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4-hydroxypiperidines containing a quaternary stereocenter by aza-Prins cyclization

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A straightforward and highly diastereoselective synthesis of *cis*-4-hydroxy-piperidines is presented. This method allows the access to C2 and C4 substituted piperidines, bearing at C4 a tetrasubstituted carbon stereocenter. *Gem*-disubstituted homoallylic amines and ketoaldehydes as carbonyl partners have been rarely used in aza-Prins cyclizations, expanding the scope of this reaction.

Introduction

Piperidine nucleus is widespread in natural products and pharmaceuticals,¹ and represents the most abundant non aromatic nitrogen containing heterocycle in FDA approved drugs. Among the methodologies employed to synthesize this 6-membered aza-cycle, the aza-Prins cyclization represents one of the most straightforward strategies.² Indeed, from readily available starting materials such as homoallylic amines **1** and carbonyl compounds **2**, three new bonds are formed in only one operation step to construct the heterocycle **3** (Figure 1). Therefore, this reaction has recently found success and led to significant progress in the preparation of compounds of potential biological interest. Noteworthy, if the Lewis acid-promoted aza-Prins processes usually give the 4-halopiperidines, syntheses of 4-hydroxy-analogues,³ which can be performed in the presence of Brønsted acids or Lewis acids bearing non-nucleophilic anions such as M(OTf)_n, are rare, in particular those leading to tertiary alcohols on the C4. Such motifs are particularly appealing for their potential biological activities. As an example, **haloperidol** is a high potency typical antipsychotic and one of the most frequently used medication worldwide,⁴ **INE963** is currently under clinical investigation for

its potent and fast-acting blood-stage antimalarial activities,⁵ **Soticlestat (TAK-935)** is now undergoing clinical trials for the treatment of Dravet syndrome and Lennox-Gastaut syndrome as a new therapy against epilepsies,⁶ and **PIPD1** exhibits potent activities against *Mycobacterium tuberculosis* via MmpL3 inhibition⁷ (Figure 1).

In continuation with our interest in the development of cutting edge Prins processes,⁸ we set about exploring the reactivity of *gem*-disubstituted homoallylic amines **4**, which have been rarely employed in aza-Prins cyclization. In particular, it has been reported that they can undergo double cyclization involving an aza-Prins process⁹ demonstrating that this reactivity has been underexplored so far.¹⁰ With the objective in mind to access piperidines functionalized by a tertiary alcohol, we turned our attention towards glyoxylic derivatives, known to mainly undergo aza-Prins/lactonization sequence,¹¹ or eventually piperidinol formation, as secondary alcohol^{3c,3g,12} (Figure 1). This finding prompted us to explore the reaction of homoallylic amines **4** and ketoaldehydes which, following the mechanism of the cyclization and in the presence of catalytic amounts of Lewis acids or Brønsted acids as promoters, should in principle deliver **5** with C4 tetrasubstituted carbon stereocenter (Figure 1).

Figure 1. Aza-Prins cyclization and biologically active piperidines containing a quaternary stereocenter at C4.

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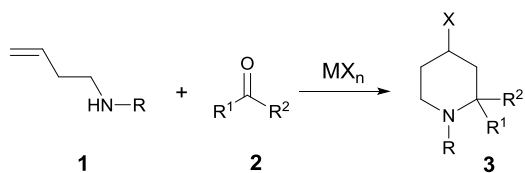
claudia.lalli@univ-rennes.fr.

^b Fluoro-agrochemicals Division, CSIR-IICST, Hyderabad 500007, India.

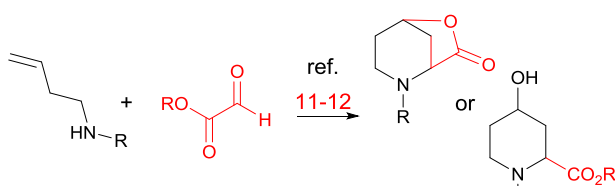
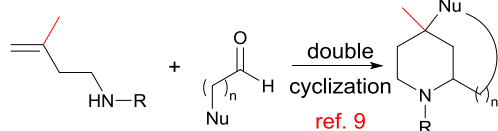
† Footnotes relating to the title and/or authors should appear here.

Supplementary Information available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

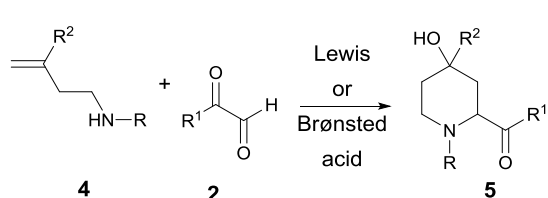
General aza-Prins



Previous works



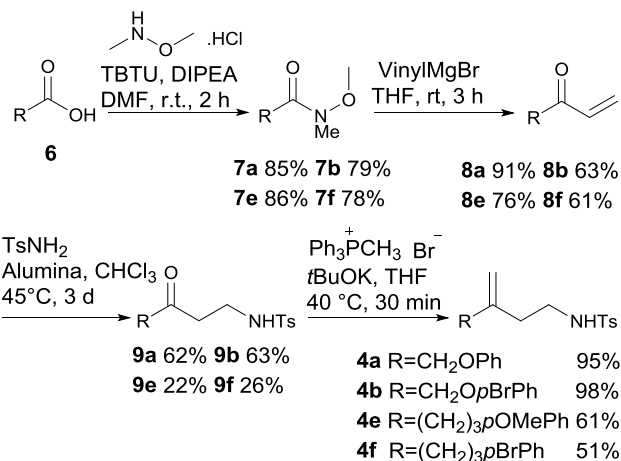
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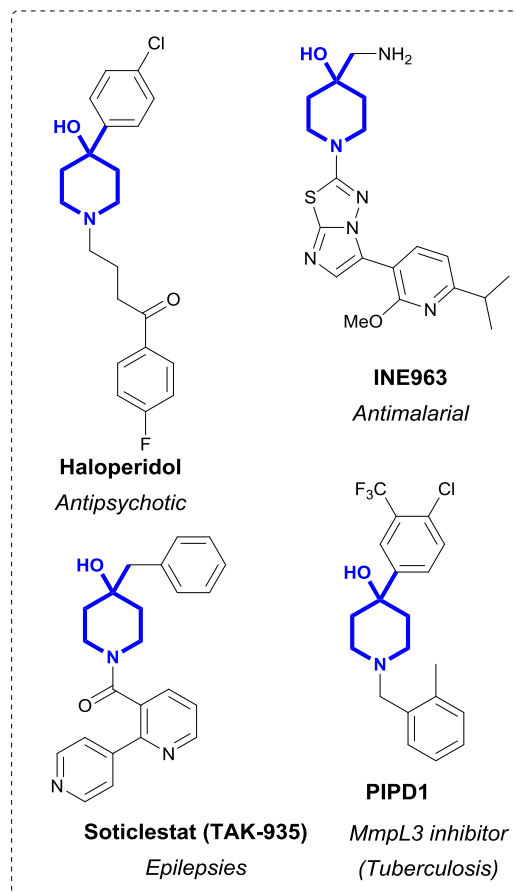
Results and discussion

We started by preparing a set of homoallylic amines of type **4** (Scheme 1).¹³ The synthesis started with the formation of the Weinreb amides **7a,b-e,f** in a 78-86% range of yields from commercially available carboxylic acids **6** in the presence of *N,O*-dimethylhydroxylamine hydrochloride, TBTU and DIPEA in DMF. Compounds **7** underwent vinylmagnesium bromide addition in THF to yield the corresponding α,β -unsaturated ketones **8** in satisfactory 61-91%. It is worth mentioning that the above two steps of the synthesis delivered enough pure crude material readily used in the next steps without any further purification. The 1,4-addition of tosylamide¹⁴ proceeded in the presence of alumina in chloroform at 45 °C for 3 days. For **9a-b** the yields were moderate, 62% and 63% respectively, while for **9e-9f** we were able to recover the desired products in only 22% and 26% respectively due to lower conversions, still acceptable to have enough material for the next and last step. Finally, the Wittig reaction in the presence of methyltriphenylphosphonium bromide and *t*BuOK as the base, proceeded smoothly for all substrates to give the desired *gem*-disubstituted homoallylic amines **4** in a 51-98% range of yields.

Scheme 1. Synthesis of homoallylic amines **4a,b-e,f**.

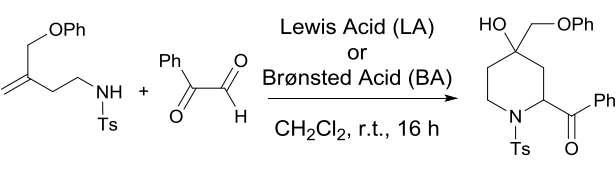


With the homoallylic amines in hands, as model reaction we studied the reactivity of **4a** with phenylglyoxal **2a**, available as its monohydrate form, with catalytic amounts of different Lewis acids. When the reaction was performed in the presence of 30 mol% of InCl₃ or BiCl₃ (Table 1, entries 1 and 2), we were disappointed to observe only the unchanged starting material in the crude reaction mixture. Gratifyingly, the use of 30 mol% of In(OTf)₃ and TMSOTf (Table 1, entries 3 and 4) led to 90% and >99% conversion respectively into the desired product **5aa**. As depicted in entries 5 and 6 in Table 1, FeCl₃ and BF₃·OEt₂ allowed to reach 74% and 92% conversion respectively. We finally decided to test the effect of Brønsted



acids. While the use of 30 mol% of trifluoroacetic acid was detrimental (Table 1, entry 7), triflic acid was surprisingly superior since the conversion observed was 95% (Table 1, entry 8). As the best result was obtained with 30 mol% of TMSOTf, the catalytic loading was decreased to 20 mol% which resulted in a drop of conversion (Table 1, entry 9). At this point TMSOTf, $\text{BF}_3 \cdot \text{OEt}_2$ and TfOH were retained as the catalysts of choice in 30 mol% loading for the rest of this study.

Table 1. Optimization of the reaction conditions between *N*-tosyl homoallylic amine **4a** and phenylglyoxal **2a**.

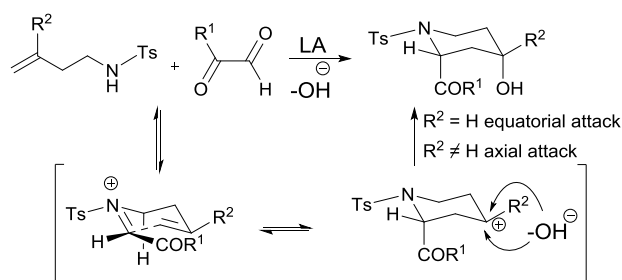


Entry ^a	LA or BA (mol%)	Conv. (%) ^b
1	InCl_3 (30)	0
2	BiCl_3 (30)	0
3	$\text{In}(\text{OTf})_3$ (30)	90
4	TMSOTf (30)	>99
5	FeCl_3 (30)	74
6	$\text{BF}_3 \cdot \text{OEt}_2$ (30)	92
7	TFA (30)	0
8	TfOH (30)	95
9	TMSOTf (20)	59

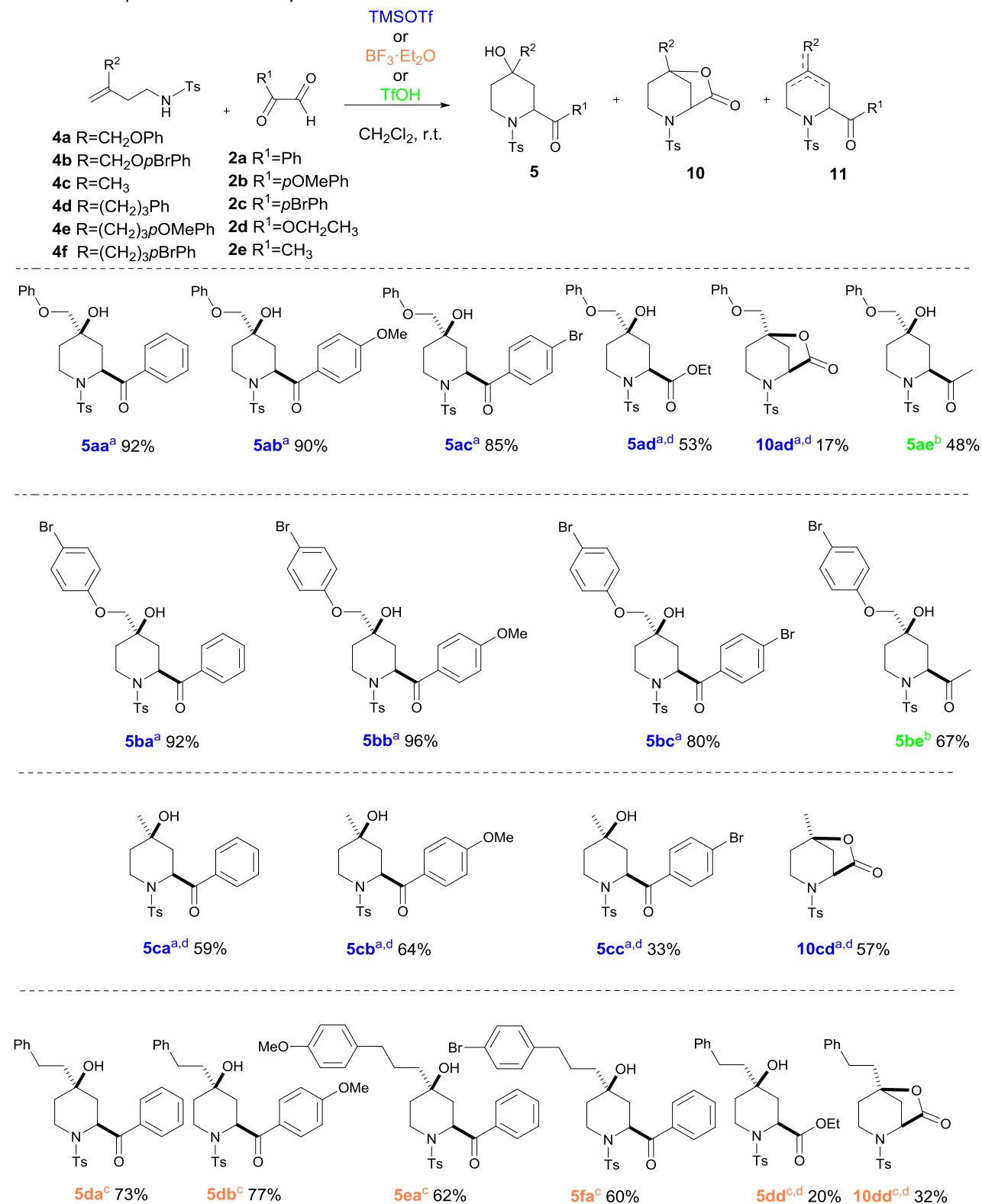
^a Unless otherwise noted, reactions were performed with homoallylamine **4a** (0.22 mmol, 1.0 equiv.), **2a** (0.24 mmol, 1.1 equiv.), in CH_2Cl_2 (0.22 M) in a sealed vial for 16 h. ^b Conversions were calculated by ^1H NMR analysis of the crude reaction mixtures with 1,3,5-trimethoxybenzene as the internal standard.

With the optimized conditions in hand, we studied the scope and limitations of our catalytic systems. The reactivity of homoallylic amines **4a** was investigated at first with a panel of different substituted ketoaldehydes **2a-e** (Scheme 3). Given that the best conversion for the reaction between **4a** and **2a** was achieved by using 30 mol% of TMSOTf (Table 1, entry 4), we decided to start with this catalyst. Product **5aa** was obtained in 92% isolated yield, as single diastereomer. Fortunately, crystals of the title compound could be grown by slow evaporation of a toluene solution and the relative *cis*-configuration of **5aa** was unambiguously confirmed by single crystal X-ray analysis as shown in Figure 2.¹⁵ A plausible explanation for this relative configuration comes from the 6 membered chair like transition state. Usually, the tosyl group on the N pushes the alpha substituent on the piperidine ring in axial and as the nucleophilic attack on the transient carbocation occurs in equatorial, generally the major product of aza-Prins cyclization is the *trans* diastereomer. In our case, the substituent present on the C4 goes preferentially in equatorial, therefore the nucleophilic attack comes in axial, delivering the *cis* diastereomer (Scheme 2).

Scheme 2. Possible transition structures and origin of the *cis* diastereoselectivity.



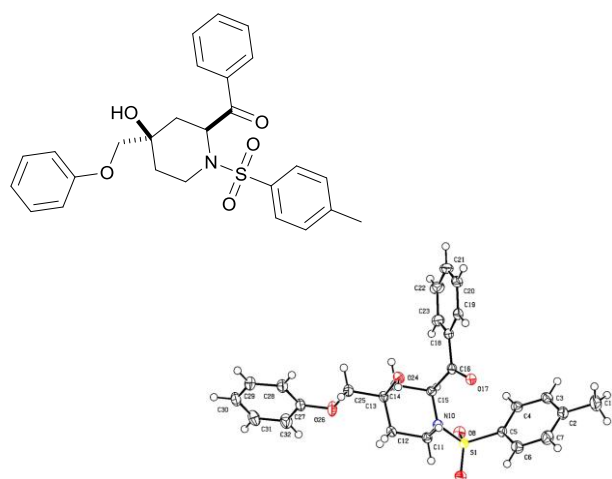
To our delight, phenylglyoxal derivatives **2b** bearing a *p*-OMe and **2c** a *p*-Br group on the aromatic ring, also participated to the reaction to give piperidines **5ab** and **5ac** in 90% and 85% yields respectively. Subsequently, we wanted to investigate the behavior of ethyl glyoxylate **2d** and pyruvaldehyde **2e**. When the reaction was performed with **2d** an equimolar mixture of the desired product **5ad** together with the piperidine lactone **10ad** was observed.^{3g,11} In order to improve the chemoselectivity towards compound **5ad**, 2 equiv. of H_2O were added, leading to **5ad** in 53% isolated yield, accompanied by the formation of **10ad** limited to 17% yield. As expected, pyruvaldehyde **2e**, used at its 40 wt. % solution in H_2O , did not participate to the reaction in the presence of TMSOTf, even after 2 days stirring. Therefore, we went back to our optimization study and chose to perform the reaction in the presence of 30 mol% of TfOH. Owing to the low conversion (30%) observed by ^1H NMR analysis of the crude reaction mixture, the preparation of **5ae** was finally carried out with an excess of triflic acid (2 equiv.) to reach 48% yield.¹³ We then explored the reactivity of substrate **4b** bearing a Br atom on the *para* position of the aromatic ring, with aldehydes **2a-c** and **2e** and the desired products **5ba**, **5bb** and **5bc** were obtained in high yield ranging from 80 to 96% whereas piperidine **5be** was obtained in 67% yield, still in the presence of TfOH (2 equiv.). To expand the scope of homoallylic amines, **4c** bringing a methyl group on the internal position of the C=C double bond was also employed with aldehydes **2a-d** in the presence of TMSOTf (30 mol%). For this substrate total conversion was observed, unfortunately a careful analysis of the crude NMR revealed the presence of significant amounts of alkenes **11** as inseparable mixture of regioisomers, as already observed by Dobbs group.^{10b} In order to decrease the byproducts and endorse the nucleophilic trapping by water, 2 equiv. of H_2O were added. In these conditions, as depicted in scheme 3, **5ca-5cc** were obtained in a 33-64% range of yields and surprisingly, when ethyl glyoxylate **2d** was employed, the piperidine-lactone **10cd** could be isolated as major compound with a fairly good yield (57%). Finally, three more homoallylic amines with two different carbon chain lengths and different substitutions on the aromatic ring have been investigated. While the use of TMSOTf did not allow to obtain the desired products from **4d** and **2a**, the employment of $\text{BF}_3 \cdot \text{OEt}_2$ (30 mol%) led to the formation of **5da** in 73% yield. Similarly, **5db** was obtained in 77% yield with aldehyde **2b**. Also, homoallylic amines **4e** and **4f** with an extra carbon atom and different substituents on the aromatic ring participated to the reaction in the presence of aldehyde **2a** delivering **5ea** and **5fa** in 62% and 60% yields respectively. In line with what was described above, ethyl glyoxylate reacted with amine **4d** in the presence of 2 equiv. of H_2O , leading to the piperidinol **5dd** in only 20% yield and to the piperidine-lactone **10dd** as major product in 32% yield.

Scheme 3. Scope of the aza-Prins cyclization.

Reaction conditions: **4** (0.22 mmol, 1 equiv.), **2** (0.24 mmol, 1.1 equiv.), in CH₂Cl₂ (0.22M) in a sealed vial. ^a General procedure A: reaction performed with TMSOTf 30 mol% for 18 h. ^b General procedure B: reactions performed with TfOH (1.5 + 0.5 equiv.) for 96 h. ^c General procedure C: reactions performed with BF₃OEt₂ 30 mol% for 18 h. ^d reaction performed with the addition of H₂O (2 equiv.). Yields were determined after purification by column chromatography on silica gel.

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Figure 2. ORTEP representation of compound **5aa** at 50% thermal ellipsoids (CCDC 2391327).



Conclusions

In summary, we have reported the synthesis of a library of *cis*-4-hydroxy piperidines, possessing a quaternary stereocenter at the C4 position, in high yield and diastereoselectivity, by the aza-Prins cyclization between glyoxal-type precursors and *gem*-disubstituted homoallylic amines. Both substrates are underexplored in aza-Prins cyclization due to their intrinsic lack of reactivity towards catalytic acidic conditions. Piperidine-lactones have also been obtained in the course of the reaction when ethyl glyoxylate was used. Therefore, this methodology provides the access to a variety of substrates from a structural and functional point of view. The post-functionalization of the piperidinols as well as the evaluations of their biological activities are in progress in our laboratories and will be reported in due course.

Experimental

General procedure A: To a solution of *N*-tosyl homoallylamine (1 equiv) in dry DCM (0.22M) were sequentially added the aldehyde (1.1 equiv) and TMSOTf (30 mol %). The reaction mixture was stirred at 20 °C for 18 hours. It was then quenched with saturated aqueous NaHCO₃ (3 mL) and extracted with EtOAc (3 x 4 mL). The combined organic phases were washed with brine (1 x 5 mL), dried over anhydrous MgSO₄ and evaporated to dryness. The residue was purified by column chromatography on silica gel.

General procedure B: To a solution of *N*-tosyl homoallylamine (1 equiv) in dry DCM (0.22M) were sequentially added the

aldehyde (1.5 equiv) and TfOH (1.5 equiv). The reaction mixture was stirred at 25 °C for 72 hours. TfOH (0.5 equiv) was again added to the mixture who was further stirred at 25 °C for 24 hours. It was then quenched with saturated aqueous NaHCO₃ (5 mL) and extracted with EtOAc (3 x 4 mL). The combined organic phases were washed with brine (1 x 5 mL), dried over anhydrous MgSO₄ and evaporated to dryness. The residue was purified by column chromatography on silica gel.

General procedure C: To a solution of *N*-tosyl homoallylamine (1 equiv) in dry DCM (0.22M) were sequentially added the aldehyde (1.1 equiv) and BF₃·OEt₂ (30 mol %). The reaction mixture was stirred at 20 °C for 18 hours. It was then quenched with saturated aqueous NaHCO₃ (3 mL) and extracted with EtOAc (3 x 4 mL). The combined organic phases were washed with brine (1 x 5 mL), dried over anhydrous MgSO₄ and evaporated to dryness. The residue was purified by column chromatography on silica gel.

((2S*,4R*)-4-Hydroxy-4-(phenoxymethyl)-1-tosylpiperidin-2-yl)-1-phenylmethanone (5aa): following **general procedure A**. Elution with DCM/EtOAc (98/2). White solid (94.2 mg, 92% yield). M.p. 94-96 °C. ¹H NMR (300 MHz, CDCl₃) δ 7.90-7.84 (m, 2H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.62-7.54 (m, 1H), 7.51-7.43 (m, 2H), 7.30-7.20 (m, 4H), 6.94 (t, *J* = 7.4 Hz, 1H), 6.80-6.73 (m, 2H), 5.70 (d, *J* = 7.0 Hz, 1H), 3.80 (dd, *J* = 13.7, 4.1 Hz, 1H), 3.71-3.58 (m, 3H), 2.85 (s, 1H), 2.41 (s, 3H), 2.37 (brd, *J* = 14.3 Hz, 1H), 2.15 (dd, *J* = 14.3, 7.3 Hz, 1H), 1.76 (td, *J* = 13.1, 5.2 Hz, 1H), 1.68-1.59 (m, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 199.5, 158.3, 143.5, 137.3, 136.0, 133.2, 129.8, 129.6, 128.9, 128.6, 127.5, 121.5, 114.6, 75.1, 69.0, 56.1, 38.4, 35.1, 32.8, 21.7. HRMS (ESI) *m/z* [M-H₂O+H]⁺ calcd for C₂₆H₂₆NO₄S 448.1577, found 448.1580. IR (UATR) $\bar{\nu}$ (cm⁻¹) 3483 (OH), 1685 (C=O). Crystals suitable for X-ray diffraction study were grown by slow evaporation of a toluene solution of the compound.

((2S*,4R*)-4-Hydroxy-4-(phenoxymethyl)-1-tosylpiperidin-2-yl)-1-(4-methoxyphenyl)methanone (5ab): following general procedure A. Elution with DCM/EtOAc (96/4). White amorphous solid (98.1 mg, 90% yield). ¹H NMR (300 MHz, CDCl₃) δ 8.02-7.95 (m, 2H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.29-7.21 (m, 4H), 6.99-6.90 (m, 3H), 6.82-6.75 (m, 2H), 5.74 (brd, *J* = 5.0 Hz, 1H), 3.89 (s, 3H), 3.84-3.73 (m, 2H), 3.69 (AB Syst., *J*_{AB} = 9.0 Hz, 1H), 3.65 (AB Syst., *J*_{AB} = 9.0 Hz, 1H), 3.67-3.55 (m, 1H), 2.41 (s, 3H), 2.29-2.12 (m, 2H), 1.77 (td, *J* = 13.3, 5.2 Hz, 1H), 1.58 (brd, *J* = 13.5 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 198.2, 164.0, 158.5, 143.6, 137.3, 131.5, 129.8, 129.6, 128.1, 127.5, 121.3, 114.6, 114.1, 75.1, 68.5, 55.7, 55.0, 38.6, 34.2, 32.6, 21.7. HRMS (ESI) *m/z* [M+Na]⁺ calcd for C₂₇H₂₉NO₆NaS 518.1608, found 518.1606. IR (UATR) $\bar{\nu}$ (cm⁻¹) 3493 (OH), 1690 (C=O).

1-(4-Bromophenyl)((2S*,4R*)-(4-hydroxy-4-(phenoxymethyl)-1-tosylpiperidin-2-yl)methanone (5ac): following general procedure A. Elution with DCM/EtOAc (98/2). White amorphous solid (101.8 mg, 85% yield). ¹H NMR (300 MHz, CDCl₃) δ 7.78-7.67 (m, 4H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.32-7.21 (m, 4H), 6.95 (t, *J* = 8.5 Hz, 1H), 6.81-6.74 (m, 2H), 5.62 (d, *J* = 7.0 Hz, 1H), 3.80 (dd, *J* = 13.8, 3.6 Hz, 1H), 3.67 (AB Syst., *J*_{AB} =

9.0 Hz, 1H), 3.63 (AB Syst., J_{AB} = 9.0 Hz, 1H), 3.65-3.53 (m, 1H), 2.78 (s, 1H), 2.42 (s, 3H), 2.33 (brd, J = 14.3 Hz, 1H), 2.11 (dd, J = 14.3, 7.2 Hz, 1H), 1.78-1.57 (m, 2H). ^{13}C NMR (75 MHz, CDCl_3) δ 198.5, 158.3, 143.7, 137.3, 134.7, 132.1, 130.1, 129.8, 129.7, 128.3, 127.5, 121.5, 114.6, 75.0, 69.0, 56.3, 38.5, 34.9, 32.6, 21.7. HRMS (ESI) m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{26}\text{H}_{26}\text{NO}_5^{79}\text{BrNaS}$ 566.0607, found 566.0607. IR (UATR) $\bar{\nu}$ (cm^{-1}) 3487 (OH), 1698 (C=O).

Ethyl (2S*,4R*)-4-Hydroxy-4-(phenoxyethyl)-1-tosylpiperidine-2-carboxylate (**5ad**): following general procedure A (H_2O (2.0 equiv.) were added). Elution with DCM/EtOAc (95/5). White solid (55.1 mg, 53% yield). M.p. 128-130 °C. ^1H NMR (300 MHz, CDCl_3) δ 7.76-7.70 (m, 2H), 7.33-7.26 (m, 4H), 7.01-6.94 (m, 1H), 6.90-6.84 (m, 2H), 4.83 (d, J = 6.4 Hz, 1H), 4.13 (dq, J = 10.7, 7.1 Hz, 1H), 3.98 (dq, J = 10.7, 7.1 Hz, 1H), 3.83-3.73 (m, 1H), 3.74 (s, 2H), 3.58 (ddd, J = 13.3, 10.4, 5.5 Hz, 1H), 2.55 (brd, J = 14.1 Hz, 1H), 2.43 (s, 3H), 2.22 (s, 1H), 1.91 (dd, J = 14.1, 6.6 Hz, 1H), 1.72-1.64 (m, 2H), 1.14 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 171.4, 158.4, 143.3, 137.7, 129.7, 129.6, 127.4, 121.6, 114.7, 75.3, 69.1, 61.5, 52.8, 38.1, 35.8, 32.9, 21.7, 14.0. HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{22}\text{H}_{26}\text{NO}_5\text{NaS}$ 416.1526, found 416.1527. IR (UATR) $\bar{\nu}$ (cm^{-1}) 3499 (OH), 1729 (C=O).

5-(Phenoxyethyl)-2-tosyl-6-oxa-2-azabicyclo[3.2.1]octan-7-one (**10ad**): following general procedure A (H_2O (2.0 equiv.) were added). Elution with DCM/EtOAc (99/1). White solid (16.7 mg, 18% yield). ^1H NMR (300 MHz, CDCl_3) δ 7.79-7.72 (m, 2H), 7.37-7.26 (m, 4H), 7.02-6.95 (m, 1H), 6.90-6.85 (m, 2H), 4.75 (d, J = 4.9 Hz, 1H), 4.12 (Syst. AB, J_{AB} = 10.5 Hz, 1H), 4.04 (Syst. AB, J_{AB} = 10.5 Hz, 1H), 4.00-3.91 (m, 1H), 2.88-2.76 (m, 1H), 2.45-2.37 (m, 1H), 2.43 (s, 3H), 2.19 (s, 1H), 2.16-2.08 (m, 2H). ^{13}C NMR (75 MHz, CDCl_3) δ 170.2, 158.1, 144.5, 133.9, 129.84, 129.76, 128.3, 121.9, 114.7, 84.6, 70.2, 57.1, 40.8, 39.0, 30.4, 21.8. HRMS (ESI) m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_5\text{NaS}$ 410.1033, found 410.1034

1-((2S*,4R*)-4-Hydroxy-4-(phenoxyethyl)-1-tosylpiperidin-2-yl)ethan-1-one (**5ae**): following general procedure B. Elution with EP/EtOAc (70/30). Colorless syrup (42.6 mg, 48% yield). ^1H NMR (300 MHz, CDCl_3) δ 7.78-7.72 (m, 2H), 7.36-7.22 (m, 4H), 7.00-6.92 (m, 1H), 6.82-6.75 (m, 2H), 4.62 (d, J = 6.8 Hz, 1H), 3.93-3.82 (m, 1H), 3.65 (Syst. AB, J_{AB} = 9.0 Hz, 1H), 3.61 (Syst. AB, J_{AB} = 9.0 Hz, 1H), 3.46 (ddd, J = 14.4, 12.5, 3.6 Hz, 1H), 2.51 (s, 1H), 2.48-2.40 (m, 1H), 2.45 (s, 3H), 2.33 (s, 3H), 1.67 (dd, J = 14.3, 6.9 Hz, 1H), 1.54-1.36 (m, 2H). ^{13}C NMR (75 MHz, CDCl_3) δ 208.3, 158.3, 143.7, 137.9, 130.0, 129.7, 127.2, 121.5, 114.5, 75.0, 68.7, 60.2, 38.6, 32.9, 31.9, 26.8, 21.7. HRMS (ESI) m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{21}\text{H}_{25}\text{NO}_5\text{NaS}$ 426.1346, found 426.1346. IR (UATR) $\bar{\nu}$ (cm^{-1}) 3493 (OH), 1723 (C=O).

((2S*,4R*)-4-((4-bromophenoxy)methyl)-4-hydroxy-1-tosylpiperidin-2-yl)-1-phenylmethanone (**5ba**): following general procedure A. Elution with DCM/EtOAc (98/2). White amorphous solid (110.2 mg, 92% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.90-7.86 (m, 2H), 7.68 (d, J = 8.3 Hz, 2H), 7.61-7.56 (m, 1H), 7.50-7.45 (m, 2H), 7.36-7.31 (m, 2H), 7.25 (d, J = 8.3 Hz, 2H), 6.69-6.64 (m, 2H), 5.72 (d, J = 7.1 Hz, 1H), 3.78 (dd, J = 13.7, 4.4 Hz, 1H), 3.67-3.57 (m, 3H), 2.96 (s, 1H), 2.41 (s, 3H), 2.33 (brd, J = 14.3 Hz, 1H), 2.14 (dd, J = 14.3, 7.3 Hz, 1H), 1.76 (td, J = 13.4, 5.2 Hz, 1H), 1.65-1.59 (m, 1H). ^{13}C JMOD NMR (125 MHz, CDCl_3) δ 199.6, 157.5, 143.6, 137.2, 135.9, 133.3, 132.5, 129.8, 128.9, 128.7, 127.5, 116.5, 113.7, 75.5, 68.9, 55.8, 38.4, 34.8, 32.8, 21.7. HRMS (ESI) m/z $[\text{M}+\text{Na}]^+$ calcd for

$\text{C}_{26}\text{H}_{26}\text{NO}_5^{79}\text{BrNaS}$ 566.0607, found 566.0609. IR (UATR) $\bar{\nu}$ (cm^{-1}) 3489 (OH), 1698 (C=O).

((2S*,4R*)-4-((4-bromophenoxy)methyl)-4-hydroxy-1-tosylpiperidin-2-yl)-1-(4-methoxyphenyl)methanone (**5bb**): following general procedure A. Elution with DCM/EtOAc (97/3). Pale yellow sirop (121.3 mg, 96% yield). ^1H NMR (500 MHz, CDCl_3) δ 8.02-7.97 (m, 2H), 7.66 (d, J = 8.3 Hz, 2H), 7.37-7.32 (m, 2H), 7.25 (d, J = 8.3 Hz, 2H), 6.98-6.93 (m, 2H), 6.70-6.65 (m, 2H), 5.76 (brd, J = 5.8 Hz, 1H), 3.91 (s, 1H), 3.89 (s, 3H), 3.76 (dd, J = 14.1, 4.0 Hz, 1H), 3.66 (AB Syst., J_{AB} = 8.9 Hz, 1H), 3.62 (AB Syst., J_{AB} = 8.9 Hz, 1H), 3.58 (td, J = 13.6, 2.7 Hz, 1H), 2.41 (s, 3H), 2.24-2.14 (m, 2H), 1.77 (td, J = 13.4, 5.1 Hz, 1H), 1.59-1.53 (m, 1H). ^{13}C JMOD NMR (125 MHz, CDCl_3) δ 198.3, 164.2, 157.7, 143.6, 137.2, 132.4, 131.6, 129.8, 128.1, 127.5, 116.5, 114.2, 113.5, 75.5, 68.4, 55.7, 54.8, 38.5, 34.0, 32.6, 21.7. HRMS (ESI) m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{27}\text{H}_{28}\text{NO}_6^{79}\text{BrNaS}$ 596.0713, found 596.0713. IR (UATR) $\bar{\nu}$ (cm^{-1}) 3491 (OH), 1690 (C=O).

((2S*,4R*)-4-((4-bromophenoxy)methyl)-4-hydroxy-1-tosylpiperidin-2-yl)-1-(4-bromophenyl)methanone (**5bc**): following general procedure A. Elution with DCM/EtOAc (99/1). White solid (109.7 mg, 80% yield). M.p. 184-186 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.77-7.73 (m, 2H), 7.68 (d, J = 8.2 Hz, 2H), 7.63-7.59 (m, 2H), 7.36-7.32 (m, 2H), 7.27 (d, J = 8.2 Hz, 2H), 6.69-6.64 (m, 2H), 5.63 (d, J = 7.0 Hz, 1H), 3.78 (dd, J = 13.7, 4.3 Hz, 1H), 3.64 (AB Syst., J_{AB} = 9.0 Hz, 1H), 3.60 (AB Syst., J_{AB} = 9.0 Hz, 1H), 3.60-3.52 (m, 1H), 2.87 (brs, 1H), 2.42 (s, 3H), 2.30 (brd, J = 14.3 Hz, 1H), 2.11 (dd, J = 14.3, 7.2 Hz, 1H), 1.71 (td, J = 13.4, 5.1 Hz, 1H), 1.62-1.57 (m, 1H). ^{13}C JMOD NMR (125 MHz, CDCl_3) δ 198.7, 157.5, 143.7, 137.2, 134.6, 132.5, 132.2, 130.2, 129.8, 128.4, 127.5, 116.5, 113.8, 75.5, 68.9, 56.0, 38.4, 34.7, 32.6, 21.7. HRMS (ESI) m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{26}\text{H}_{25}\text{NO}_5^{79}\text{Br}_2\text{NaS}$ 643.9712, found 643.9712. IR (UATR) $\bar{\nu}$ (cm^{-1}) 3438 (OH), 1697 (C=O).

1-((2S*,4R*)-4-((4-bromophenoxy)methyl)-4-hydroxy-1-tosylpiperidin-2-yl)ethan-1-one (**5be**): following general procedure B. Elution with DCM/EtOAc (90/10). Colorless syrup (71.1 mg, 67% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.77-7.73 (m, 2H), 7.38-7.30 (m, 4H), 6.69-6.65 (m, 2H), 4.63 (d, J = 6.8 Hz, 1H), 3.90-3.84 (m, 1H), 3.62 (Syst. AB, J_{AB} = 8.9 Hz, 1H), 3.58 (Syst. AB, J_{AB} = 8.9 Hz, 1H), 3.43 (ddd, J = 14.4, 12.9, 3.2 Hz, 1H), 2.50 (brs, 1H), 2.45 (s, 3H), 2.45-2.40 (m, 1H), 2.33 (s, 3H), 1.66 (dd, J = 14.3, 6.9 Hz, 1H), 1.51-1.46 (m, 1H), 1.41 (td, J = 13.2, 4.9 Hz, 1H). ^{13}C NMR (125 MHz, CDCl_3) δ 208.4, 157.5, 143.8, 137.9, 132.5, 130.0, 127.2, 116.4, 113.7, 75.4, 68.7, 60.2, 38.6, 32.7, 31.8, 26.8, 21.7. HRMS (ESI) m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{21}\text{H}_{24}\text{NO}_5^{79}\text{BrNaS}$ 504.0451, found 504.0452. IR (UATR) $\bar{\nu}$ (cm^{-1}) 3493 (OH), 1724 (C=O).

((2S*,4R*)-4-Hydroxy-4-methyl-1-tosylpiperidin-2-yl)-1-(phenyl)methanone (**5ca**): following general procedure A (H_2O (2.0 equiv.) were added). Elution with DCM/EtOAc (90/10). White amorphous solid (52.9 mg, 59% yield). ^1H NMR (300 MHz, CDCl_3) δ 7.86-7.79 (m, 2H), 7.66-7.61 (m, 2H), 7.60-7.53 (m, 1H), 7.49-7.42 (m, 2H), 7.22 (d, J = 8.0 Hz, 2H), 5.63 (d, J = 7.2 Hz, 1H), 3.72 (brdd, J = 13.6, 4.0 Hz, 1H), 3.57 (td, J = 13.0, 3.3 Hz, 1H), 2.39 (s, 3H), 2.20 (dt, J = 14.3, 1.8 Hz, 1H), 2.09 (s, 1H), 1.99 (dd, J = 14.3, 7.4 Hz, 1H), 1.73-1.51 (m, 2H), 1.15 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 200.1, 143.4, 137.1, 136.0, 133.3, 129.6, 128.9, 128.5, 127.5, 67.4, 56.0, 39.5, 39.0, 37.4, 31.1, 21.7. HRMS (ESI) m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{23}\text{NO}_4\text{NaS}$ 396.1240, found 396.1241. IR (UATR) $\bar{\nu}$ (cm^{-1}) 3502 (OH), 1698 (C=O).

((2*S**,4*R**)-4-Hydroxy-4-methyl-1-tosylpiperidin-2-yl)-1-(4-methoxyphenyl)methanone (**5cb**): following general procedure A (H₂O (2.0 equiv.) were added). Elution with DCM/EtOAc (90/10). Pale yellow amorphous solid (62.0 mg, 64% yield). ¹H NMR (300 MHz, CDCl₃) δ 7.94-7.87 (m, 2H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 8.2 Hz, 2H), 6.96-6.89 (m, 2H), 5.64 (d, *J* = 7.2 Hz, 1H), 3.87 (s, 3H), 3.75-3.65 (m, 1H), 3.62-3.50 (m, 1H), 3.04 (brs, 1H), 2.38 (s, 3H), 2.12 (brd, *J* = 14.4 Hz, 1H), 1.96 (dd, *J* = 14.4, 7.4 Hz, 1H), 1.72-1.51 (m, 2H), 1.14 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 198.9, 164.0, 143.5, 137.0, 131.3, 129.6, 128.3, 127.4, 114.1, 66.9, 55.7, 54.8, 39.1, 38.8, 37.3, 31.0, 21.6. HRMS (ESI) *m/z* [M+Na]⁺ calcd for C₂₁H₂₅NO₅NaS 426.1346, found 426.1344. IR (UATR) $\bar{\nu}$ (cm⁻¹) 3514 (OH), 1690 (C=O).

Ethyl ((2*S**,4*R**)-4-hydroxy-4-methyl-1-tosylpiperidine-2-carboxylate (**5cc**): following general procedure A (H₂O (2.0 equiv.) were added). Elution with DCM/EtOAc (95/5). White amorphous solid (35.8 mg, 33% yield). ¹H NMR (300 MHz, CDCl₃) δ 7.72-7.56 (m, 6H), 7.27-7.21 (m, 2H), 5.53 (d, *J* = 7.1 Hz, 1H), 3.71 (brdd, *J* = 13.6, 4.0 Hz, 1H), 3.53 (td, *J* = 13.1, 3.4 Hz, 1H), 2.40 (s, 3H), 2.18 (dt, *J* = 14.3, 1.8 Hz, 1H), 2.01-1.91 (m, 2H), 1.69-1.47 (m, 2H), 1.14 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 199.1, 143.6, 137.2, 134.9, 132.2, 130.0, 129.7, 128.3, 127.4, 67.5, 56.3, 39.4, 39.0, 37.3, 31.1, 21.7. HRMS (ESI) *m/z* [M+Na]⁺ calcd for C₂₀H₂₂NO₄⁷⁹BrNaS 474.0345, found 474.0349. IR (UATR) $\bar{\nu}$ (cm⁻¹) 3506 (OH), 1690 (C=O).

5-Methyl-2-tosyl-6-oxa-2-azabicyclo[3.2.1]octan-7-one (**10cd**): following general procedure A (H₂O (2.0 equiv.) were added). Elution with PE/EtOAc (75/25). White solid (40.4 mg, 57% yield). M.p. 142-144 °C. ¹H NMR (300 MHz, CDCl₃) δ 7.76-7.70 (m, 2H), 7.35-7.28 (m, 2H), 4.68-4.64 (m, 1H), 3.84 (dd, *J* = 12.2, 6.6 Hz, 1H), 2.73 (ddd, *J* = 12.2, 11.3, 5.5 Hz, 1H), 2.42 (s, 3H), 2.11-2.07 (m, 2H), 2.02-1.82 (m, 2H), 1.47 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 170.9, 144.3, 134.0, 129.8, 128.2, 84.2, 57.9, 43.0, 41.1, 34.5, 24.7, 21.7. HRMS (ESI) *m/z* [M+Na]⁺ calcd for C₁₄H₁₇NO₄NaS 318.0770, found 318.0770. IR (UATR) $\bar{\nu}$ (cm⁻¹) 1779 (C=O).

((2*S**,4*R**)-4-Hydroxy-4-phenethyl-1-tosylpiperidin-2-yl)-1-(phenyl)methanone (**5da**): following general procedure C. Elution with DCM/EtOAc (97/3). White solid (74.5 mg, 73% yield). M.p. 146-148 °C. ¹H NMR (300 MHz, CDCl₃) δ 7.90-7.83 (m, 2H), 7.67-7.55 (m, 3H), 7.51-7.44 (m, 2H), 7.26-7.14 (m, 5H), 7.11-7.06 (m, 2H), 5.67 (d, *J* = 7.1 Hz, 1H), 3.78-3.68 (m, 1H), 3.56 (ddd, *J* = 13.7, 11.8, 4.1 Hz, 1H), 2.63-2.55 (m, 2H), 2.39 (s, 3H), 2.38 (s, 1H), 2.26 (brd, *J* = 14.3 Hz, 1H), 2.00 (dd, *J* = 14.3, 7.4 Hz, 1H), 1.74-1.60 (m, 4H). ¹³C NMR (75 MHz, CDCl₃) δ 200.3, 143.6, 141.9, 137.1, 135.9, 133.4, 129.7, 128.9, 128.7, 128.6, 128.4, 127.5, 126.0, 69.1, 55.9, 45.5, 38.9, 37.8, 35.6, 29.1, 21.7. HRMS (ESI) *m/z* [M+Na]⁺ calcd for C₂₇H₂₉NO₄NaS 486.1710, found 486.1714. IR (UATR) $\bar{\nu}$ (cm⁻¹) 3505 (OH), 1697 (C=O).

((2*S**,4*R**)-4-Hydroxy-4-phenethyl-1-tosylpiperidin-2-yl)-1-(4-methoxyphenyl)methanone (**5db**): following general procedure C. Elution with DCM/EtOAc (95/5). White amorphous solid (83.6 mg, 77% yield). ¹H NMR (300 MHz, CDCl₃) δ 8.00-7.93 (m, 2H), 7.64-7.58 (m, 2H), 7.28-7.15 (m, 5H), 7.14-7.09 (m, 2H), 6.99-6.92 (m, 2H), 5.71 (d, *J* = 7.2 Hz, 1H), 3.89 (s, 3H), 3.77-3.67 (m, 1H), 3.62-3.47 (m, 1H), 3.41 (s, 1H), 2.67-2.56 (m, 2H), 2.39 (s, 3H), 2.18 (brd, *J* = 14.4 Hz, 1H), 1.98 (dd, *J* = 14.4, 7.4 Hz, 1H), 1.71-1.59 (m, 4H). ¹³C NMR (75 MHz, CDCl₃) δ 199.0, 164.2, 143.6, 142.2, 136.9, 131.5, 129.7, 128.5, 128.4, 128.2, 127.5, 125.9, 114.1, 68.4, 55.7, 54.7, 45.8, 39.0, 37.1, 35.7, 29.1, 21.7. HRMS (ESI) *m/z* [M+Na]⁺ calcd for

C₂₈H₃₁NO₅NaS 516.1815, found 516.1818. IR (UATR) $\bar{\nu}$ (cm⁻¹) 3506 (OH), 1689 (C=O).

Ethyl ((2*S**,4*R**)-4-hydroxy-4-phenethyl-1-tosylpiperidine-2-carboxylate (**5dd**): following general procedure C (H₂O (2.0 equiv.) were added). Elution with EP/EtOAc (80/20). Colorless syrup (18.1 mg, 20% yield). ¹H NMR (300 MHz, CDCl₃) δ 7.75-7.68 (m, 2H), 7.32-7.24 (m, 4H), 7.22-7.13 (m, 3H), 4.77 (d, *J* = 6.4 Hz, 1H), 4.10 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.96 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.77-3.67 (m, 1H), 3.49 (ddd, *J* = 13.3, 11.1, 4.8 Hz, 1H), 2.70-2.62 (m, 2H), 2.42 (s, 3H), 2.35 (brd, *J* = 14.1 Hz, 1H), 1.86 (dd, *J* = 14.1, 6.6 Hz, 1H), 1.78-1.70 (m, 2H), 1.65-1.53 (m, 2H), 1.43 (s, 1H), 1.13 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 171.9, 143.3, 141.8, 137.7, 129.6, 128.7, 128.4, 127.4, 126.2, 69.5, 61.5, 53.0, 45.5, 38.5, 35.7, 29.2, 21.7, 14.0. HRMS (ESI) *m/z* [M+Na]⁺ calcd for C₂₃H₂₉NO₅NaS 454.1659, found 454.1659. IR (UATR) $\bar{\nu}$ (cm⁻¹) 3514 (OH), 1730 (C=O).

5-Phenethyl-2-tosyl-6-oxa-2-azabicyclo[3.2.1]octan-7-one (**10dd**): following general procedure C (H₂O (2.0 equiv.) were added). Elution with EP/EtOAc (80/20). White solid (25.9 mg, 32% yield). M.p. 145-147 °C. ¹H NMR (300 MHz, CDCl₃) δ 7.77-7.72 (m, 2H), 7.36-7.25 (m, 4H), 7.24-7.13 (m, 3H), 4.68 (d, *J* = 4.7 Hz, 1H), 3.93-3.83 (m, 1H), 2.82-2.63 (m, 3H), 2.43 (s, 3H), 2.15 (ddd, *J* = 12.2, 4.6, 1.9 Hz, 1H), 2.09-1.91 (m, 5H). ¹³C NMR (75 MHz, CDCl₃) δ 170.8, 144.4, 140.6, 134.0, 129.8, 128.8, 128.3, 128.2, 126.5, 86.2, 57.6, 41.0, 39.6, 32.8, 29.4, 21.8. HRMS (ESI) *m/z* [M+Na]⁺ calcd for C₂₁H₂₃NO₄NaS 408.1240, found 408.1237. IR (UATR) $\bar{\nu}$ (cm⁻¹) 1780 (C=O).

((2*S**,4*R**)-4-Hydroxy-4-(3-(4-methoxyphenyl)propyl)-1-tosylpiperidin-2-yl)-1-(phenyl)methanone (**5ea**): following general procedure C. Elution with DCM/EtOAc (96/4). Colorless syrup (69.2 mg, 62% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.85-7.81 (m, 2H), 7.62 (d, *J* = 8.2 Hz, 2H), 7.59-7.54 (m, 1H), 7.48-7.43 (m, 2H), 7.21 (d, *J* = 8.2 Hz, 2H), 7.02 (d, *J* = 8.5 Hz, 2H), 6.80 (d, *J* = 8.5 Hz, 2H), 5.62 (d, *J* = 7.2 Hz, 1H), 3.77 (s, 3H), 3.70 (brdd, *J* = 13.6, 3.9 Hz, 1H), 3.54 (td, *J* = 13.3, 3.0 Hz, 1H), 2.47 (t, *J* = 7.5 Hz, 2H), 2.37 (s, 3H), 2.15 (brd, *J* = 14.3 Hz, 1H), 2.12 (brs, 1H) 1.94 (dd, *J* = 14.3, 7.4 Hz, 1H), 1.63-1.48 (m, 4H), 1.39-1.34 (m, 2H). ¹³C NMR (125 MHz, CDCl₃) δ 200.3, 157.9, 143.5, 137.2, 136.1, 134.2, 133.3, 129.7, 129.3, 128.9, 128.6, 127.5, 113.9, 69.2, 56.0, 55.4, 43.3, 38.9, 37.9, 35.4, 35.2, 24.9, 21.6. HRMS (ESI) *m/z* [M+Na]⁺ calcd for C₂₉H₃₃NO₅NaS 530.1972, found 530.1973. IR (UATR) $\bar{\nu}$ (cm⁻¹) 3509 (OH), 1698 (C=O).

((2*S**,4*R**)-4-(3-(4-Methoxyphenyl)propyl)-4-hydroxy-1-tosylpiperidin-2-yl)-1-(phenyl)methanone (**5fa**): following general procedure C. Elution with DCM/EtOAc (97/3). White amorphous solid (52.6 mg, 43% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.87-7.82 (m, 2H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.60-7.55 (m, 1H), 7.48-7.43 (m, 2H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 8.2 Hz, 2H), 6.98 (d, *J* = 8.3 Hz, 2H), 5.64 (d, *J* = 7.2 Hz, 1H), 3.69 (brdd, *J* = 13.7, 3.8 Hz, 1H), 3.52 (td, *J* = 13.3, 3.1 Hz, 1H), 2.49 (t, *J* = 7.6 Hz, 2H), 2.37 (s, 3H), 2.32 (s, 1H), 2.14 (brd, *J* = 14.4 Hz, 1H), 1.93 (dd, *J* = 14.4, 7.5 Hz, 1H), 1.63-1.48 (m, 4H), 1.38-1.33 (m, 2H). ¹³C NMR (125 MHz, CDCl₃) δ 200.5, 143.5, 141.1, 137.1, 135.9, 133.4, 131.5, 130.2, 129.7, 128.9, 128.7, 127.5, 119.7, 69.0, 55.8, 43.3, 38.9, 37.6, 35.54, 35.45, 24.4, 21.6. HRMS (ESI) *m/z* [M+Na]⁺ calcd for C₂₈H₃₀NO₄⁷⁹BrNaS 578.0971, found 578.0973; IR (UATR) $\bar{\nu}$ (cm⁻¹) 3508 (OH), 1697 (C=O).

Author contributions

M.L.R., N.G., J.R., G.A., S.B. performed the methodology, investigation and data curation. T.R. solved the XR structure. N.G. and C.L. did the conceptualization and project administration. N.G., B.V.S.R. and C.L. supervised the research. All authors contributed to the writing and reviewing and they approved its final version.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the Supplementary Information. Crystallographic data for 5aa has been deposited at the CCDC number 2391327 and can be obtained from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

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