

Synthesis of Nitrogenated Heterocycles by Asymmetric Transfer Hydrogenation of *N*-(*tert*- Butylsulfinyl)haloimines

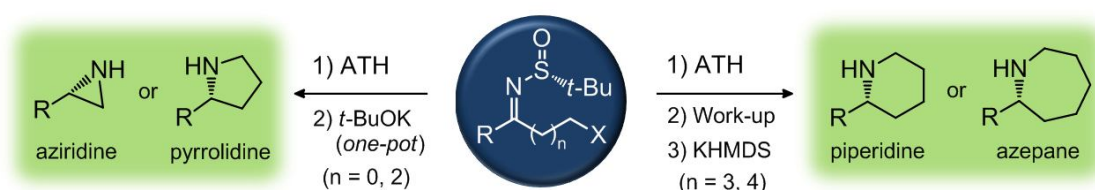
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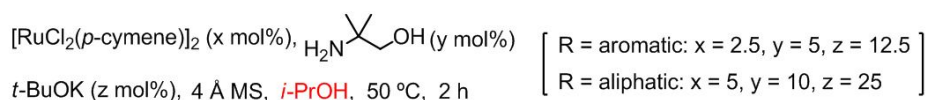
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TOC graphic:



ATH conditions:



Abstract: Highly optically enriched protected nitrogenated heterocycles with different ring sizes have been synthesized by a very efficient methodology consisting in the asymmetric transfer hydrogenation of *N*-(*tert*-butylsulfinyl)haloimines followed by treatment with a base to promote an

intramolecular nucleophilic substitution process. *N*-Protected aziridines, pyrrolidines, piperidines and azepanes bearing aromatic, heteroaromatic and aliphatic substituents have been obtained in very high yields and diastereomeric ratios up to > 99:1. The free heterocycles can be easily obtained by a simple and mild desulfinylation procedure. Both enantiomers of the free heterocycles can be prepared with the same good results by changing the absolute configuration of the sulfur atom of the sulfinyl group.

Keywords: *N*-heterocycles; nitrogenated heterocycles; asymmetric transfer hydrogenation; ATH; haloimine; *N*-sulfinylimines; ruthenium catalyst; isopropyl alcohol.

Introduction

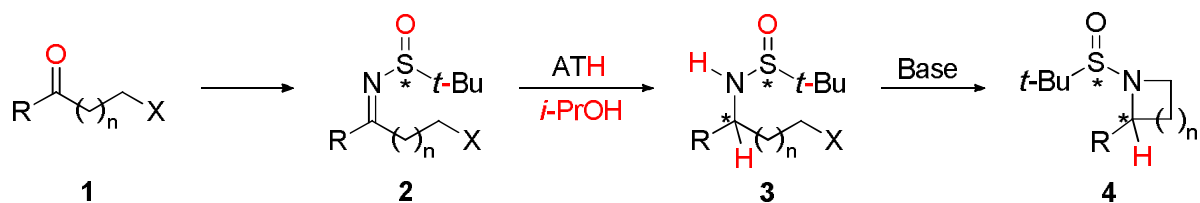
The synthesis of chiral nitrogen-containing saturated heterocycles has attracted the attention of organic chemists worldwide.¹ Some features of those compounds that make them so interesting are: (a) they are key structures present in many natural and synthetic products that display biological and pharmacological activity,² playing a crucial role in the design of new drugs; (b) they have found applications as either chiral ligands or organocatalysts in asymmetric synthesis.³ Among the different methods to build those heterocyclic scaffolds in enantiomerically enriched form, the cyclization of chiral haloamines has shown to be very straightforward and effective. The precursor haloamines can be synthesized by addition or reduction methodologies from imines bearing a chiral auxiliary bonded to the nitrogen atom. In recent years, the *tert*-butylsulfinyl group has arisen as an outstanding chiral auxiliary that leads to excellent diastereoselectivities in a wide assortment of synthetic approaches⁴ and shows the advantage of an easy removal from the nitrogen atom under mild acidic conditions.⁵ The asymmetric synthesis of saturated nitrogenated heterocycles from *N*-(*tert*-butylsulfinyl)haloimines has been accomplished through addition of nucleophiles to the iminic carbon⁶ or, to a lesser extent, via reduction of the C=N bond with either boron or aluminium hydrides.⁷

Functionalized amines are appropriate substrates for the preparation of nitrogenated heterocycles.¹ A very useful methodology for the stereoselective synthesis of chiral amines is the asymmetric transfer hydrogenation (ATH) of imines.⁸ However, this reduction procedure has seldom been used as a tool to prepare nitrogenated heterocycles and, to the best of our knowledge, there are only a few examples reported so far which consist in the reduction of other unsaturated heterocyclic compounds containing endocyclic imine functions.⁹ In the last years, several of our research activities have focused on diastereoselective processes using enantiomerically pure *N*-(*tert*-butylsulfinyl)imines as substrates.¹⁰ We have developed a very effective method for the preparation of highly enantiomerically enriched aromatic and aliphatic amines by ruthenium-catalyzed ATH of *N*-(*tert*-butylsulfinyl)ketimines in isopropyl alcohol followed by desulfinylation of the nitrogen atom.¹¹ Recently, we have used this hydrogen transfer based reduction methodology as a key step to accomplish the synthesis of optically enriched γ -, δ -, and ϵ -lactams from *N*-(*tert*-butylsulfinyl)iminoesters.¹² Herein we describe the application of the ATH of *N*-(*tert*-butylsulfinyl)haloimines to the synthesis of highly enantiomerically enriched aziridines, pyrrolidines, piperidines and azepanes.

Results and Discussion

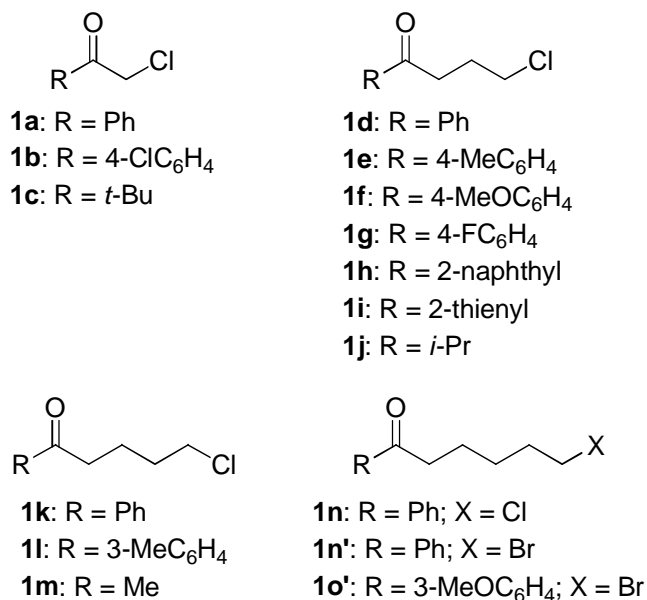
Encouraged by the excellent results that we had obtained in the synthesis of enantiomerically enriched amines through a ruthenium-catalyzed ATH of sulfinylimines,¹¹ we decided to try to extend this methodology to the diastereoselective reduction of *N*-(*tert*-butylsulfinyl)ketimines **2** bearing halogen atoms that could later act as leaving groups in intramolecular nucleophilic substitution processes that would lead to *N*-protected saturated heterocycles **4** (Scheme 1). Since the sulfinyl group can easily be removed,⁵ this sequence would represent an interesting way of preparing nitrogenated heterocyclic compounds.

Scheme 1. Blueprint for the Preparation of Chiral Saturated *N*-Protected Heterocycles **4**

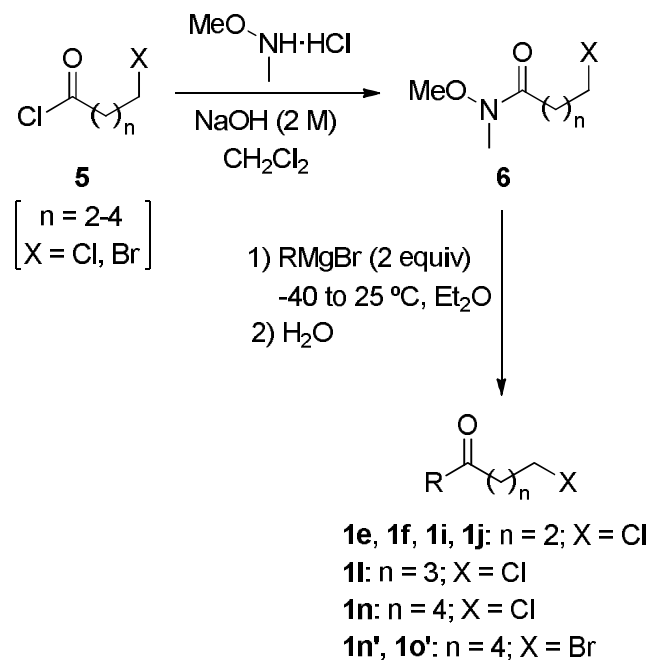


Our first goal was the synthesis of haloimines **2**, for which we needed the corresponding haloketones **1** as precursors. Chart 1 shows all the haloketones that we have used, some of which were commercially available (**1a-1d**, **1g**, **1h**, **1k** and **1m**). Chloroketones **1e**, **1f**, **1i**, **1j**, **1l** and **1n** and bromoketones **1n'** and **1o'** were prepared from halogen-containing acid chlorides **5** as indicated in Scheme 2. First, the acid chlorides were transformed into the corresponding Weinreb amides **6**, which reacted with several Grignard reagents to give, after hydrolysis, the expected haloketones **1e**, **1f**, **1i**, **1j**, **1l**, **1n**, **1n'** and **1o'** in 61-93% overall yields. The starting acid chlorides were commercially available, except for the one bearing a bromine atom, which was prepared by treatment of the corresponding carboxylic acid with thionyl chloride.

Chart 1

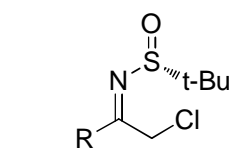
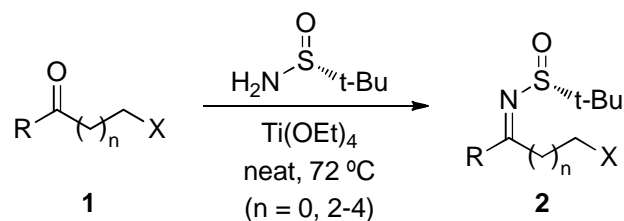


Scheme 2. Preparation of Haloketones **1e**, **1f**, **1i**, **1j**, **1l**, **1n**, **1n'** and **1o'**



Having all the haloketones **1** in hand, the required haloimines **2** were prepared by condensation of those haloketones with (*R*)-2-methylpropane-2-sulfinamide in the presence of titanium tetraethoxide under neat conditions (Scheme 3), following our reported procedure.¹³ Thereby, the expected enantiomerically pure (*R*)-*N*-(*tert*-butylsulfinyl)haloimines **2** were isolated in good yields after column chromatography. In the case of the aliphatic imine **2m**, an 86:14 (*E/Z*) mixture of geometrical isomers was obtained, from which the pure (*E*) isomer was isolated after column chromatography. The (*S*)-haloimine *ent*-**2e** was also prepared by the same procedure but using the (*S*) enantiomer of 2-methylpropane-2-sulfinamide. Unfortunately, all attempts to prepare β-haloimines failed due to elimination processes that led to α,β-unsaturated imines, together with some unreacted β-haloketones.

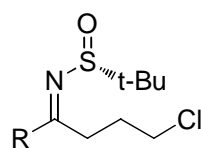
Scheme 3. Synthesis of Haloimines **2 and *ent*-**2e**^a**



2a: R = Ph (78%)

2b: R = 4-ClC₆H₄ (75%)

2c: R = *t*-Bu (64%)



2d: R = Ph (86%)

2e: R = 4-MeC₆H₄ (92%)

[*ent*-**2e** (88%)]^b

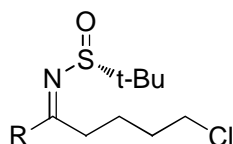
2f: R = 4-MeOC₆H₄ (91%)

2g: R = 4-FC₆H₄ (85%)

2h: R = 2-naphthyl (84%)

2i: R = 2-thienyl (77%)

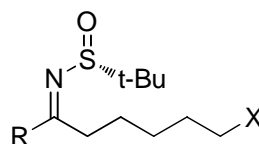
2j: R = *i*-Pr (68%)



2k: R = Ph (88%)

2l: R = 3-MeC₆H₄ (93%)

2m: R = Me (27%; *E*)^c



2n: R = Ph; X = Cl (87%)

2n': R = Ph; X = Br (76%)

2o': R = 3-MeOC₆H₄; X = Br (84%)

^a In parentheses, yield of isolated product after column chromatography (silica gel, hexane/ethyl acetate) based on the starting haloketones **1**. All isolated haloimines **2** and *ent*-**2e** were $\geq 95\%$ pure (300 MHz ¹H NMR).

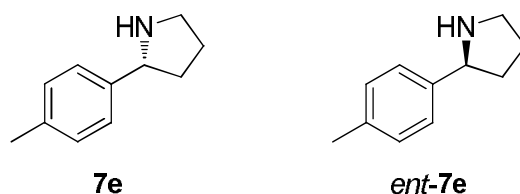
^b (*S*)-2-methylpropane-2-sulfinamide was used in this case.

^c A mixture of geometrical isomers with an estimated *E/Z* ratio = 86:14 was obtained in the crude reaction mixture. The (*E*) isomer could be separated in pure form by column chromatography (silica gel, hexane/ethyl acetate) in 27% yield.

Once we had obtained haloimines **2**, we tried to reduce them employing our hydrogen transfer methodology. Haloimine **2e** was chosen as a model substrate and it was submitted to our optimal reaction conditions for the ATH of *N*-(*tert*-butylsulfinyl)ketimines:^{11c,d} isopropyl alcohol as a hydrogen source, a ruthenium catalyst prepared from [RuCl₂(*p*-cymene)]₂ and the achiral ligand 2-amino-2-methylpropan-1-ol and a reaction temperature of 50 °C. Under these conditions, the reduction of compound **2e** was complete in 2 h. At this time, a 0.3 M solution of *tert*-BuOK in isopropyl alcohol was added to the reaction flask and the mixture was stirred at 50 °C for 1 h in order

to attempt the one-pot cyclization. Gratifyingly, the ^1H NMR spectrum of the reaction crude showed that the *N*-sulfinyl pyrrolidine **4e** (Scheme 4) was the major product, with an estimated diastereomeric ratio of 99:1. After column chromatography, pyrrolidine **4e** was isolated in 90% yield. In order to validate the dr value estimated by ^1H NMR, haloimine *ent*-**2e** was submitted to the same one-pot ATH-cyclization sequence and product *ent*-**4e** was obtained with a dr > 99:1 (according to the ^1H NMR spectrum of the reaction crude) and in 91% yield. Desulfinylation of both **4e** and *ent*-**4e** by treatment with a solution of HCl in MeOH led to the corresponding free pyrrolidines **7e** and *ent*-**7e** (Chart 2) in almost quantitative yields, which were then benzoylated and analyzed by HPLC, giving ee values of 98% (for benzoylated **7e**) and 99% (for benzoylated *ent*-**7e**) (see the Supporting Information for details). These enantiomeric excesses match very well with the diastereomeric ratios previously estimated by ^1H NMR for compounds **4e** and *ent*-**4e**. Therefore, the estimation by ^1H NMR seems to be an appropriate way to determine the diastereoselectivities of these ATH processes. The absolute configurations of pyrrolidines **7e** and *ent*-**7e** were determined by comparison of the sign of their optical rotation values with the ones reported in the literature.^{7c} As it was the case in our ATH of simple ketimines, (*R*)-configured haloimines **2** led to (*R*)-configured nitrogenated heterocycles.

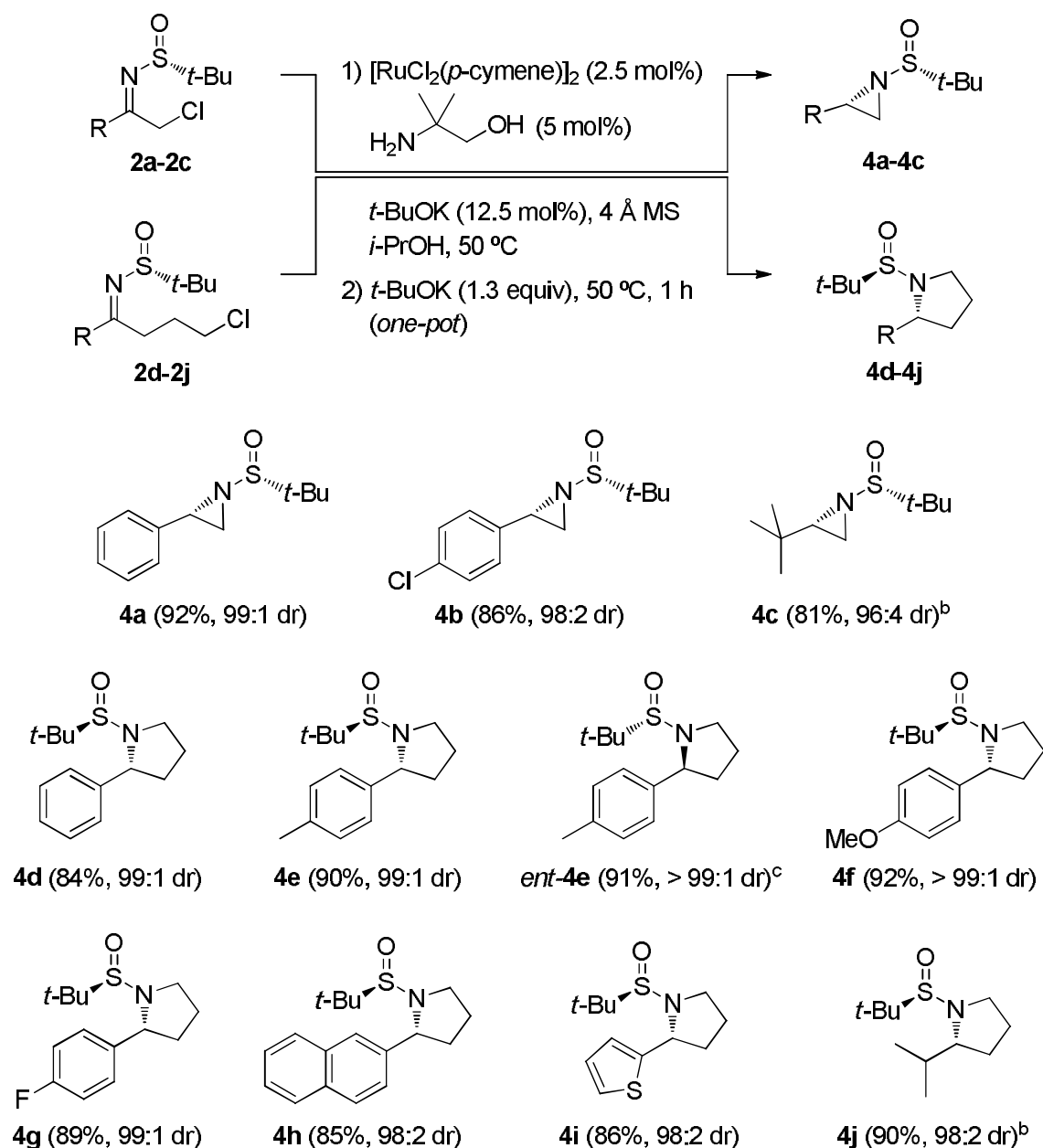
Chart 2



Next, we studied the reaction scope by applying our one-pot ATH-cyclization sequence to haloimines **2d-2j** (Scheme 4) with the aim of preparing some other substituted pyrrolidines. *N*-protected pyrrolidines bearing phenyl substituents with either electron-releasing (**4f**) or electron-withdrawing groups (**4g**) could be prepared with excellent results. We were able to get a single

crystal of compound **4g** and the corresponding X-ray structure confirmed that the stereogenic center generated in the ATH process had the (*R*) absolute configuration (see Figure 1).

Scheme 4. One-pot ATH-Cyclization Sequence. Synthesis of *N*-Protected Aziridines **4a-4c and Pyrrolidines **4d-4j** and *ent-4e*^a**



^a In parentheses, yield of isolated product after column chromatography (based on the starting haloimine **2** or *ent-2e*) and diastereomeric ratio (estimated from the ¹H NMR spectrum of the crude reaction mixture). All isolated compounds **4** and *ent-4e* were ≥ 95% pure (300 MHz ¹H NMR).

^b $[\text{RuCl}_2(p\text{-cymene})]_2$ (5 mol%), 2-amino-2-methylpropan-1-ol (10 mol%) and *tert*-BuOK (25 mol%) were used in this reaction.

^c (*S*)-Chloroimine *ent*-**2e** was used as substrate in this reaction.

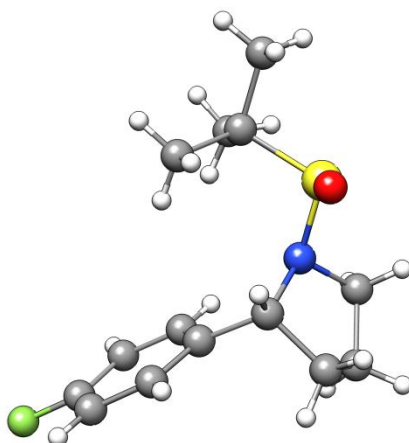


Figure 1. X-Ray Structure of Compound 4g (for an ORTEP plot and detailed crystallographic information, see the Supporting Information)

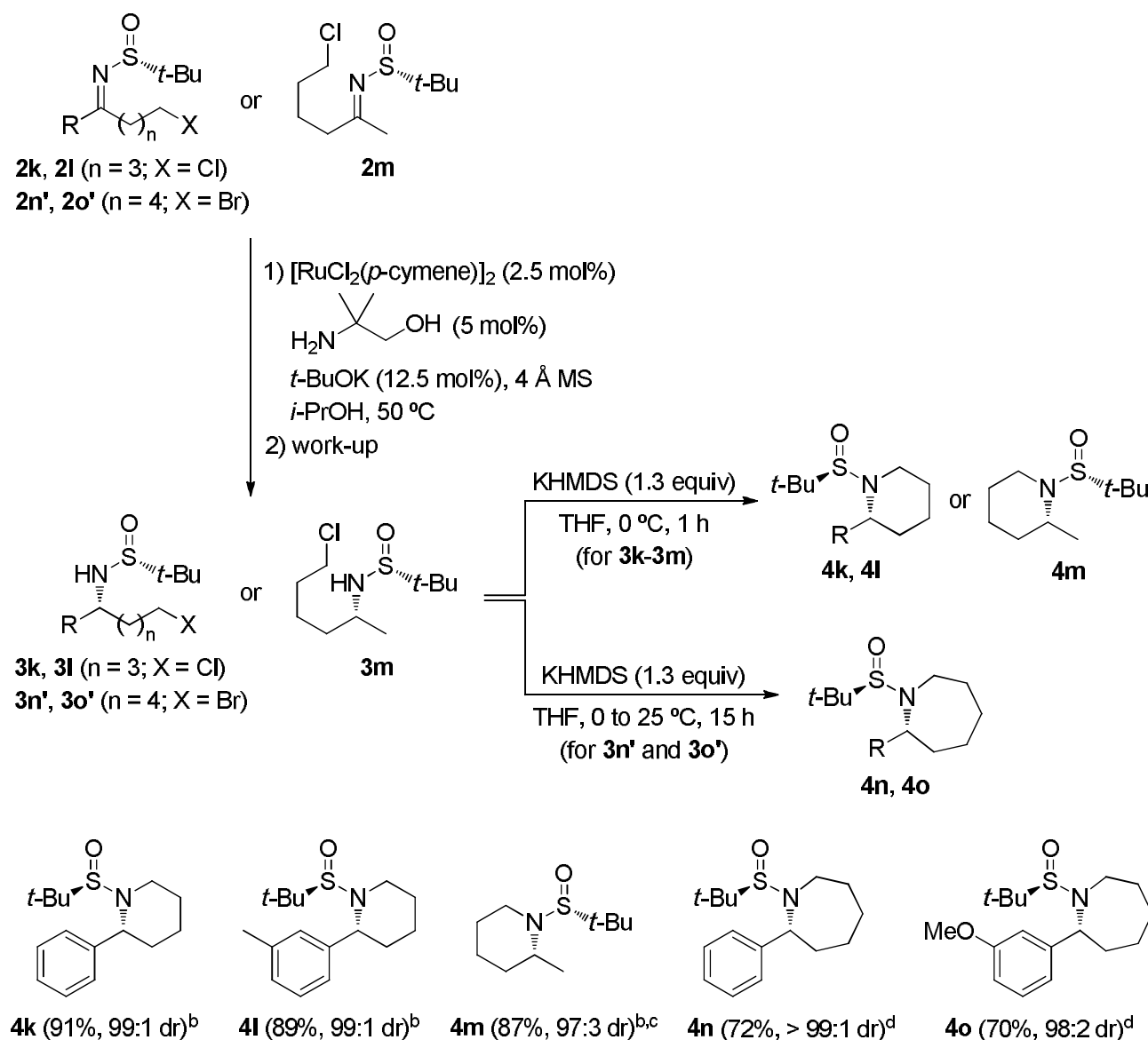
Other pyrrolidines with aromatic substituents different from phenyl, such as 2-naphthyl (**4h**) or 2-thienyl (**4i**), could be prepared with equal efficiency. According to our previous observations,^{11d,12} the catalyst loading for the reduction of the aliphatic imine **2j** had to be increased to assure full conversion of the starting material,¹⁴ but it is worth noting that the expected aliphatic pyrrolidine **4j** was obtained in 90% yield with a 98:2 dr.

This one-pot ATH-cyclization routine was also applied to α -chloroimines **2a-2c** in order to try to synthesize the corresponding chiral aziridines (Scheme 4). We were glad to see that *N*-protected 3-membered ring heterocycles with either aromatic (**4a** and **4b**) or aliphatic substituents (**4c**) could be obtained in high yields and diastereomeric ratios. As before, a higher catalyst loading was necessary to achieve complete reduction of the aliphatic imine **2c**.¹⁴

These promising results encouraged us to try to extend this one-pot ATH-cyclization protocol to the synthesis of piperidines and azepanes from the corresponding δ - and ϵ -haloimines, respectively. However, the cyclization did not take place under those reaction conditions: when we used δ -chloroimine **2k** as substrate, the corresponding chlorosulfonamide **3k** was obtained instead of the expected piperidine.¹⁵ Fortunately, a two-step procedure allowed the formation of *N*-protected

piperidine **4k**: when the ATH reaction was finished, the usual work-up was performed^{11c,d} and the crude residue was dissolved in THF, KHMDS was added at 0 °C and the mixture was stirred at the same temperature for 1 h. Under these conditions, a highly optically enriched piperidine **4k** was isolated in 91% overall yield (Scheme 5). The same two-step methodology applied to imine **2l** yielded compound **4l** with the same good results concerning both yield and diastereoselectivity. It is worth noting that the protected aliphatic piperidine **4m** could also be obtained with a 97:3 dr using the same amount of catalyst as for the reduction of the other aliphatic imines **2c** and **2j**.¹⁶

Scheme 5. ATH Followed by Treatment with KHMDS. Synthesis of Piperidines 4k-4m and Azepanes 4n, 4o^a



- ^a In parentheses, yield of isolated product after column chromatography (based on the starting haloimine **2**) and diastereomeric ratio (estimated from the ¹H NMR spectrum of the crude reaction mixture). All isolated compounds **4** were $\geq 95\%$ pure (300 MHz ¹H NMR).
- ^b The ATH crude was dissolved in anhydrous THF, KHMDS (1.3 equiv, 1 M solution in THF) was added at 0 °C and the reaction mixture was stirred at the same temperature for 1 h.
- ^c [RuCl₂(*p*-cymene)]₂ (5 mol%), 2-amino-2-methylpropan-1-ol (10 mol%) and *tert*-BuOK (25 mol%) were used in this reaction.
- ^d The ATH crude was dissolved in anhydrous THF, KHMDS (1.3 equiv, 1 M solution in THF) was added at 0 °C and the reaction mixture was stirred allowing it to reach room temperature and then stirred overnight.

The two-step procedure did not work for the preparation of 7-membered ring heterocycles from ϵ -chloroimine **2n**. Treatment of chlorosulfinamide **3n** with KHMDS failed to form the cyclization product, even at higher temperatures and increasing the amount of base. Fortunately, this problem could be solved by starting from imines **2n'** and **2o'**, both having a bromine atom as a leaving group instead of a chlorine. Treatment of bromine-containing sulfinamides **3n'** and **3o'** with KHMDS overnight at room temperature led to the corresponding azepanes **4n** and **4o** in high yields and with excellent diastereoselectivities (Scheme 5). We were able to get an X-ray structure of compound **4n**, which confirmed that the stereogenic center generated in the ATH process had the (*R*) absolute configuration (Figure 2). To the best of our knowledge, the synthesis of azepanes through ATH processes had never been reported so far.

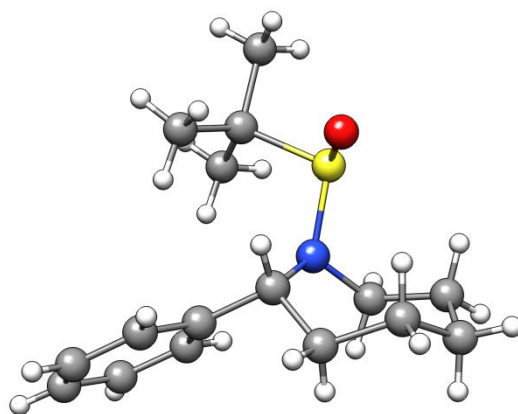


Figure 2. X-Ray Structure of Compound 4n (for an ORTEP plot and detailed crystallographic information, see the Supporting Information)

In our opinion, the methodology described herein represents a very efficient route to prepare saturated nitrogenated heterocycles from halogen-containing *N*-(*tert*-butylsulfinyl)ketimines and presents some advantages in comparison with the few procedures found in the literature that allow a similar transformation:⁷ (a) we use a catalytic ATH method to reduce the imine function, while the reported procedures employ stoichiometric reagents such as boron or aluminium hydrides which could lead to the formation of side products; (b) the achiral ligand that we use in the ruthenium catalyst is very cheap, thus reducing the reaction costs; (c) isopropyl alcohol, which acts as a solvent and as a hydrogen source in our ATH reaction, is environmentally friendly and is a convenient solvent for industrial scale processes;¹⁷ (d) our methodology is more versatile, since we have been able to prepare nitrogenated heterocycles with a variety of ring sizes.

Conclusion

We have presented herein a simple, versatile and very effective procedure for the synthesis of highly optically enriched *N*-protected aziridines, pyrrolidines, piperidines and azepanes by applying our ATH protocol to the diastereoselective reduction of *N*-(*tert*-butylsulfinyl)haloimines. A one-pot ATH-cyclization sequence enables the preparation of both aziridines and pyrrolidines, whilst piperidines and azepanes become accessible through a two-step protocol. The free saturated nitrogenated heterocycles can be easily obtained by removal of the sulfinyl group from the nitrogen atom under mild acidic conditions. Nitrogenated heterocycles bearing aromatic, heteroaromatic or aliphatic substituents can be prepared in very high yields and optical purities. The absolute configuration of the final product can be tuned up simply by choosing the adequate configuration on the sulfinyl chiral auxiliary.

Experimental Section

General Information

All glassware was dried in an oven at 100 °C and cooled to room temperature under argon before use. All reactions were carried out under an argon atmosphere. Haloketones **1a-1d**, **1g**, **1h**, **1k** and **1m**, (*R*)- and (*S*)-*tert*-BuSONH₂, Ti(OEt)₄ (33% TiO₂ min), [RuCl₂(*p*-cymene)]₂, 2-amino-2-methylpropan-1-ol and all the starting materials needed for the synthesis of haloketones **1e**, **1f**, **1i**, **1j**, **1l**, **1n**, **1n'** and **1o'** were commercially available and were used as received. *tert*-BuOK was heated in a Kugel-Rohr distillation apparatus at 170-180 °C under vacuum for 4 h before use. Commercially available 4 Å molecular sieves were dried in a Kugel-Rohr distillation apparatus at 120 °C under vacuum for 5h before use. Commercially available anhydrous isopropyl alcohol was used as solvent in all the transfer hydrogenation reactions. Column chromatography was performed with silica gel 60 of 230–400 mesh. Thin layer chromatography (TLC) was performed on precoated silica gel plates; detection was done by UV₂₅₄ light and staining with phosphomolybdic acid (solution of 1 g of phosphomolybdic acid in 24 mL of absolute ethanol); *R_f* values are given under these conditions. Melting points (mp) are uncorrected. Unless otherwise stated, NMR samples were prepared using CDCl₃ as solvent. The internal references used for NMR spectra were tetramethylsilane (TMS) for ¹H NMR and CDCl₃ for ¹³C NMR; chemical shifts are given in δ (ppm) and coupling constants (*J*) in Hz. ¹³C NMR assignments were made on the basis of DEPT experiments. Infrared (FT-IR) spectra were obtained on a spectrophotometer equipped with an attenuated total reflectance (ATR) accessory. Mass spectra (EI) were obtained at 70 eV; fragment ions in *m/z* with relative intensities (%) in parenthesis are given. HRMS were measured with electron impact (EI) ionization at 70 eV and a double focusing mass analyzer (magnetic and electric fields). Optical rotation measurements and HPLC analyses were performed at 20 °C.

Preparation of Weinreb Amides **6**. General Procedure

A 2 M NaOH aqueous solution (15 mL) was added to a suspension of Me(MeO)NH·HCl (926 mg, 9.5 mmol) in CH₂Cl₂ (15 mL) at 0 °C. Then, the corresponding acid chloride (10.0 mmol) was added dropwise during *ca.* 1 min, the reaction mixture was allowed to reach room temperature and it was

stirred overnight. The reaction mixture was extracted with CH_2Cl_2 (2×5 mL) and the combined organic layers were washed with a 2 M NaOH aqueous solution (10 mL) and dried (Na_2SO_4). After filtration and evaporation of the solvents, the expected Weinreb amides were obtained, which were used in the next step without purification.

For the preparation of bromoketones **1n'** and **1o'**, 6-bromohexanoyl chloride was required, which was prepared by refluxing a mixture of 6-bromohexanoic acid (2.34 g, 12.0 mmol) and SOCl_2 (60.0 mmol) in CH_2Cl_2 (20 mL) for 5 h. Solvent and the excess of SOCl_2 were evaporated and the residue was used directly for the synthesis of the corresponding Weinreb amide.

Addition of Grignard Reagents to Weinreb Amides 6. Synthesis of Haloketones 1e, 1f, 1i, 1j, 1l, 1n, 1n' and 1o'. General Procedure

A solution of the Grignard reagent¹⁸ (16.0 mmol) was added dropwise over a period of 40 minutes with the aid of a syringe pump to a solution of the corresponding Weinreb amide (8.0 mmol) in anhydrous Et_2O (30 mL) at -40 °C with vigorous stirring, and the mixture was stirred at the same temperature for 1 h. The temperature was slowly risen to room temperature (by switching the cryostat off and keeping the reaction flask inside the cooling bath) and the reaction was stirred overnight. Then, a saturated aqueous NH_4Cl solution (25 mL) was carefully added (in small portions and cooling the flask at 0 °C) and the mixture was extracted with Et_2O (3×15 mL). The combined organic layers were dried (Na_2SO_4). After filtration and evaporation of the solvent, the resulting residue was purified by column chromatography (silica gel, hexane/ethyl acetate), giving the expected haloketones **1e** (1.416 g, 90%), **1f** (1.565 g, 92%), **1i** (1.328 g, 88%), **1j** (0.725 g, 61%), **1l** (1.466 g, 87%), **1n** (1.568 g, 93%), **1n'** (1.837 g, 90%) and **1o'** (1.939 g, 85%). Compounds **1e**,¹⁹ **1f**,¹⁹ **1i**,²⁰ **1j**,²¹ **1n**²² and **1n'**²³ were identified by comparison of their physical and spectroscopic data with the ones reported in the literature. The corresponding physical, spectroscopic and analytical data for haloketones **1l** and **1o'** follow.

5-Chloro-1-(3-methylphenyl)pentan-1-one (11): colorless oil; R_f 0.56 (hexane/ethyl acetate: 9/1); IR (neat) 3058, 1683 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.77-2.00 (4H, m), 2.41 (3H, s), 3.00 (2H, t, $J = 7.0$ Hz), 3.58 (2H, t, $J = 6.3$ Hz), 7.29-7.41 (2H, m), 7.67-7.79 (2H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 21.3, 21.5, 32.0, 37.5, 44.7, 125.2, 128.4, 128.5, 133.8, 136.8, 138.4, 199.8; m/z 212 ($\text{M}^+ + 2$, 2%), 210 (M^+ , 7%), 134 (25), 119 (100), 91 (29); HRMS: M^+ found 210.0817, $\text{C}_{12}\text{H}_{15}\text{ClO}$ requires 210.0811.

6-Bromo-1-(3-methoxyphenyl)hexan-1-one (10'): white solid; mp 52 $^\circ\text{C}$; R_f 0.50 (hexane/ethyl acetate: 9/1); IR (neat) 3054, 1683, 1255 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.47-1.63, 1.73-1.83, 1.88-1.97 (2H each, 3 m), 2.99 (2H, t, $J = 7.3$ Hz), 3.44 (2H, t, $J = 6.8$ Hz), 3.86 (3H, s), 7.11 (1H, ddd, $J = 8.1, 2.7, 0.9$ Hz), 7.38 (1H, t, $J = 8.1$ Hz), 7.49 (1H, dd, $J = 2.7, 1.5$ Hz), 7.54 (1H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 23.3, 27.8, 32.6, 33.6, 38.4, 55.4, 112.2, 119.4, 120.6, 129.5, 138.3, 159.8, 199.8; m/z 286 ($\text{M}^+ + 2$, 9%), 284 (M^+ , 9%), 205 (48), 176 (100), 107 (26); HRMS: M^+ found 284.0415, $\text{C}_{13}\text{H}_{17}\text{BrO}_2$ requires 284.0412.

Synthesis of Haloimines **2** and *ent*-**2e**. General Procedure

N-(*tert*-Butylsulfinyl)haloimines were prepared by condensation of the corresponding haloketones **1** with (*R*)-2-methylpropane-2-sulfinamide (for **2**) or (*S*)-2-methylpropane-2-sulfinamide (for *ent*-**2e**) following our recently reported procedure,¹³ as follows: a mixture of haloketone **1** (5.0 mmol), (*R*)- or (*S*)-*tert*-BuSONH₂ (612 mg, 5.0 mmol) and Ti(OEt)₄ (2.1 mL, 10.0 mmol) was stirred overnight under argon at 72 $^\circ\text{C}$ (oil bath temperature). After cooling to room temperature, the mixture was diluted with ethyl acetate (10 mL) and poured into brine (3 mL) while rapidly stirring. The resulting suspension was filtered through a plug of celite and the filter cake was washed with ethyl acetate. After evaporation of the solvent, the resulting residue was purified by column chromatography (silica gel, hexane/ethyl acetate), to give the expected haloimines **2** and *ent*-**2e** in the yields indicated in Scheme 3. Compounds **2a**,^{11b} **2d**,^{7d} **2e**,^{7c} *ent*-**2e**,^{7c} **2f**,^{7d} **2g**,^{7d} **2i**,^{7d} **2k**,^{7d} and **2n**^{7d} were identified by comparison of their physical and spectroscopic data with the ones reported in the literature. The

corresponding physical, spectroscopic and analytical data for haloimines **2b**, **2c**, **2h**, **2j**, **2l**, **2m**, **2n'** and **2o'** follow.

(R)-N-[2-Chloro-1-(4-chlorophenyl)ethyliden]-2-methylpropane-2-sulfinamide (2b): yellow oil; R_f 0.69 (hexane/ethyl acetate: 2/1); $[\alpha]_D^{20}$ -20.0 (c 1.2, CH_2Cl_2); IR (neat) 3070, 1576, 1070 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.36 (9H, s), 5.00, 5.14 (1H each, 2 d, $J = 11.0$ Hz each), 7.43, 7.81 (2H each, 2 d, $J = 8.6$ Hz each); ^{13}C NMR (100 MHz, CDCl_3) δ 23.2, 35.2, 59.8, 128.8, 129.0, 134.3, 138.3, 168.2; m/z (DIP) 291 (M^+ , <1%), 237 (32), 235 (47), 201 (20), 199 (56), 151 (14), 138 (27), 137 (20), 57 (100); HRMS: $\text{M}^+ - \text{C}_4\text{H}_8$ found 234.9638, $\text{C}_8\text{H}_7\text{Cl}_2\text{NOS}$ requires 234.9625.

(R)-N-[1-Chloro-3,3-dimethyl-2-butyliden]-2-methylpropane-2-sulfinamide (2c): yellow oil; R_f 0.54 (hexane/ethyl acetate: 4/1); $[\alpha]_D^{20}$ -426.0 (c 1.2, CH_2Cl_2); IR (neat) 3068, 1601, 1076 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.23 (9H, s), 1.29 (9H, s), 4.25, 4.92 (1H each, 2 d, $J = 10.5$ Hz each); ^{13}C NMR (75 MHz, CDCl_3) δ 22.7, 27.6, 34.3, 43.1, 58.0, 182.8; m/z (DIP) 237 (M^+ , <1%), 183 (15), 181 (38), 120 (17), 118 (53), 83 (41), 57 (100); HRMS: M^+ found 237.0970, $\text{C}_{10}\text{H}_{20}\text{ClNOS}$ requires 237.0954.

(R)-N-[4-Chloro-1-(2-naphthyl)butyliden]-2-methylpropane-2-sulfinamide (2h): yellow oil; R_f 0.41 (hexane/ethyl acetate: 4/1); $[\alpha]_D^{20}$ $+31.0$ (c 1.7, CH_2Cl_2); IR (neat) 3058, 1588, 1065 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.37 (9H, s), 2.14-2.32 (2H, m), 3.32-3.63 (2H, m), 3.66-3.71 (2H, m), 7.51-7.60 (2H, m), 7.86 (2H, d, $J = 8.6$ Hz), 7.93, 8.02 (1H each, 2 d, $J = 7.6$ Hz each), 8.33 (1H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 22.7, 29.9, 31.8, 44.8, 57.9, 124.0, 126.7, 127.6, 128.0, 128.2, 128.4, 129.3, 132.7, 134.7, 134.8, 177.8; m/z (DIP) 335 (M^+ , <1%), 281 (17), 279 (46), 196 (13), 169 (100), 154 (23), 153 (21), 127 (23), 57 (15); HRMS: M^+ found 335.1122, $\text{C}_{18}\text{H}_{22}\text{ClNOS}$ requires 335.1111.

(R)-N-(6-Chloro-2-methyl-3-hexyliden)-2-methylpropane-2-sulfinamide (2j): yellow oil; R_f 0.35 (hexane/ethyl acetate: 85/15); $[\alpha]_D^{20}$ -120.5 (c 1.8, CH_2Cl_2); IR (neat) 1620, 1069 cm^{-1} ; ^1H NMR

(300 MHz, CDCl₃) δ 1.14 (6H, d, J = 6.8 Hz), 1.24 (9H, s), 2.04-2.14 (2H, m), 2.45-3.05 (3H, m), 3.59 (2H, t, J = 6.1 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 20.1, 20.2, 22.3, 30.6, 32.4, 39.5, 44.5, 56.9, 190.0; m/z (DIP) 251 (M⁺, <1%), 197 (35), 195 (100), 161 (21), 110 (43), 57 (71); HRMS: M⁺ found 251.1118, C₁₁H₂₂ClNOS requires 251.1111.

(R)-N-[5-Chloro-1-(3-methylphenyl)pentyliden]-2-methylpropane-2-sulfinamide (2l): yellow oil; R_f 0.31 (hexane/ethyl acetate: 4/1); $[\alpha]_D^{20}$ -18.5 (c 1.9, CH₂Cl₂); IR (neat) 3055, 1573, 1070 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.33 (9H, s), 1.76-1.97 (4H, m), 2.40 (3H, s), 3.07-3.41 (2H, m), 3.58-3.73 (2H, m), 7.29-7.38, 7.54-7.73 (2H each, 2 m); ¹³C NMR (100 MHz, CDCl₃) δ 21.5, 22.7, 25.9, 31.4, 32.2, 44.3, 57.6, 124.5, 127.9, 128.5, 132.3, 137.4, 138.3, 179.3; m/z (DIP) 313 (M⁺, <1%), 259 (36), 257 (100), 240 (21), 174 (23), 146 (37), 118 (26), 57 (23); HRMS: M⁺ found 313.1278, C₁₆H₂₄ClNOS requires 313.1267.

(R,E)-N-(6-Chloro-2-hexyliden)-2-methylpropane-2-sulfinamide (2m):²⁴ yellowish oil; R_f 0.61 (hexane/ethyl acetate: 1/1); $[\alpha]_D^{20}$ -145.0 (c 1.3, CH₂Cl₂); IR (neat) 1622, 1070 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.24 (9H, s), 1.67-1.88 (4H, m), 2.33 (3H, s), 2.37-2.52 (2H, m), 3.55 (2H, t, J = 6.1 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 22.1, 22.5, 23.0, 31.7, 42.2, 44.6, 56.2, 184.6; m/z (DIP) 237 (M⁺, <1%), 183 (31), 181 (100), 147 (11), 57 (48).

(R)-N-(6-Bromo-1-phenylhexyliden)-2-methylpropane-2-sulfinamide (2n⁹): yellow oil; R_f 0.43 (hexane/ethyl acetate: 4/1); $[\alpha]_D^{20}$ -20.0 (c 1.2, CH₂Cl₂); IR (neat) 3056, 1590, 1070 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.33 (9H, s), 1.52-1.75 (4H, m), 1.85-1.94 (2H, m), 3.09-3.33 (2H, m), 3.40 (2H, t, J = 6.7 Hz), 7.38-7.52 (3H, m), 7.84 (2H, d, J = 7.1 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 22.7, 27.8, 28.3, 32.15, 32.2, 33.6, 57.6, 127.4, 128.6, 131.5, 137.7, 179.5; m/z (DIP) 357 (M⁺, <1%), 303 (100), 301 (98), 252 (10), 174 (28), 167 (19), 132 (30), 119 (25), 104 (34), 103 (24), 77 (14), 57 (32); HRMS: M⁺ found 357.0777, C₁₆H₂₄BrNOS requires 357.0762.

(R)-N-[6-Bromo-1-(3-methoxyphenyl)hexyliden]-2-methylpropane-2-sulfinamide (2o'): yellow oil; R_f 0.35 (hexane/ethyl acetate: 4/1); $[\alpha]_D^{20}$ -2.0 (c 1.6, CH_2Cl_2); IR (neat) 3075, 1604, 1572, 1073 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.33 (9H, s), 1.51-1.62, 1.64-1.76, 1.84-1.94 (2H each, 3 m), 3.06-3.34 (2H, m), 3.40 (2H, t, $J = 6.7$ Hz), 3.84 (3H, s), 7.03 (1H, d, $J = 7.5$ Hz), 7.35 (1H, t, $J = 8.1$ Hz), 7.37-7.51 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 22.6, 27.8, 28.2, 32.1, 32.2, 33.5, 55.3, 57.6, 112.8, 117.0, 119.7, 129.5, 139.1, 159.6, 179.2; m/z (DIP) 387 (M^+ , <1%), 333 (56), 331 (55), 316 (25), 314 (24), 149 (100), 134 (20), 57 (22); HRMS: M^+ found 387.0870, $\text{C}_{17}\text{H}_{26}\text{BrNO}_2\text{S}$ requires 387.0868.

One-Pot ATH-Cyclization Sequence. Synthesis of Aziridines 4a-4c and Pyrrolidines 4d-4j and ent-4e. General Procedure

A mixture of $[\text{RuCl}_2(p\text{-cymene})]_2$ (14 mg, 0.023 mmol), 2-amino-2-methylpropan-1-ol (4 mg, 0.045 mmol), 4 Å molecular sieves (0.3 g), and anhydrous *i*-PrOH (1.5 mL) under argon was heated up to 90 °C (oil bath temperature) for 20 min {for aliphatic haloimines **2c** and **2j**, $[\text{RuCl}_2(p\text{-cymene})]_2$ (28 mg, 0.045 mmol) and 2-amino-2-methylpropan-1-ol (8 mg, 0.090 mmol) were used}. During this heating period, the initially orange reaction mixture turned into a dark red color. The reaction was then cooled to 50 °C, and a solution of the haloimine **2a-2j** or *ent*-**2e** (0.9 mmol) in *i*-PrOH (6.3 mL) and *tert*-BuOK (1.13 mL of a 0.1 M solution in *i*-PrOH, 0.113 mmol) were successively added [for aliphatic haloimines **2c** and **2j**, *tert*-BuOK (2.25 mL of a 0.1 M solution in *i*-PrOH, 0.225 mmol) was used]. After completion of the ATH reaction (generally 2 h, monitored by TLC), *tert*-BuOK (3.9 mL of a 0.3 M solution in *i*-PrOH, 1.17 mmol) was added to the reaction mixture and it was stirred for 1 h at 50 °C. Then, the reaction mixture was passed through a small column of silica gel, the column was washed with ethyl acetate, the combined organic phases were evaporated and the resulting residue was purified by column chromatography (silica gel, hexane/ethyl acetate), giving the expected *N*-protected aziridines **4a-4c** and pyrrolidines **4d-4j** and *ent*-**4e** with the yields and diastereomeric ratios indicated in Scheme 4. Compounds **4a**,^{7a} **4b**,^{7a} **4c**,^{6c} **4d**,^{7d} **4e**,^{6f} *ent*-**4e**,^{6f} **4f**,^{7d} **4g**^{7d} and **4i**^{7d} were identified by comparison of their physical and

spectroscopic data with the ones reported in the literature. The corresponding physical, spectroscopic and analytical data for compounds **4h** and **4j** follow.

(*R,S,R*)-*N*-(*tert*-Butylsulfinyl)-2-(2-naphthyl)pyrrolidine (4h**):** white solid; mp 118 °C; R_f 0.32 (hexane/ethyl acetate: 2/1); $[\alpha]_D^{20} +237.0$ (c 1.5, MeOH, 98:2 dr); IR (neat) 3056, 1095, 1058 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.05 (9H, s), 1.77-1.96 (3H, m), 2.14-2.28 (1H, m), 3.62 (1H, dt, $J = 10.7, 6.9$ Hz), 3.70-3.82 (1H, m), 5.23 (1H, dd, $J = 8.2, 2.1$ Hz), 7.37 (1H, dd, $J = 8.5, 1.6$ Hz), 7.40-7.50 (2H, m), 7.69 (1H, s), 7.73-7.86 (3H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 23.0, 24.2, 36.4, 55.1, 57.4, 57.5, 124.8, 125.0, 125.5, 126.1, 127.6, 127.7, 128.2, 132.3, 133.2, 142.0; m/z (DIP) 301 (M^+ , <1%), 245 (34), 197 (16), 160 (18), 57 (100); HRMS: M^+ found 301.1507, $\text{C}_{18}\text{H}_{23}\text{NOS}$ requires 301.1500.

(*R,S,R*)-*N*-(*tert*-Butylsulfinyl)-2-isopropylpyrrolidine (4j**):** colorless oil; R_f 0.46 (hexane/ethyl acetate: 7/3); $[\alpha]_D^{20} +19.5$ (c 0.9, MeOH, 98:2 dr); IR (neat) 2957, 1470, 1069 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.89, 0.92 (3H each, 2 d, $J = 6.9$ Hz each), 1.20 (9H, s), 1.59-1.81 (4H, m), 2.04-2.16 (1H, m), 3.17-3.26, 3.32-3.41 (1H each, 2 m), 3.57-3.67 (1H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 16.6, 20.1, 23.4, 25.4, 26.1, 31.0, 50.5, 57.6, 62.7; m/z (DIP) 217 (M^+ , <1%), 161 (72), 113 (14), 57 (100); HRMS: M^+ found 217.1509, $\text{C}_{11}\text{H}_{23}\text{NOS}$ requires 217.1500.

Removal of the Sulfinyl Group. Isolation of Pyrrolidines **7e and *ent*-**7e**. General Procedure**

Product **4e** or *ent*-**4e** (133 mg, 0.5 mmol) was dissolved in a 2 M solution of HCl in methanol (7 mL; prepared by dropwise addition of SOCl_2 to methanol at 0 °C) and stirred overnight at room temperature. Then, the solvent was evaporated, a 2 M aqueous HCl solution (10 mL) was added and the mixture was extracted with ethyl acetate (3×10 mL). The organic layers were discarded. The aqueous layer was basified with a buffer solution of NH_3 (2 M) / NH_4Cl (2 M) (10 mL) and a 2 M aqueous NaOH solution to ensure $\text{pH} > 11$. The mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried (Na_2SO_4). After filtration and evaporation of the solvent,

the pure pyrrolidine **7e** (78 mg, 97%) or *ent-7e* (80 mg, 99%) was obtained. Compounds **7e** and *ent-7e* were identified by comparison of their physical and spectroscopic data with the ones reported in the literature.^{7c}

Benzoylation of Pyrrolidines **7e and *ent-7e*. Determination of the Enantiomeric Excess of Compounds **7e** and *ent-7e***

A solution of **7e** or *ent-7e* (24 mg, 0.2 mmol) in CH₂Cl₂ (5 mL) was cooled to 0 °C. An aqueous 2 M NaOH solution (5 mL) was added, followed by benzoyl chloride (46 μL, 0.4 mmol) and the resulting mixture was stirred for 4 h at room temperature. The organic layer was separated, washed with an aqueous 2 M NaOH solution (2 × 5 mL) and dried (Na₂SO₄). Filtration and evaporation of the solvent afforded the corresponding benzamide, which was analyzed by HPLC on a ChiralCel OD-H column using a 254 nm UV detector, 10% *i*-PrOH in hexane as eluent and a flow rate of 0.5 mL/min. The retention times of the two enantiomers were 25.6 min (*S*) and 29.5 min (*R*) (see the Supporting Information for details).

Two-Step Procedure ATH + Cyclization. Synthesis of Piperidines **4k-4m and Azepanes **4n, 4o**. General Procedure**

Haloimine **2k-2m**, **2n'** or **2o'** was reduced by the same ATH procedure used for the preparation of aziridines and pyrrolidines (see above). After completion of the ATH process (generally 2 h, monitored by TLC), the reaction mixture was directly passed through a small column of silica gel, the column was washed with ethyl acetate, and the combined organic phases were evaporated, giving halosulfonamide **3k-3m**, **3n'** or **3o'**, which was submitted to the cyclization step without further purification.

KHMDS (1.17 mL of a 1 M solution in THF, 1.17 mmol) was added to a solution of the halosulfonamide **3k-3m**, **3n'** or **3o'** (0.9 mmol) in anhydrous THF (4 mL) at 0 °C. For the synthesis of piperidines **4k-4m**, the reaction was then stirred for 1 h at 0 °C. For the preparation of azepanes **4n** and **4o**, the cooling bath was removed and the reaction mixture was stirred overnight at room

temperature. After completion of the cyclization step, Et₂O (10 mL) and a saturated aqueous NH₄Cl solution (5 mL) were added. The mixture was extracted with Et₂O (3 × 5 mL) and the combined organic layers were dried (Na₂SO₄). After filtration and evaporation of the solvent, the resulting residue was purified by column chromatography (silica gel, hexane/ethyl acetate), giving the expected *N*-protected heterocycles **4k-4o** with the yields and diastereomeric ratios indicated in Scheme 5. Compound **4k**^{7d} was identified by comparison of its physical and spectroscopic data with the ones reported in the literature. The corresponding physical, spectroscopic and analytical data for compounds **4l**, **4m**, **4n** and **4o** follow.

(*R*_S,*R*)-*N*-(*tert*-Butylsulfinyl)-2-(3-methylphenyl)piperidine (4l**):** colorless oil; *R*_f 0.51 (hexane/ethyl acetate: 7/3); [α]_D²⁰ +111.0 (*c* 1.2, MeOH, 99:1 dr); IR (neat) 3045, 1455, 1073 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.16 (9H, s), 1.39-1.52 (1H, m), 1.54-1.72 (3H, m), 1.97-2.08, 2.15-2.24 (1H each, 2 m), 2.37 (3H, s), 3.29 (2H, m), 4.63 (1H, t, *J* = 4.2 Hz), 7.06 (1H, d, *J* = 6.7 Hz), 7.19-7.28 (3H, m); ¹³C NMR (100 MHz, CDCl₃) δ 20.4, 21.7, 23.0, 25.6, 31.2, 44.1, 57.3, 58.7, 124.4, 127.4, 128.1, 128.4, 138.1, 140.1; *m/z* (DIP) 279 (M⁺, 7%), 223 (100), 175 (21), 91 (12), 57 (49); HRMS: M⁺ found 279.1660, C₁₆H₂₅NOS requires 279.1657.

(*R*_S,*R*)-*N*-(*tert*-Butylsulfinyl)-2-methylpiperidine (4m**):** yellowish oil; *R*_f 0.53 (hexane/ethyl acetate: 3/2); [α]_D²⁰ -36.0 (*c* 1.0, MeOH, 97:3 dr); IR (neat) 2971, 2932, 1455, 1360, 1073 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.17 (9H, s), 1.24 (3H, d, *J* = 6.5 Hz), 1.42-1.81 (6H, m), 2.77-2.92 (1H, m), 3.20-3.40 (2H, m); ¹³C NMR (75 MHz, CDCl₃) δ 19.6, 22.0, 23.4, 26.0, 34.0, 42.3, 55.0, 57.6; *m/z* (DIP) 203 (M⁺, <1%), 147 (59), 98 (11), 57 (100); HRMS: M⁺ found 203.1339, C₁₀H₂₁NOS requires 203.1344.

(*R*_S,*R*)-*N*-(*tert*-Butylsulfinyl)-2-phenylazepane (4n**):** white solid; mp 64 °C; *R*_f 0.65 (hexane/ethyl acetate: 4/1); [α]_D²⁰ +271.0 (*c* 1.7, CH₂Cl₂, > 99:1 dr); IR (neat) 3062, 1448, 1059 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.02 (9H, s), 1.20-1.34, 1.58-1.67, 1.70-1.96, 2.17-2.31 (1H, 1H, 5H and 1H,

respectively, 4 m), 3.40-3.48 (1H, m), 3.56 (1H, d, $J = 15.2$ Hz), 4.68 (1H, dd, $J = 10.8, 5.7$ Hz), 7.18-7.35 (5H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 23.1, 25.3, 29.6, 30.1, 38.9, 48.0, 56.7, 57.8, 126.3, 126.4, 128.4, 145.4; m/z (DIP) 279 (M^+ , <1%), 223 (100), 175 (45), 117 (22), 91 (80), 57 (21); HRMS: $\text{M}^+ - \text{C}_4\text{H}_8$ found 223.1022, $\text{C}_{12}\text{H}_{17}\text{NOS}$ requires 223.1031. See the Supporting Information for X-ray structure details.

(*R,S,R*)-*N*-(*tert*-Butylsulfinyl)-2-(3-methoxyphenyl)azepane (4o): yellowish solid; mp 80-81 °C; R_f 0.73 (hexane/ethyl acetate: 7/3); $[\alpha]_D^{20} +209.0$ (c 0.6, CH_2Cl_2 , 98:2 dr); IR (neat) 3030, 1579, 1278, 1063 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.03 (9H, s), 1.17-1.34, 1.57-1.95, 2.19-2.31 (1H, 6H and 1H, respectively, 3 m), 3.34-3.49 (1H, m), 3.56 (1H, d, $J = 15.3$ Hz), 3.80 (3H, s), 4.66 (1H, dd, $J = 10.9, 5.7$ Hz), 6.74 (1H, dd, $J = 8.2, 2.3$ Hz) 6.78-6.88 (2H, m), 7.23 (1H, t, $J = 7.9$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 23.1, 25.2, 29.7, 30.0, 38.8, 48.1, 55.1, 56.5, 57.8, 111.3, 112.3, 118.7, 129.5, 147.1, 159.6; m/z (DIP) 309 (M^+ , <1%), 253 (100), 205 (39), 57 (43); HRMS: $\text{M}^+ - \text{C}_4\text{H}_8$ found 253.1132, $\text{C}_{13}\text{H}_{19}\text{NO}_2\text{S}$ requires 253.1136.

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Supporting Information. HPLC traces for the determination of the enantiomeric excesses of pyrrolidines **7e** and *ent*-**7e**; copies of ^1H NMR and ^{13}C NMR spectra for haloketones **1e**, **1f**, **1i**, **1j**, **1l**, **1n**, **1n'** and **1o'**, haloimines **2**, saturated *N*-protected heterocycles **4** and free pyrrolidine **7e**; crystallographic information for compounds **4g** and **4n**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(15) Some modifications of the one-pot ATH-cyclization sequence, such as prolonging the reaction time or increasing either the amount of *tert*-BuOK or the reaction temperature, led to the formation of only traces of the cyclized product according to the ¹H NMR spectrum of the crude mixture.

(16) The comparison of the structures of piperidines **4k-4l** with **4m** in Scheme 5 may induce to think that the sense of the asymmetric induction of the reduction step that led to the formation of the latter has changed. However, it should be pointed out that the ATH of imine **2m** followed the general reduction model established by us (see reference 11d), leading to the expected (*R*) configuration in the asymmetric carbon atom of chlorosulfinamide **3m**. The apparently different structure of piperidine **4m** is due to the fact that the chlorine atom that acts as a leaving group in the cyclization step is located on a different substituent of the iminic carbon (it is located on the substituent that is *trans* to the sulfinyl group in **2m**, whereas the substituent that bears the chlorine atom in imines **2k** and **2l** is *cis* to the sulfinyl group). Therefore, the cyclization step takes place in a different direction in the case of the synthesis of **4m**.

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