C12), 141.9 (ArC), 138.4 (C9), 132.7 (C4), 129.4 (C11), 128.3 (ArC), 128.3 (ArC), 127.0 (C10), 125.7 (ArC), 121.5 (C3), 53.6 (C2), 40.4 (C6), 36.8 (C5), 32.8 (C8), 28.1 (C7), 23.2 (C14), 21.5 (C13); *m/z* (CI) (mixture) 356 (MH^+, 100), 250 (25), 202 (37); HRMS (ES) found $[M + H]^+$ (mixture) 356.1682, $C_{21}H_{26}NO_2S$ requires 356.1679.

(±)-4-Methyl-2-phenethyl-1-tosyl-1,2,5,6-tetrahydropyridine. δ_H (300 MHz; $CDCl_3$) 7.79-7.75 (2H, m, H-C10), 7.38-7.34 (2H, m, H-C11), 7.39-7.23 (5H, m, Ar–H), 5.40-5.35 (1H, m, H-C5), 4.31-4.23 (1H, m, H-C2), 4.26-4.18 (1H, m, H-C6), 3.77-3.62 (1H, m, H-C6), 2.88-2.70 (2H, m, H-C8), 2.51 (3H, s, H-C13), 2.24-2.12 (1H, m, H-C3), 1.87-1.71 (2H, m, H-C7), 1.77-1.65 (1H, m, H-C3), 1.60 (3H, s, H-C14); δ_C (75.5 MHz; $CDCl_3$) 142.9 (C12), 141.7 (ArC), 137.9 (C9), 131.0 (C4), 129.5 (C11), 128.4 (ArC), 128.3 (ArC), 126.9 (C10), 125.9 (ArC), 116.0 (C5), 50.7 (C2), 45.3 (C6), 38.5 (C3), 32.7 (C8), 27.5 (C7), 23.4 (C14), 21.5 (C13).

(±)-2-Heptyl-4-methyl-1-tosyl-1,2,3,6-tetrahydropyridine and (±)-2-heptyl-4-methyl-1-tosyl-1,2,5,6-tetrahydropyridine (Table 4 Entry 2). Following the general procedure, 4-methyl-*N*-(3-methylbut-3-enyl)benzenesulfonamide (250 mg, 1.04 mmol), in the presence of octanal (200 mg, 1.56 mmol), was consumed based on analysis by TLC after 2 h of stirring at room temperature. The work up afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the *title compounds* (265 mg, 0.76 mmol, 73%) as a pale yellow oil.

(±)-2-Heptyl-4-methyl-1-tosyl-1,2,3,6-tetrahydropyridine (major regioisomer). ν_{max}(neat)/cm^{-1} 2927, 1598 (mixture); δ_H (300 MHz; $CDCl_3$) 7.73-7.68 (2H, m, H-C15), 7.27-7.23 (2H, m, H-C16), 5.36-5.30 (1H, m, H-C3), 4.31-4.16 (1H, m, H-C2), 3.82 (1H, dd, *J* 14.6, 6.2, H-C6), 3.11 (1H, ddd, *J* 14.6, 11.9, 4.7, H-C6), 2.40 (3H, s, H-C18), 1.77-1.58 (1H, m, H-C5), 1.58-1.44 (1H, m, H-C5), 1.55 (3H, s, H-C19), 1.46-1.34 (2H, m, H-C7), 1.38-1.11 (10H, m, H-C8 to H-C12), 0.91-0.84 (3H, m, H-C13); δ_C (75.5 MHz; $CDCl_3$) 142.8 (C17), 138.6 (C14), 132.1 (C4), 129.3 (C16), 127.0 (C15), 121.9 (C3), 53.8 (C2), 38.4 (C6), 32.7 (C5), 31.8 (C11), 31.6 (C7), 29.5 (C9), 29.2 (C10), 26.2 (C8), 23.2 (C19), 22.6 (C12), 21.5 (C18), 14.1 (C13); *m/z* (CI) (mixture) 350 (MH^+, 100), 250 (12), 196 (40); HRMS (ES) found $[M + H]^+$ (mixture) 350.2148, $C_{20}H_{32}NO_2S$ requires 350.2149.

(±)-2-Heptyl-4-methyl-1-tosyl-1,2,5,6-tetrahydropyridine (minor regioisomer). δ_H (300 MHz; $CDCl_3$) 7.68-7.64 (2H, m, H-C15), 7.23-7.19 (2H, m, H-C16), 5.29-5.22 (1H, m, H-C5), 4.14-4.03 (1H, m, H-C6), 4.09-4.01 (1H, m, H-C2), 3.58-3.46 (1H, m, H-C6), 2.40 (3H, s, H-C18), 2.16-1.98 (1H, m, H-C3), 1.58-1.47 (1H, m, H-C3), 1.49 (3H, s, H-C19), 1.55-1.41 (2H, m, H-C7), 1.38-1.11 (10H, m, H-C8 to H-C12), 0.91-0.84 (3H, m, H-C13); δ_C (75.5 MHz; $CDCl_3$) 142.8 (C17), 138.0 (C14), 131.1 (C4), 129.4 (C16), 126.9 (C15), 116.0 (C5), 50.9 (C2), 40.3 (C6), 35.2 (C3), 31.8 (C11), 31.2 (C7), 29.3 (C9), 29.2 (C10), 26.4 (C8), 23.5 (C19), 22.7 (C12), 21.5 (C18), 14.1 (C13).

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