Synthesis of γ-, δ-, and ε-Lactams by Asymmetric Transfer Hydrogenation of *N*-(*tert*-Butylsulfinyl)iminoesters§

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§Dedicated to Professor Elias J. Corey on occasion of his 85th birthday

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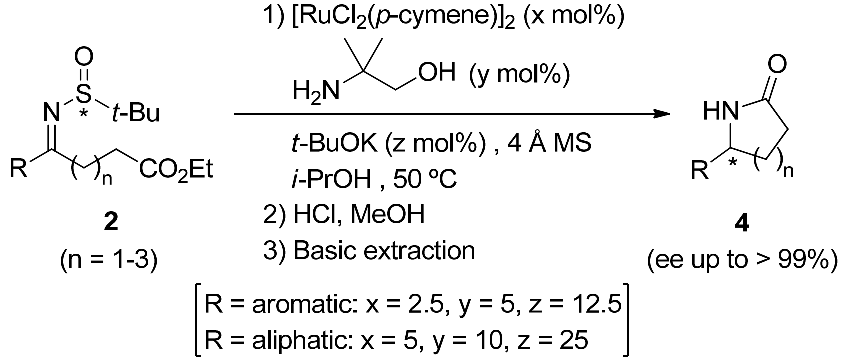


Abstract: Highly enantiomerically enriched γ- and δ-lactams have been prepared by a simple and very efficient procedure that involves the asymmetric transfer hydrogenation of *N*-(*tert*-butylsulfinyl)iminoesters followed by desulfinylation of the nitrogen atom and spontaneous cyclization to the desired lactams during the basic work-up procedure. Five- and six-membered ring lactams bearing aromatic, heteroaromatic and aliphatic substituents have been obtained in very high yields and ee's up to > 99%. A slight modification of the procedure also allowed the preparation of ε-lactams in good yields and very high enantioselectivities. Both enantiomers of the final lactams could be prepared with equal efficiency by changing the absolute configuration of the sulfinyl chiral auxiliary.

Keywords: lactams; asymmetric transfer hydrogenation; ATH; iminoester; *N*-sulfinylimines; ruthenium catalyst; isopropyl alcohol.

Introduction

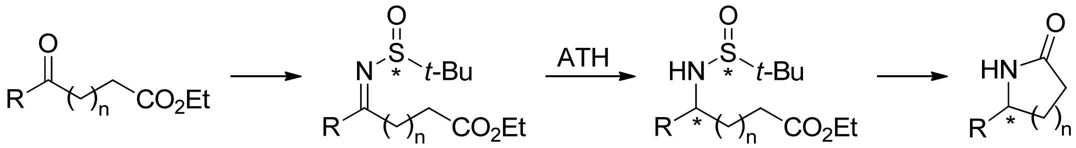
Chiral lactams occupy a remarkable position among the nitrogen heterocycles because they have shown to possess important biological activities and have found interesting applications in medicinal chemistry and pharmacology.[1] Lactams display antitumor activities,[2] operate as inhibitors of a variety of biochemical processes,[3] and act as high performance antibiotics.[4] Enantiomerically pure lactams have also been used as chiral ligands in asymmetric synthesis.[5] For all of these reasons, the synthesis of optically enriched lactams has aroused the interest of several research groups.[6] One of the most direct methods for the asymmetric synthesis of lactams is the cyclization of aminoesters, which can be prepared from the corresponding iminoesters through addition of nucleophiles to the imino group[7] or selective reduction of the C=N bond.[8] Among the iminoesters, the ones bearing a *tert*-butylsulfinyl group bonded to the nitrogen atom are very interesting starting materials for the asymmetric synthesis of enantiomerically enriched aminoesters. The *tert*-butylsulfinyl group has proved to be an excellent chiral auxiliary, showing high levels of asymmetric induction in a variety of processes.[9] Moreover, it presents the advantage to be easily removable under mild acidic conditions.[10] However, only a few examples of the use of *N*-(*tert*-butylsulfinyl)iminoesters as substrates for the asymmetric synthesis of chiral lactams can be found in the literature.[7,8b,d]

In the last years, our research group has been studying the use of enantiomerically pure *N*-(*tert*-butylsulfinyl)imines as substrates for diastereoselective transformations. Thus, we have performed their diastereoselective alkylation with organozinc reagents,[11] allylation using indium metal[12] and reaction with functionalized nucleophiles.[13] In addition, we have recently developed the synthesis of highly optically enriched amines by asymmetric transfer hydrogenation (ATH) of *N*-(*tert*-butylsulfinyl)ketimines.[14,15] Employing a ruthenium catalyst bearing the achiral 2-amino-2-methylpropan-1-ol as a ligand and isopropyl alcohol as the hydrogen source, we have been able to prepare a variety of aromatic and aliphatic chiral primary amines with very high enantiomeric purities and we have also studied the reaction mechanism.[14c,d] Herein we describe the use of the ATH of *N*-(*tert*-butylsulfinyl)iminoesters as a key step to achieve the synthesis of different highly enantiomerically enriched γ-, δ- and ε-lactams.

Results and Discussion

The ATH is a reduction methodology which is very useful from a synthetic point of view because it allows the selective reduction of ketones or imines in the presence of ester moieties.[16] We aimed to find an effective method for the asymmetric synthesis of lactams **4** (Scheme 1) and, according to our experience in the ATH of sulfinylimines, we thought that we could take advantage of the chemoselectivity indicated above and try to perform the selective reduction of the C=N bond of *N*-(*tert*-butylsulfinyl)iminoesters **2** by using our ATH protocol, to obtain the protected aminoesters **3**, which could be converted to the desired lactams by deprotection of the nitrogen atom and subsequent cyclization by intramolecular nucleophilic substitution on the ester moiety.

Scheme 1. Synthetic Plan for the Preparation of Chiral Lactams 4



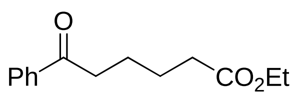
1 2 3 4

The starting point of our proposed synthetic route are ketoesters **1** (Scheme 1). Therefore, our first goal was the preparation of those starting materials. Chart 1 shows all the ketoesters that we have used. Some of them (**1a**, **1b**, **1e** and **1g**) were commercially available. Compounds **1d**, **1f** and **1h-1k** were easily prepared in 85-93% overall yields by iron-catalyzed addition of the corresponding Grignard reagents to succinic or glutaric anhydride (Scheme 2; n = 1 or 2, respectively),[17] followed by standard esterification of the crude ketoacids. Compounds **1c** and **1l** were prepared in 97 and 98% yield, respectively, from the corresponding commercially available ketoacids as indicated in Scheme 2.

Chart 1

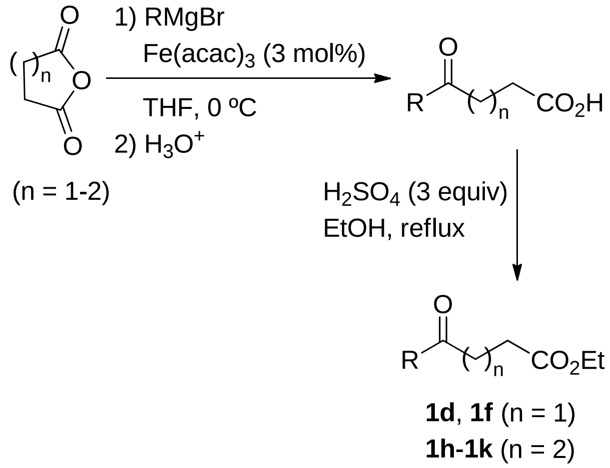
1a: R = Ph
1b: R = 4-MeOC_6H_4
1c: R = 4-ClC_6H_4
1d: R = *c*-C_5H_9
1e: R = *c*-C_6H_{11}
1f: R = *i*-Pr

1g: R = Ph
1h: R = 4-MeOC_6H_4
1i: R = 2-naphthyl
1j: R = 2-thienyl
1k: R = *i*-Pr



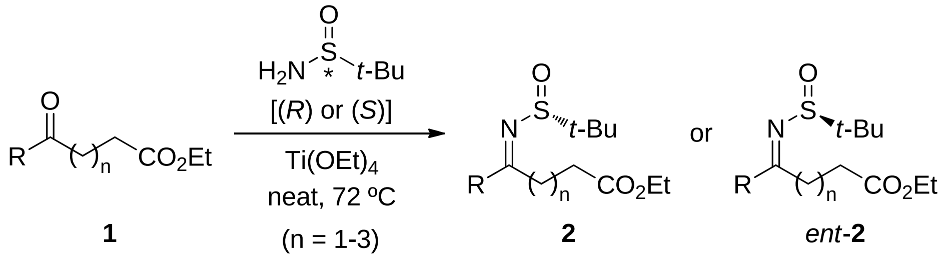
1l

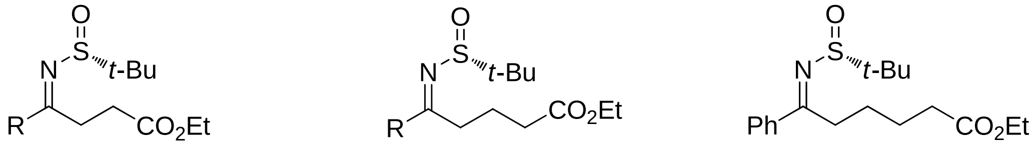
Scheme 2. Synthesis of Ketoesters 1d, 1f and 1h-1k



Next, the required iminoesters were prepared by reaction of ketoesters **1** with either (*R*)- or (*S*)-2-methylpropane-2-sulfinamide in the presence of titanium tetraethoxide under neat conditions (Scheme 3), according to a procedure recently reported by us.[18] Thus, the expected enantiomerically pure *N*-(*tert*-butylsulfinyl)iminoesters with (*R*) (compounds **2**) or (*S*) (compounds *ent*-**2**) absolute configuration were isolated in good yields after column chromatography.

Scheme 3. Preparation of the Iminoesters 2 and *ent*-2[a]





2a: R = Ph (84%) [*ent*-**2a** (80%)]
2b: R = 4-MeOC$_6$H$_4$ (74%) [*ent*-**2b** (77%)]
2c: R = 4-ClC$_6$H$_4$ (63%) [*ent*-**2c** (60%)]
2d: R = *c*-C$_5$H$_9$ (68%) [*ent*-**2d** (70%)]
2e: R = *c*-C$_6$H$_{11}$ (61%) [*ent*-**2e** (59%)]
2f: R = *i*-Pr (75%) [*ent*-**2f** (75%)]

2g: R = Ph (81%) [*ent*-**2g** (82%)]
2h: R = 4-MeOC$_6$H$_4$ (79%) [*ent*-**2h** (80%)]
2i: R = 2-naphthyl (85%) [*ent*-**2i** (84%)]
2j: R = 2-thienyl (61%) [*ent*-**2j** (59%)]
2k: R = *i*-Pr (58%) [*ent*-**2k** (65%)]

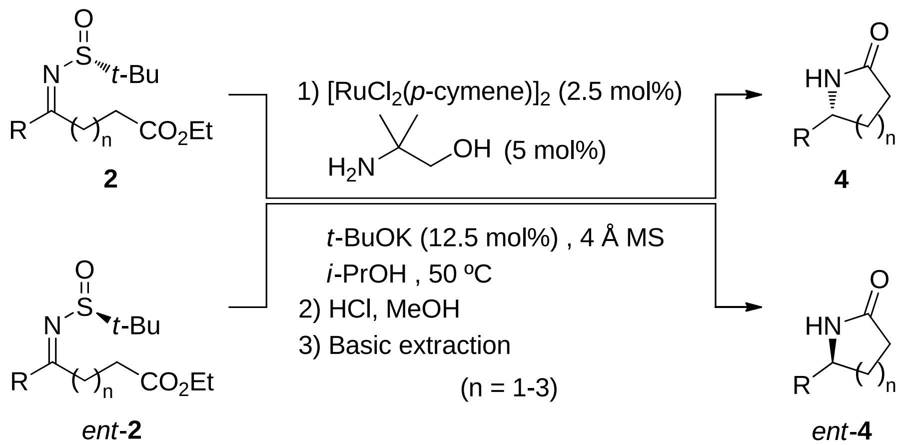
2l (72%) [*ent*-**2l** (70%)]

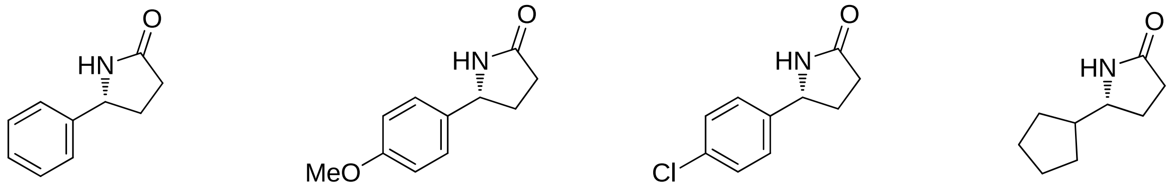
[a] In brackets, isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting ketoester **1**. All isolated compounds **2** and *ent*-**2** were ≥ 95% pure (300 MHz ^{1}H NMR).

Once we had prepared the desired sulfinyl iminoesters, we tried to reduce them using our ATH protocol. Iminoester **2a** was chosen as a model substrate and our optimized conditions for the reduction of *N*-(*tert*-butylsulfinyl)ketimines[14c,d] were tried for its reduction. Gratifyingly, the hydrogen transfer to compound **2a** from isopropyl alcohol catalyzed by a ruthenium complex bearing the achiral ligand 2-amino-2-methylpropan-1-ol led to a selective reduction of the imine functionality in a short reaction time (2 h). No evidence for a possible reduction of the ester moiety could be observed in the ^{1}H NMR spectrum of the reaction mixture. The crude protected aminoester was treated with a solution of HCl in MeOH in order to remove the sulfinyl group from the nitrogen atom. After performing a basic extraction process, lactam **4a** was obtained as the only reaction product in 93% yield (Scheme 4). Thus, the initially formed deprotected aminoester spontaneously cyclizes during the basic work-up procedure through an intramolecular nucleophilic substitution reaction on the ester functionality by the free amino group.[19] Therefore, a separate cyclization step was not needed. Noteworthy, the obtained lactam **4a** was pure according to the ^{1}H NMR spectrum, making any purification process unnecessary. Analysis of **4a** by HPLC gave a 96% ee, the (*R*) enantiomer being the major one.

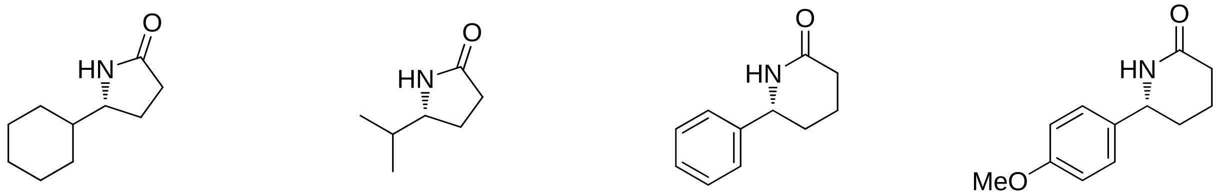
Next, we studied the reaction scope by applying the same protocol to the other γ-iminoesters **2b-2f**. The corresponding lactams **4b-4f** were also obtained in very high yields and enantioselectivities (Scheme 4). The procedure worked with equal efficiency for the synthesis of γ-lactams bearing R groups which could be aromatic [substituted with either electron-releasing (**4b**) or electron-withdrawing groups (**4c**)] or aliphatic (**4d-4f**). When our ATH procedure was applied to the reduction of the aliphatic iminoesters **2d-2f**, the catalyst loading had to be increased, as previously described by us.[14c,d,20]

Scheme 4. Asymmetric Transfer Hydrogenation of *N*-(*tert*-butylsulfinyl)iminoesters 2 and *ent*-2. Preparation of Lactams 4 and *ent*-4[a]

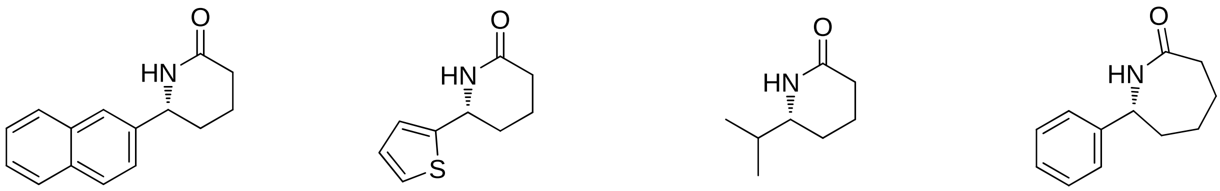




4a (93%, 96% ee) [*ent*-**4a** (93%, 95% ee)]; **4b** (92%, >99% ee) [*ent*-**4b** (92%, >99% ee)]; **4c** (94%, 97% ee) [*ent*-**4c** (91%, 96% ee)]; **4d** (90%, 90% ee)[b] [*ent*-**4d** (91%, 90% ee)[b]]



4e (89%, 95% ee)[b] [*ent*-**4e** (88%, 94% ee)[b]]; **4f** (89%, 95% ee)[b] [*ent*-**4f** (90%, 94% ee)[b]]; **4g** (96%, 99% ee) [*ent*-**4g** (97%, 99% ee)]; **4h** (90%, 98% ee) [*ent*-**4h** (91%, 98% ee)]



4i (94%, 98% ee) [*ent*-**4i** (93%, 97% ee)]; **4j** (92%, 98% ee) [*ent*-**4j** (90%, 98% ee)]; **4k** (95%, >99% ee)[b] [*ent*-**4k** (92%, >99% ee)[b]]; **4l** (70%, 98% ee)[c] [*ent*-**4l** (72%, 98% ee)[c]]

[a] In brackets, isolated yield (based on the starting iminoester **2** or *ent*-**2**) and enantiomeric excess (determined by HPLC using a chiral column). All isolated compounds **4** and *ent*-**4** were ≥ 95% pure (300 MHz ^{1}H NMR).

[b] $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), 2-amino-2-methylpropan-1-ol (10 mol%) and *t*-BuOK (25 mol%) were used in this reaction.

[c] The ATH reaction crude was successively treated with 2 M HCl in MeOH/Et_2O and then with MeONa to afford the lactam. Isolated yields of lactams **4l** and *ent*-**4l** are given after column chromatography (silica gel, hexane/ethyl acetate).

Encouraged by the good results obtained, we tried to extend our methodology to the preparation of δ- and ε-lactams from the corresponding *N*-(*tert*-butylsulfinyl)iminoesters **2g-2l** (Scheme 3). We were delighted to see that δ-lactams bearing several aromatic (**4g-4i**) and heteroaromatic (**4j**) substituents were also obtained in pure form in excellent yields and enantiomeric excesses (Scheme 4). Noteworthy, a highly optically enriched (ee > 99%) aliphatic *δ*-lactam **4k** could also be prepared in 95% yield.[20] However, when the synthesis of the 7-membered ring lactam **4l** (Scheme 4) from iminoester **2l** was attempted using the same procedure, the corresponding free aminoester was isolated after the final basic extraction process instead of the expected lactam. Fortunately, the desired ε-lactam **4l** could be prepared in good yield and excellent enantiomeric excess by a slight modification of the experimental procedure: when the desulfinylation of the ATH product was complete, a freshly prepared solution of MeONa in MeOH was added and the mixture was stirred overnight. Thus, this modified procedure allowed us to extend the substrate scope to ε-iminoesters.

Our methodology is equally efficient for the synthesis of both enantiomers of the final lactams. As expected, when imino esters *ent*-**2**, bearing the (*S*)-*N*-(*tert*-butylsulfinyl) chiral auxiliary, were used as substrates, the (*S*)-lactams *ent*-**4** were obtained with yields and enantiomeric excesses which are almost identical to the ones observed in the corresponding (*R*)-lactams **4** (compare the corresponding enantiomeric products in Scheme 4).

Conclusion

We have presented here a simple, versatile and very effective procedure for the synthesis of highly optically enriched γ-, δ- and ε-lactams by application of our ATH protocol to the highly diastereoselective reduction of *N*-(*tert*-butylsulfinyl)iminoesters. The fact that chiral lactams bearing aromatic, heteroaromatic or aliphatic substituents can be prepared in similar and very high yields and enantiomeric excesses is a remarkable feature of our methodology. The absolute configuration of the final lactam can be tuned up simply by choosing the proper configuration on the sulfur atom of the sulfinyl moiety of the iminoester. To the best of our knowledge, the preparation of chiral lactams through metal-catalyzed ATH processes had not been described so far.

Experimental Section

General Information

All glassware was dried in an oven at 100 ºC and cooled to room temperature under argon before use. All reactions were carried out under an argon atmosphere. Ketoesters **1a**, **1b**, **1e** and **1g**, (*R*)- and (*S*)-*t*-BuSONH$_2$, Ti(OEt)$_4$ (33% TiO$_2$ min), [RuCl$_2$(*p*-cymene)]$_2$, 2-amino-2-methylpropan-1-ol and all the starting materials needed for the synthesis of ketoesters **1c**, **1d**, **1f**, and **1h-1l** were commercially available and were used as received. *t*-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 ºC 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 UV$_{254}$ 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 CDCl$_3$ as solvent. The internal references used for NMR spectra were tetramethylsilane (TMS) for ^{1}H NMR and CDCl$_3$ for ^{13}C NMR; chemical shifts are given in δ (ppm) and coupling constants (*J*) in Hz. ^{13}C 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 ºC.

Synthesis of Ketoesters 1c, 1d, 1f, and 1h-1l. General Procedure

A round-bottomed flask was charged with succinic anhydride (for compounds **1d** and **1f**) or glutaric anhydride (for compounds **1h-1k**) (10.0 mmol), Fe(acac)$_3$ (106 mg, 0.3 mmol) and anhydrous THF (12 mL) and it was cooled down to 0 ºC. A solution of the corresponding Grignard reagent[21] (8.3 mmol) was added over a period of 45 minutes with the aid of a syringe pump and the reaction was stirred overnight at the same temperature. Then, the mixture was acidified with a 2 M aqueous HCl solution (40 mL) and extracted with Et_2O (3 × 20 mL). The combined organic phases were extracted with a 1 M aqueous NaOH solution (3 × 15 mL), discarding the organic layer. The combined aqueous basic phases were acidified with a 2 M aqueous HCl solution in order to obtain a pH around 1, and this mixture was extracted with Et_2O (3 × 20 mL). The combined organic phases were dried (Na_2SO_4). After filtration and evaporation of the solvent, the expected ketoacids were obtained, which were used in the next step without purification.

The obtained ketoacid (7.0 mmol) was dissolved in EtOH (40 mL), concentrated H_2SO_4 (1.1 mL, 21.0 mmol) was added at room temperature and then, the reaction mixture was refluxed overnight. After evaporation of the solvent, H_2O (10 mL) was added and the mixture was neutralized with a 2 M aqueous NaOH solution and extracted with Et_2O (3 × 15 mL). The combined organic phases were dried (Na_2SO_4). After filtration and evaporation of the solvent, the expected ketoesters **1d** (1.249 g, 90%), **1f** (1.121 g, 93%), **1h** (1.559 g, 89%), **1i** (1.665 g, 88%), **1j** (1.457 g, 92%) and **1k** (1.108 g, 85%) were obtained in pure form. The same esterification procedure was also used for the preparation of ketoesters **1c** (1.634 g, 97%) and **1l** (1.607 g, 98%) from the corresponding commercially available ketoacids. Ketoesters **1c**,[22] **1f**,[23] **1h**,[24] **1j**,[25] **1k**[26] and **1l**[27] were identified by comparison of their physical and spectroscopic data with the ones reported in the literature. The corresponding physical and spectroscopic data for compounds **1d** and **1i** follow.

Ethyl 4-(cyclopentyl)-4-oxobutanoate (1d): yellowish oil; R_f 0.76 (hexane/ethyl acetate: 3/1); IR (neat) 1733, 1710, 1174 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (3H, t, J = 7.1 Hz), 1.53-1.70, 1.73-1.88 (4H each, 2 m), 2.58 (2H, t, J = 6.6 Hz), 2.77 (2H, t, J = 6.6 Hz), 2.91 (1H, quintet, J = 7.8 Hz), 4.13 (2H, q, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 25.9, 28.0, 28.8, 36.1, 51.2, 60.5, 172.9, 211.1; *m/z* 198 (M^+, 4%), 153 (27), 129 (50), 111 (18), 101 (77), 69 (100); HRMS: M^+ found 198.1259, $C_{11}H_{18}O_3$ requires 198.1256.

Ethyl 5-(2-naphthyl)-5-oxopentanoate (1i): yellow solid; mp 63 ºC; R_f 0.57 (hexane/ethyl acetate: 3/1); IR (KBr) 3056, 1731, 1688, 1185 cm^{-1}; ^{1}H-RMN (400 MHz, $CDCl_3$) δ 1.24 (3H, t, J = 7.1 Hz), 2.09-2.17 (2H, quintet, J = 7.2 Hz), 2.47 (2H, t, J = 7.2 Hz), 3.19 (2H, t, J = 7.2 Hz), 4.14 (2H, q, J = 7.1 Hz), 7.47-7.61 (2H, m), 7.88 (2H, t, J = 7.8 Hz), 7.96 (1H, d, J = 7.8 Hz), 8.03 (1H, dd, J = 8.6, 1.7 Hz), 8.48 (1H, s); ^{13}C-RMN (100 MHz, $CDCl_3$) δ 14.2, 19.5, 33.3, 37.5, 60.3, 123.7, 126.7, 127.7, 128.4, 129.5, 129.6, 132.4, 134.1, 135.5, 172.9, 199.3; *m/z* 270 (M^+, 18%), 225 (12), 156 (12), 155 (100), 127 (41); HRMS: M^+ found 270.1260, $C_{17}H_{18}O_3$ requires 270.1256.

Synthesis of Iminoesters 2 and *ent*-2. General Procedure

N-(*tert*-Butylsulfinyl)iminoesters **2** and *ent*-**2** were prepared by reaction of (*R*)-2-methylpropane-2-sulfinamide (for **2**) or (*S*)-2-methylpropane-2-sulfinamide (for *ent*-**2**) with the corresponding ketoester according to our recently reported procedure,[18] as follows: the mixture of ketoester **1** (5.0 mmol), (*R*)- or (*S*)-*t*-BuSONH$_2$ (612 mg, 5.0 mmol) and Ti(OEt)$_4$ (2.1 mL, 10.0 mmol) was stirred overnight under argon at 72 ºC (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 products **2** and *ent*-**2** in the yields indicated in Scheme 3. The corresponding physical, spectroscopic and analytical data for the obtained iminoesters follow.

Ethyl 4-[(*R*)-*tert*-butylsulfinylimino]-4-phenylbutanoate (2a): yellow oil; R_f 0.35 (hexane/ethyl acetate: 7/3); $[\alpha]_D^{20}$ −6.0 (*c* 2.4, CH_2Cl_2); IR (neat) 3062, 1732, 1604, 1595, 1181, 1074 cm^{-1}; ^{1}H NMR

(300 MHz, $CDCl_3$) δ 1.24 (3H, t, J = 7.0 Hz), 1.33 (9H, s), 2.50-2.94 (2H, m), 3.01-3.72 (2H, m), 4.12 (2H, q, J = 7.0 Hz), 7.37-7.54 (3H, m), 7.75-7.90 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 22.7, 27.6, 32.9, 57.8, 60.8, 127.4, 128.7, 131.7, 137.2, 171.8, 177.7; *m/z* (DIP) 309 (M^+, <1%), 253 (37), 207 (51), 206 (12), 205 (95), 162 (19), 160 (18), 159 (14), 132 (100), 57 (23); HRMS: M^+ found 309.1393, $C_{16}H_{23}NO_3S$ requires 309.1399.

Ethyl 4-[(*S*)-*tert*-butylsulfinylimino]-4-phenylbutanoate (*ent*-2a): its physical and spectroscopic data are identical to the ones of iminoester **2a**, except for the optical rotation: $[\alpha]_D^{20}$ +6.1 (*c* 1.5, CH_2Cl_2).

Ethyl 4-[(*R*)-*tert*-butylsulfinylimino]-4-(4-methoxyphenyl)butanoate (2b): yellow oil; R_f 0.47 (hexane/ethyl acetate: 1/1); $[\alpha]_D^{20}$ +32.0 (*c* 1.6, CH_2Cl_2); IR (neat) 3055, 1730, 1587, 1254, 1174, 1076 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (3H, t, J = 7.1 Hz), 1.31 (9H, s), 2.53-2.84 (2H, m), 3.34-3.61 (2H, m), 3.86 (3H, s), 4.13 (2H, q, J = 7.1 Hz), 6.93 (2H, d, J = 9.0 Hz), 7.70-8.01 (2H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.5, 27.6, 33.1, 55.4, 57.4, 60.8, 113.9, 129.4, 129.7, 162.5, 172.0, 177.1; *m/z* (DIP) 339 (M^+, <1%), 283 (41), 237 (28), 235 (55), 190 (17), 189 (30), 163 (23), 162 (100), 147 (18), 134 (39), 133 (21), 57 (31); HRMS: M^+ - C_4H_8 found 283.0888, $C_{13}H_{17}NO_4S$ requires 283.0878.

Ethyl 4-[(*S*)-*tert*-butylsulfinylimino]-4-(4-methoxyphenyl)butanoate (*ent*-2b): its physical and spectroscopic data are identical to the ones of iminoester **2b**, except for the optical rotation: $[\alpha]_D^{20}$ −32.5 (*c* 1.4, CH_2Cl_2).

Ethyl 4-[(*R*)-*tert*-butylsulfinylimino]-4-(4-chlorophenyl)butanoate (2c): greenish oil; R_f 0.26 (hexane/ethyl acetate: 3/1); $[\alpha]_D^{20}$ +29.5 (*c* 1.1, CH_2Cl_2); IR (neat) 3064, 1732, 1601, 1585, 1179, 1090 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (3H, t, J = 7.1 Hz), 1.32 (9H, s), 2.50-2.84 (2H, m), 3.15-3.74

(2H, m), 4.13 (2H, q, J = 7.1 Hz), 7.40 (2H, d, J = 8.4 Hz), 7.63-7.90 (2H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.6, 27.4, 32.7, 57.9, 60.8, 128.6, 128.8, 135.6, 137.9, 171.6, 176.3; *m/z* (DIP) 343 (M^+, <1%), 289 (13), 287 (36), 243 (22), 241 (87), 239 (95), 168 (33), 166 (100), 137 (18), 57 (48); HRMS: M^+ found 343.1018, $C_{16}H_{22}ClNO_3S$ requires 343.1009.

Ethyl 4-[(*S*)-*tert*-butylsulfinylimino]-4-(4-chlorophenyl)butanoate (*ent*-2c): its physical and spectroscopic data are identical to the ones of iminoester **2c**, except for the optical rotation: $[\alpha]_D^{20}$ −29.0 (c 1.0, CH_2Cl_2).

Ethyl 4-[(*R*)-*tert*-butylsulfinylimino]-4-cyclopentylbutanoate (2d): an inseparable mixture of geometric isomers in ca. 3:1 ratio was obtained. The following characterization data are reported for the mixture of isomers with the relative integration for each signal: pale yellow oil; R_f 0.34 (hexane/ethyl acetate: 3/1); $[\alpha]_D^{20}$ −63.0 (c 1.0, CH_2Cl_2); IR (neat) 1733, 1614, 1176, 1070 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16-1.29 (12.2H, m), 1.56-1.98 (8.2H, m), 2.50-3.05 (4.4H, m), 3.60-3.81 (0.6H, m), 4.01-4.23 (2.0H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 21.8, 22.0, 22.3, 25.5, 25.86, 25.91, 29.4, 30.3, 30.6, 30.7, 31.1, 31.5, 31.9, 45.9, 50.3, 55.9, 56.8, 60.4, 60.3, 171.9, 172.9, 188.7, 189.9; *m/z* (DIP) 301 (M^+, <1%), 273 (30), 227 (42), 225 (100), 179 (21), 151 (26), 138 (84), 109 (21), 57 (32); HRMS: M^+ - C_4H_8 found 245.1086, $C_{11}H_{19}NO_3S$ requires 245.1086.

Ethyl 4-[(*S*)-*tert*-butylsulfinylimino]-4-cyclopentylbutanoate (*ent*-2d): its physical and spectroscopic data are identical to the ones of iminoester **2d**, except for the optical rotation: $[\alpha]_D^{20}$ +62.0 (c 0.9, CH_2Cl_2).

Ethyl 4-[(*R*)-*tert*-butylsulfinylimino]-4-cyclohexylbutanoate (2e): an inseparable mixture of geometric isomers in ca. 3:1 ratio was obtained. The following characterization data are reported for the mixture of isomers with the relative integration for each signal: pale yellow oil; R_f 0.26 (hexane/ethyl acetate: 3/1); $[\alpha]_D^{20}$ −65.0 (*c* 0.9, CH_2Cl_2); IR (neat) 1732, 1616, 1180, 1069 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93-1.54 (17.1H, m), 1.64-1.92 (5.1H, m), 2.21-2.30 (0.2H, m), 2.45-3.07 (3.7H, m), 3.25-3.50 (0.6H, m), 4.04-4.20 (2.0H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.0, 22.4, 25.6, 25.8, 29.3, 29.7, 30.2, 30.5, 30.7, 32.1, 45.5, 49.6, 56.0, 56.9, 60.4, 60.8, 172.0, 172.9, 188.7, 190.7; *m/z* (DIP) 315 (M^+, <1%), 287 (12), 259 (43), 239 (100), 193 (17), 152 (61), 57 (53); HRMS: M^+ - C_4H_8 found 259.1254, $C_{12}H_{21}NO_3S$ requires 259.1242.

Ethyl 4-[(*S*)-*tert*-butylsulfinylimino]-4-cyclohexylbutanoate (*ent*-2e): its physical and spectroscopic data are identical to the ones of iminoester **2e**, except for the optical rotation: $[\alpha]_D^{20}$ +66.0 (*c* 1.1, CH_2Cl_2).

Ethyl 4-[(*R*)-*tert*-butylsulfinylimino]-5-methylhexanoate (2f): pale yellow oil; R_f 0.38 (hexane/ethyl acetate: 7/3); $[\alpha]_D^{20}$ −123.5 (*c* 1.9, CH_2Cl_2); IR (neat) 1733, 1618, 1173, 1072 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (6H, d, J = 6.9 Hz), 1.21 (9H, s), 1.25 (3H, t, J = 7.1 Hz), 2.51-3.05 (4H, m), 3.60-3.84 (1H, m), 4.11 (2H, t, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 19.5, 20.3, 22.0, 29.1, 29.2, 34.6, 56.0, 60.4, 172.8, 191.1; *m/z* (DIP) 275 (M^+, <1%), 219 (14), 172 (11), 171 (100), 125 (27), 98 (38), 57 (34); HRMS: M^+ - C_4H_8 found 219.0917, $C_9H_{17}NO_3S$ requires 219.0929.

Ethyl 4-[(*S*)-*tert*-butylsulfinylimino]-5-methylhexanoate (*ent*-2f): its physical and spectroscopic data are identical to the ones of iminoester **2f**, except for the optical rotation: $[\alpha]_D^{20}$ +124.0 (*c* 1.0, CH_2Cl_2).

Ethyl 5-[(*R*)-*tert*-butylsulfinylimino]-5-phenylpentanoate (2g): yellow oil; R_f 0.35 (hexane/ethyl acetate: 3/1); $[\alpha]_D^{20}$ −10.5 (*c* 1.1, CH_2Cl_2); IR (neat) 3050, 1729, 1591, 1181, 1068 cm^{-1}; ^1H NMR (300

MHz, $CDCl_3$) δ 1.26 (3H, t, J = 7.1 Hz), 1.33 (9H, s), 1.95-2.08 (2H, m), 2.46 (2H, t, J = 7.1 Hz), 3.11-3.44 (2H, m), 4.14 (2H, q, J = 7.1 Hz), 7.39-7.52 (3H, m), 7.92 (2H, d, J = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 22.7, 23.8, 31.6, 33.7, 57.7, 60.4, 127.5, 128.6, 131.6, 137.6, 173.0, 178.8; *m/z* (DIP) 323 (M^+, <1%), 267 (15), 221 (21), 220 (14), 219 (94), 145 (18), 144 (19), 132 (100), 104 (19), 103 (21), 77 (15), 57 (35); HRMS: M^+ - C_4H_8 found 267.0936, $C_{13}H_{17}NO_3S$ requires 267.0929.

Ethyl 5-[(*S*)-*tert*-butylsulfinylimino]-5-phenylpentanoate (*ent*-2g): its physical and spectroscopic data are identical to the ones of iminoester **2g**, except for the optical rotation: $[\alpha]_D^{20}$ +10.5 (*c* 1.0, CH_2Cl_2).

Ethyl 5-[(*R*)-*tert*-butylsulfinylimino]-5-(4-methoxyphenyl)pentanoate (2h): yellow oil; R_f 0.26 (hexane/ethyl acetate: 3/1); $[\alpha]_D^{20}$ +19.0 (*c* 1.1, CH_2Cl_2); IR (neat) 3068, 1729, 1606, 1586, 1254, 1174, 1067 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (3H, t, J = 7.1 Hz), 1.32 (9H, s), 1.95-2.04 (2H, m), 2.46 (2H, t, J = 7.1 Hz), 3.03-3.40 (2H, m), 3.86 (3H, s), 4.15 (2H, q, J = 7.1 Hz), 6.93 (2H, d, J = 9.0 Hz), 7.93 (2H, br d, apparent J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 22.6, 24.0, 31.6, 33.7, 55.4, 57.3, 60.4, 113.8, 129.5, 130.1, 162.5, 173.1, 178.3; *m/z* (DIP) 353 (M^+, <1%), 297 (29), 249 (61), 175 (30), 163 (20), 162 (100), 161 (20), 149 (18), 135 (34), 134 (21), 133 (18), 57 (20); HRMS: M^+ - C_4H_8 found 297.1040, $C_{14}H_{19}NO_4S$ requires 297.1035.

Ethyl 5-[(*S*)-*tert*-butylsulfinylimino]-5-(4-methoxyphenyl)pentanoate (*ent*-2h): its physical and spectroscopic data are identical to the ones of iminoester **2h**, except for the optical rotation: $[\alpha]_D^{20}$ −19.0 (*c* 1.1, CH_2Cl_2).

Ethyl 5-[(*R*)-*tert*-butylsulfinylimino]-5-(2-naphthyl)pentanoate (2i): yellow oil; R_f 0.32 (hexane/ethyl acetate: 4/1); $[\alpha]_D^{20}$ +9.0 (*c* 3.0, CH_2Cl_2); IR (neat) 3058, 1729, 1610, 1588, 1186, 1068 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 1.26 (3H, t, *J* = 7.1 Hz), 1.37 (9H, s), 2.04-2.14 (2H, m), 2.50 (2H, t, *J* = 7.1 Hz), 3.14-3.39, 3.40-3.60 (1H each, 2 m), 4.16 (2H, q, *J* = 7.1 Hz), 7.51-7.58 (2H, m), 7.85 (2H, d, *J* = 8.6 Hz), 7.95 (1H, d, *J* = 7.3 Hz), 8.05 (1H, d, *J* = 7.9 Hz), 8.41 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 14.2, 22.7, 24.1, 31.6, 33.7, 57.7, 60.4, 124.1, 126.6, 127.4, 127.8, 128.2, 128.4, 129.3, 132.7, 134.76, 134.83, 172.9, 178.6; *m/z* (DIP) 373 (M^+, <1%), 317 (26), 269 (100), 195 (16), 182 (22), 142 (14), 127 (29), 57 (43); HRMS: M^+ - C_4H_8 found 317.1082, $C_{17}H_{19}NO_3S$ requires 317.1086.

Ethyl 5-[(*S*)-*tert*-butylsulfinylimino]-5-(2-naphthyl)pentanoate (*ent*-2i): its physical and spectroscopic data are identical to the ones of iminoester **2i**, except for the optical rotation: $[\alpha]_D^{20}$ −8.5 (*c* 2.0, CH_2Cl_2).

Ethyl 5-[(*R*)-*tert*-butylsulfinylimino]-5-(2-thienyl)pentanoate (2j): yellow oil; R_f 0.38 (hexane/ethyl acetate: 3/1); $[\alpha]_D^{20}$ +99.0 (*c* 1.0, CH_2Cl_2); IR (neat) 3075, 1729, 1572, 1182, 1071 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 1.27 (3H, t, *J* = 7.1 Hz), 1.31 (9H, s), 2.05-2.15 (2H, m), 2.47 (2H, t, *J* = 6.9 Hz), 3.07-3.18, 3.22-3.32 (1H each, 2 m), 4.16 (2H, q, *J* = 7.1 Hz), 7.10 (1H, dd, *J* = 5.0, 3.8 Hz), 7.49 (1H, dd, *J* = 5.0, 0.9 Hz), 7.67 (1H, dd, *J* = 3.8, 0.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 14.2, 22.5, 24.4, 32.4, 33.6, 57.8, 60.4, 128.1, 129.9, 132.1, 145.1, 173.0, 173.2; *m/z* (DIP) 329 (M^+, <1%), 273 (33), 211 (11), 198 (13), 197 (100), 156 (17), 124 (25), 57 (30); HRMS: M^+ - C_4H_8 found 273.0499, $C_{11}H_{15}NO_3S_2$ requires 273.0493.

Ethyl 5-[(*S*)-*tert*-butylsulfinylimino]-5-(2-thienyl)pentanoate (*ent*-2j): its physical and spectroscopic data are identical to the ones of iminoester **2j**, except for the optical rotation: $[\alpha]_D^{20}$ −100.0 (*c* 0.9, CH_2Cl_2).

Ethyl 5-[(*R*)-*tert*-butylsulfinylimino]-6-methylheptanoate (2k): pale yellow oil; R_f 0.44 (hexane/ethyl acetate: 3/2); $[\alpha]_D^{20}$ −143.0 (*c* 2.2, CH_2Cl_2); IR (neat) 1733, 1620, 1182, 1071 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.08-1.19 (6H, m), 1.24 (9H, s), 1.26 (3H, t, J = 7.1 Hz), 1.85-2.00 (2H, m), 2.25-2.53 (3H, m), 2.57-2.88 (2H, m), 4.14 (2H, q, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 20.1, 20.3, 22.3, 22.7, 33.9, 34.0, 39.1, 56.7, 60.3, 172.8, 190.8; *m/z* (DIP) 289 (M^+, <1%), 186 (12), 185 (100), 140 (15), 139 (42), 98 (68), 96 (21), 57 (54); HRMS: M^+ - C_4H_8SO found 185.1415, $C_{10}H_{19}NO_2$ requires 185.1416.

Ethyl 5-[(*S*)-*tert*-butylsulfinylimino]-6-methylheptanoate (*ent*-2k): its physical and spectroscopic data are identical to the ones of iminoester **2k**, except for the optical rotation: $[\alpha]_D^{20}$ +142.0 (*c* 2.0, CH_2Cl_2).

Ethyl 6-[(*R*)-*tert*-butylsulfinylimino]-6-phenylhexanoate (2l): yellow oil; R_f 0.32 (hexane/ethyl acetate: 3/1); $[\alpha]_D^{20}$ −22.0 (*c* 0.9, CH_2Cl_2); IR (neat) 3061, 1731, 1593, 1179, 1071 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (3H, t, J = 7.1 Hz), 1.33 (9H, s), 1.67-1.81 (4H, m), 2.34 (2H, t, J = 7.3 Hz), 3.07-3.39 (2H, m), 4.10 (2H, q, J = 7.1 Hz), 7.40-7.50 (3H, m), 7.84 (2H, d, J = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 22.7, 25.0, 28.1, 32.1, 33.8, 57.5, 60.3, 127.4, 128.6, 131.5, 137.7, 173.3, 179.4; *m/z* (DIP) 337 (M^+, <1%), 281 (15), 234 (18), 233 (100), 171 (32), 144 (22), 143 (54), 132 (92), 104 (25), 103 (21), 57 (41); HRMS: M^+ - C_4H_8 found 281.1093, $C_{14}H_{19}NO_3S$ requires 281.1086.

Ethyl 6-[(*S*)-*tert*-butylsulfinylimino]-6-phenylhexanoate (*ent*-2l): its physical and spectroscopic data are identical to the ones of iminoester **2l**, except for the optical rotation: $[\alpha]_D^{20}$ +22.5 (*c* 1.0, CH_2Cl_2).

Asymmetric Transfer Hydrogenation of Iminoesters 2 and *ent*-2. General Procedure

A mixture of $[RuCl_2(p\text{-cymene})]_2$ (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) was heated up to 90 ºC (oil bath temperature) for 20 min. During this heating period, the initially orange reaction mixture turned into a dark red color. The reaction was then cooled to 50 ºC and a solution of the iminoester **2** or *ent*-**2** (0.9 mmol) in *i*-PrOH (6.3 mL) and *t*-BuOK (1.13 mL of a 0.1 M solution in *i*-PrOH, 0.113 mmol) were successively added. After completion of the reaction (monitored by TLC), the reaction mixture was passed through a small column of silica gel, the column was washed with ethyl acetate and the combined organic phases were evaporated to give a residue that was directly submitted to the desulfinylation step.

For aliphatic iminoesters **2d-f**, **2k**, *ent*-**2d-f** and *ent*-**2k**, $[RuCl_2(p\text{-cymene})]_2$ (28 mg, 0.045 mmol), 2-amino-2-methylpropan-1-ol (8 mg, 0.090 mmol) and *t*-BuOK (2.25 mL of a 0.1 M solution in *i*-PrOH, 0.225 mmol) were used.

General Procedure for the Removal of the Sulfinyl Group. Isolation of Lactams 4a-4k and (*ent*-4a)-(*ent*-4k)

The crude mixture of the transfer hydrogenation reaction was dissolved in a 2 M solution of HCl in methanol (7 mL; prepared by dropwise addition of $SOCl_2$ to methanol at 0 ºC) 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 pH > 11. After ca. 10 minutes, 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, pure γ- and δ-lactams **4a**-**4k** and (*ent*-**4a**)-(*ent*-**4k**) were obtained in the yields indicated in Scheme 4. The ee values were determined by HPLC using a chiral column (see the Supporting Information for details). The following pairs of enantiomeric lactams **4a** and *ent*-**4a**,[8a] **4d** and *ent*-**4d**,[28]

4e and *ent*-**4e**,[29] **4f** and *ent*-**4f**,[30] **4g** and *ent*-**4g**,[8a] **4h** and *ent*-**4h**,[31] **4k** and *ent*-**4k**,[32] were identified by comparison of their physical and spectroscopic data with the ones reported in the literature for one of the enantiomers. The corresponding physical and spectroscopic data for lactams **4b**, *ent*-**4b**, **4c**, *ent*-**4c**, **4i**, *ent*-**4i**, **4j** and *ent*-**4j** follow.

(*R*)-5-(4-Methoxyphenyl)pyrrolidin-2-one (4b): white solid; mp 92-94 ºC; R_f 0.28 (hexane/ethyl acetate: 1/3); $[\alpha]_D^{20}$ +40.5 (*c* 0.7, CH_2Cl_2, >99% ee); IR (neat) 3222, 3036, 1712, 1656, 1507, 1238 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88-1.97, 2.47-2.56 (1H each, 2 m), 2.33-2.46 (2H, m), 3.79 (3H, s), 4.69 (1H, t, J = 7.1 Hz), 6.76 (1H, br s), 6.88, 7.21 (2H each, 2 d, J = 8.8 Hz each); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.4, 31.3, 55.2, 57.6, 114.1, 126.8, 134.4, 159.1, 178.5; *m/z* 191 (M^+, 100%), 190 (71), 160 (15), 135 (18), 134 (50), 77 (27); HRMS: M^+ found 191.0927, $C_{11}H_{13}NO_2$ requires 191.0946.

(*S*)-5-(4-Methoxyphenyl)pyrrolidin-2-one (*ent*-4b): its physical and spectroscopic data are identical to the ones of lactam **4b**, except for the optical rotation: $[\alpha]_D^{20}$ −41.0 (*c* 0.8, CH_2Cl_2, >99% ee).

(*R*)-5-(4-Chlorophenyl)pyrrolidin-2-one (4c): white solid; mp 121-123 ºC; R_f 0.23 (hexane/ethyl acetate: 2/3); $[\alpha]_D^{20}$ +46.0 (*c* 0.6, CH_2Cl_2, 97% ee); IR (neat) 3196, 3088, 1696, 1664, 1259, 1088 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.87-1.97, 2.52-2.63 (1H each, 2 m), 2.36-2.50 (2H, m), 4.74 (1H, t, J = 7.1 Hz), 6.65 (1H, br s) 7.24, 7.34 (2H each, 2 d, J = 8.5 Hz each); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.2, 31.3, 57.5, 127.0, 129.0, 133.6, 141.0, 178.6; *m/z* 197 (M^+ + 2, 7%), 195 (M^+, 21%), 160 (100), 140 (42), 138 (31), 22 (84), 75 (12); HRMS: M^+ found 195.0451, $C_{10}H_{10}ClNO$ requires 195.0451.

(*S*)-5-(4-Chlorophenyl)pyrrolidin-2-one (*ent*-4c): its physical and spectroscopic data are identical to the ones of lactam **4c**, except for the optical rotation: $[\alpha]_D^{20}$ −45.5 (*c* 0.7, CH_2Cl_2, 96% ee).

(*R*)-6-(2-Naphthyl)piperidin-2-one (4i): white solid; mp 182-184 ºC; R_f 0.37 (hexane/ethyl acetate: 2/3); $[\alpha]_D^{20}$ +46.0 (*c* 0.6, CH_2Cl_2, 98% ee); IR (neat) 3267, 3050, 1658, 1622, 1467, 1368 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.62-1.98 (3H, m), 2.10-2.23 (1H, m), 2.38-2.57 (2H, m), 4.71 (1H, dd, J = 8.0, 4.5 Hz), 6.12 (1H, br s), 7.38 (1H, dd, J = 8.5, 1.7 Hz), 7.45-7.53 (2H, m), 7.74 (1H, s), 7.78-7.89 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 31.3, 31.9, 57.7, 124.0, 124.8, 126.1, 126.5, 127.6, 127.8, 128.7, 132.9, 133.2, 139.8, 172.4; *m/z* 225 (M^+, 100%), 224 (39), 196 (24), 168 (21), 155 (56), 154 (64), 129 (19), 69 (17); HRMS: M^+ found 225.1180, $C_{15}H_{15}NO$ requires 225.1154.

(*S*)-6-(2-Naphthyl)piperidin-2-one (*ent*-4i): its physical and spectroscopic data are identical to the ones of lactam **4i**, except for the optical rotation: $[\alpha]_D^{20}$ −44.0 (*c* 0.7, CH_2Cl_2, 97% ee).

(*R*)-6-(2-Thienyl)piperidin-2-one (4j): white solid; mp 97-98 ºC; R_f 0.26 (hexane/ethyl acetate: 1/3); $[\alpha]_D^{20}$ +63.0 (*c* 0.7, CH_2Cl_2, 98% ee); IR (neat) 3266, 3080, 1653, 1619, 1480 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.70-1.86 (2H, m), 1.89-1.99, 2.12-2.24 (1H each, 2 m), 2.34-2.51 (2H, m), 4.85 (1H, dd, J = 7.0, 5.0 Hz), 6.31 (1H, br s), 6.94-7.01 (2H, m), 7.25 (1H, dd, J = 4.5, 1.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 31.1, 32.2, 53.2, 124.2, 124.7, 126.8, 146.3, 171.7; *m/z* 181 (M^+, 100%), 180 (21), 152 (30), 112 (35), 110 (38), 69 (17); HRMS: M^+ found 181.0566, $C_9H_{11}NOS$ requires 181.0561.

(*S*)-6-(2-Thienyl)piperidin-2-one (*ent*-4j): its physical and spectroscopic data are identical to the ones of lactam **4j**, except for the optical rotation: $[\alpha]_D^{20}$ −64.0 (*c* 0.7, CH_2Cl_2, 99% ee).

Desulfinylation of the ATH Product from Iminoesters 2l and *ent*-2l. Isolation of ε-Lactams 4l and *ent*-4l

The crude mixture of the transfer hydrogenation of iminoester **2l** or *ent*-**2l** was dissolved in dry MeOH (2 mL) and a 2 M solution of HCl in Et_2O (9 mL, 18 mmol) was added dropwise at 0 ºC. The reaction was stirred overnight at room temperature. Then, a 1.5 M solution of MeONa in MeOH [freshly prepared by adding carefully sodium (690 mg, 30 mmol) to MeOH (20 mL) in an open flask at room temperature] was added at 0 ºC and the reaction was stirred overnight at room temperature. Then, solvents were evaporated, a 0.5 M aqueous NaOH solution (10 mL) was added and the mixture was extracted with Et_2O (3 × 10 mL). The combined organic phases were dried (Na_2SO_4). After filtration and evaporation of the solvent, the residue was purified by column chromatography (silica gel, hexane/ethyl acetate) to afford ε-lactams **4l** and *ent*-**4l** in the yields indicated in Scheme 4. The ee values were determined by HPLC using a ChiralCel OD-H column (see the Supporting Information for details). The corresponding physical and spectroscopic data for compounds **4l** and *ent*-**4l** follow.

(*R*)-7-phenylazepan-2-one (4l):[33] white solid; mp 136 ºC; R_f 0.31 (hexane/ethyl acetate: 2/3); $[\alpha]_D^{20}$ +44.0 (*c* 0.5, $CHCl_3$, 98% ee); IR (neat) 3208, 3067, 1647, 1406 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.66-1.79 (2H, m), 1.87-2.15 (4H, m), 2.51-2.66 (2H, m), 4.47 (1H, ddd, J = 9.3, 4.1, 2.0 Hz), 5.68 (1H, br s), 7.30-7.42 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1, 29.9, 37.1, 37.2, 58.7, 126.2, 128.2, 129.2, 142.4, 177.2; *m/z* 189 (M^+, 32%), 161 (42), 106 (100), 104 (33), 91 (18), 79 (19).

(*S*)-7-phenylazepan-2-one (*ent*-4l):[33] its physical and spectroscopic data are identical to the ones of lactam **4l**, except for the optical rotation: $[\alpha]_D^{20}$ −44.5 (*c* 0.6, $CHCl_3$, 98% ee).

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Supporting Information. Details for the determination of the enantiomeric excesses of lactams **4** and *ent*-**4**; copies of ^{1}H NMR and ^{13}C NMR spectra for ketoesters **1c**, **1d**, **1f**, and **1h**-**1l**, iminoesters **2** and lactams **4**; HPLC traces for the determination of the enantiomeric excesses of lactams **4** and *ent*-**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Negwer, M.; Scharnow, H.-G. *Organic-Chemical Drugs and their Synonyms*; 8th ed.; Wiley-VCH, 2001. (b) Elguero, J.; Goya, P.; Jagerovic, N.; Silva, A. M. S. In *Targets Heterocycl. Syst.* 2002, p 52. (c) Pattabiraman, V. R.; Bode, J. W. *Nature* **2011**, *480*, 471-479.

(2) (a) Fenical, W.; Jensen, P. R.; Palladino, M. A.; Lam, K. S.; Lloyd, G. K.; Potts, B. C. *Bioorg. Med. Chem.* **2009**, *17*, 2175-2180. (b) Pérez-Faginas, P.; Aranda, M. T.; García-López, M. T.; Francesch, A.; Cuevas, C.; González-Muñiz, R. *Eur. J. Med. Chem.* **2011**, *46*, 5108-5119.

(3) (a) Brouillette, W. J.; Atigadda, V. R.; Luo, M.; Air, G. M.; Babu, Y. S.; Bantia, S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1901-1906. (b) Atigadda, V. R.; Brouillette, W. J.; Duarte, F.; Ali, S. M. *J. Med. Chem.* **1999**, *42*, 2332-2343. (c) Kim, H. M.; Hong, S. H.; Kim, M. S.; Lee, C. W.; Kang, J. S.; Lee, K.; Park, S.-K.; Han, J. W.; Lee, H. Y.; Choi, Y.; Kwon, H. J.; Han, G. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6234-6238. (d) Hoye, A. T.; Wipf, P. *Org. Lett.* **2011**, *13*, 2634-2637. (e) Chavan, S. P.; Harale, K. R.; Puranik, V. G.; Gawade, R. L. *Tetrahedron Lett.* **2012**, *53*, 2647-2650.

(4) (a) Aminov, R. I. *Environ. Microbiol.* **2009**, *11*, 2970-2988. (b) Drawz, S. M.; Bonomo, R. A. *Clin. Microbiol. Rev.* **2010**, *23*, 160-201.

(5) Nakagawa, Y.; Matsumoto, K.; Tomioka, K. *Tetrahedron* **2000**, *56*, 2857-2863.

(6) (a) Lebedev, A. *Chem. Heterocyclic Comp.* **2007**, *43*, 673-684. (b) Aranda, M. T.; Pérez-Faginas, P.; González-Muñiz, R. *Curr. Org. Synth.* **2009**, *6*, 325-341. (c) Royer, J. *Asymmetric Synthesis of Nitrogen Heterocycles*; Wiley-VCH: Weinheim, 2009. (d) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; David, R. B. *Tetrahedron* **2003**, *59*, 2953-2989.

(7) See, for instance: (a) Voituriez, A.; Ferreira, F.; Chemla, F. *J. Org. Chem.* **2007**, *72*, 5358-5361. (b) Almansa, R.; Guijarro, D.; Yus, M. *Tetrahedron: Asymmetry* **2008**, *19*, 2484-2491. (c) González-Gómez, J. C.; Foubelo, F.; Yus, M. *J. Org. Chem.* **2009**, *74*, 2547-2553. (d) Sun, X.-W.; Liu, M.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2008**, *10*, 1259-1262. (e) Fadeyi, O. O.; Senter, T. J.; Hahn, K. N.; Lindsley, C. W. *Chem. Eur. J.* **2012**, *18*, 5826-5831.

(8) See, for instance: (a) Cheemala, M. N.; Knochel, P. *Org. Lett.* **2007**, *9*, 3089-3092. (b) Zhang, F.; Liu, Z.-J.; Liu, J.-T. *Tetrahedron* **2010**, *66*, 6864-6868. (c) Xue, Z.-Y.; Liu, L.-X.; Jiang, Y.; Yuan, W.-C.; Zhang, X.-M. *Eur. J. Org. Chem.* **2012**, 251-255. (d) Reddy, L. R.; Prasad, K.; Prashad, M. *J. Org. Chem.* **2012**, *77*, 6296-6301.

(9) (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984-995. (b) Ellman, J. A. *Pure Appl. Chem.* **2003**, *75*, 39-46. (c) Senanayake, C. H.; Krishnamurthy, D.; Lu, Z.-H.; Han, Z.; Gallou, I. *Aldrichimica Acta* **2005**, *38*, 93-104. (d) Lin, G.-Q.; Xu, M.-H.; Zhong, Y.-W.; Sun, X.-W. *Acc. Chem. Res.* **2008**, *41*, 831-840. (e) Ferreira, F.; Botuha, C.; Chemla, F.; Pérez-Luna, A. *Chem. Soc. Rev.* **2009**, *38*, 1162-1186. (f) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600-3740.

(10) See, for instance: (a) Sun, X.; Wang, S.; Sun, S.; Zhu, J.; Deng, J. *Synlett* **2005**, 2776-2780. (b) Kosciolowicz, A.; Rozwadowska, M. D. *Tetrahedron: Asymmetry* **2006**, *17*, 1444-1448. (c) Denolf, B.; Mangelinckx, S.; Toernroos, K. W.; De Kimpe, N. *Org. Lett.* **2006**, *8*, 3129-3132.

(11) For the last paper on this topic from our group, see: Almansa, R.; Collados, J. F.; Guijarro, D.; Yus, M. *Tetrahedron: Asymmetry* **2010**, *21*, 1421-1431, and references cited therein.

(12) (a) For a recent review on enantioselective allylation of imines, see: Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2011**, *111*, 7774-7854. (b) For the last paper on this topic from our group, see: Bosque, I.; González-Gómez, J. C.; Guijarro, A.; Foubelo, F.; Yus, M. *J. Org. Chem.* **2012**, *77*, 10340-10346, and references cited therein.

(13) For the last paper on this topic from our group, see: Dema, H. K.; Foubelo, F.; Yus, M. *Helv. Chim. Acta* **2012**, *95*, 1790-1798, and references cited therein.

(14) (a) Guijarro, D.; Pablo, O.; Yus, M. *Tetrahedron Lett.* **2009**, *50*, 5386-5388. (b) Guijarro, D.; Pablo, O.; Yus, M. *J. Org. Chem.* **2010**, *75*, 5265-5270. (c) Guijarro, D.; Pablo, O.; Yus, M. *Tetrahedron Lett.* **2011**, *52*, 789-791. (d) Pablo, O.; Guijarro, D.; Kovács, G.; Lledós, A.; Ujaque, G.; Yus, M. *Chem. Eur. J.* **2012**, *18*, 1969-1983.

(15) The asymmetric transfer hydrogenation of prochiral imines bearing other substituents on the nitrogen atom has been reported. See, for instance: (a) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069-1094. (b) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045-2061. (c) Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Keßeler, M.; Stürmer, R.; Zelinski, T. *Angew. Chem. Int. Ed.* **2004**, *43*, 788-824. (d) Wills, M. In *Modern Reduction Methods;* Andersson, P. G.; Munslow, I. J. Eds.; Wiley-VCH: Weinheim, 2008; pp. 271-296. (e) Wang, C.; Wu, X.; Xiao, J. *Chem. Asian J.* **2008**, *3*, 1750-1770. (f) Darwish, M.; Wills, M. *Catal. Sci. Technol.* **2012**, *2*, 243-255.

(16) See, for instance: (a) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97-102. (b) Kang, Q.; Zhao, Z.-A.; You, S.-L. *Org. Lett.* **2008**, *10*, 2031-2034.

(17) Barberis, M.; Pérez-Prieto, J. *Tetrahedron Lett.* **2003**, *44*, 6683-6685.

(18) Collados, J. F.; Toledano, E.; Guijarro, D.; Yus, M. *J. Org. Chem.* **2012**, *77*, 5744-5750.

(19) Some other examples of similar cyclization processes have been reported. See, for instance: (a) references 7b and 8d. (b) Davis, F. A.; Chao, B.; Fang, T.; Szewczyk, J. M. *Org. Lett.* **2000**, *2*, 1041-1043. (c) Xu, C.-P.; Huang, P.-Q.; Py, S. *Org. Lett.* **2012**, *14*, 2034-2037.

(20) We did not try to perform the reduction of aliphatic iminoesters with two linear substituents on the iminic carbon atom because in our previous work on the asymmetric transfer hydrogenation of *N*-(*tert*-butylsulfinyl)imines in isopropyl alcohol using the same ruthenium catalyst as here, only moderate stereoselectivities were obtained in those cases due to the isolation of the imines as mixtures of geometrical isomers. See reference 14d.

(21) *i*-PrMgCl and PhMgCl were commercially available. The other Grignard reagents were freshly prepared by slow addition (in order to keep a gentle reflux) of the corresponding alkyl or aryl halide to a suspension of magnesium turnings (1.3 equiv) in Et_2O (ca. 1 mL/mmol of halide) at room temperature, followed by a reflux period of 1 h.

(22) Starodubtseva, E. V.; Turova, O. V.; Vinogradov, M. G.; Gorshkova, L. S.; Ferapontov, V. A.; Struchkova, M. *Tetrahedron* **2008**, *64*, 11713-11717.

(23) Xue, S.; Liu, Y.-K.; Li, L.-Z.; Guo, Q.-X. *J. Org. Chem.* **2005**, *70*, 8245-8247.

(24) Nambu, H.; Hata, K.; Matsugi, M.; Kita, Y. *Chem. Eur. J.* **2005**, *11*, 719-727.

(25) Nishiwaki, T. *Tetrahedron* **1967**, *23*, 2979-2986.

(26) Berthelot, P.; Vaccher, C.; Devergnies, M.; Flouquet, N.; Debaert, M. *J. Heterocyclic Chem.* **1988**, *25*, 1525-1529.

(27) Li, L.; Cai, P.; Guo, Q.; Xue, S. *J. Org. Chem.* **2008**, *73*, 3516-3522.

(28) Burgess, L. E.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 1656-1662.

(29) Cividino, P.; Py, S.; Delair, P.; Greene, A. E. *J. Org. Chem.* **2007**, *72*, 485-493.

(30) Kotkar, S. P.; Chavan, V. B.; Sudalai, A. *Org. Lett.* **2007**, *9*, 1001-1004.

(31) Salvador González, A.; Gómez Arrayás, R.; Rodríguez Rivero, M.; Carretero, J. C. *Org. Lett.* **2008**, *10*, 4335-4337.

(32) Burke, A. J.; Davies, S. G.; Garner, A. C.; McCarthy, T. D.; Roberts, P. M.; Smith, A. D.; Rodriguez-Solla, H.; Vickers, R. J. *Org. Biomol. Chem.* **2004**, *2*, 1387-1394.

(33) Yanagisawa, H.; Ishihara, S.; Ando, A.; Kanazaki, T.; Miyamoto, S.; Koike, H.; Iijima, Y.; Oizumi, K.; Matsushita, Y.; Hata, T. *J. Med. Chem.* **1988**, *31*, 422-428.