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Asymmetric Synthesis of Chiral *N*-Sulfinyl 3-Alkyl- and 3-Arylpiperidines by α-Alkylation of *N*-Sulfinyl Imidates with 1-Chloro-3-iodopropane

Filip Colpaert, Sven Mangelinckx,[†] and Norbert De Kimpe*

Department of Sustainable Organic Chemistry and Technology, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium. [†]*Postdoctoral Fellow of the Research Foundation − Vlaanderen (FWO).*

norbert.dekimpe@UGent.be

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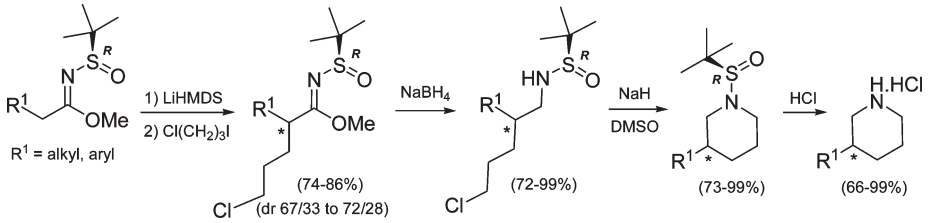

α-Alkylation of *N*-sulfinyl imidates with 1-chloro-3-iodopropane successfully led to 2-substituted *N*-*tert*-butanesulfinyl-5-chloropentanimidates in acceptable diastereomeric ratios (dr 67/33 to 72/28) and good yields (74−86%). Subsequent reduction with $NaBH_4$ led to the corresponding 2-substituted *N*-*tert*-butanesulfinyl-5-chloropentylamines, which could be cyclized to a range of new chiral 3-substituted *N*-*tert*-butanesulfinylpiperidines using NaH in DMSO. Finally, the *N*-*tert*-butanesulfinylpiperidines could be efficiently deprotected to enantiomerically pure 3-alkyl- and 3-arylpiperidine hydrochlorides.

Introduction

Piperidines are a very important class of compounds, commonly found in natural products and drugs.[1] The piperidine subunit can be frequently recognized in the structure of numerous naturally occurring alkaloids and synthetic compounds with interesting biological and pharmacological properties.[1e,2] For these reasons, the development of general methods for the synthesis of enantiopure piperidine derivatives has attracted considerable synthetic attention over the last years.[3] Recently, our group demonstrated that an efficient and stereoselective α-alkylation of *N*-sulfinyl imidates can be achieved leading to chiral α-substituted *N*-sulfinyl imidates as useful intermediates in the synthesis of enantiopure amides and esters.[4] The significantly more nucleophilic metalloenamines derived from *N*-sulfinyl imidates were sufficiently reactive to enable α-alkylation in contrast to metalloenamines

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derived from *N*-*tert*-butanesulfinyl imines. Therefore, it was envisioned that the α-alkylation of *N*-sulfinyl imidates with 1,3-dihalopropanes [$X^1(CH_2)_3X^2$; X^1, X^2 = halogen) could be a valuable new approach toward the synthesis of new chiral *N*-sulfinyl 3-alkyl and 3-arylpiperidines, and the results are described herein.

Enantiopure 3-alkylpiperidines are an important group of compounds, since their heterocyclic skeleton is present in a large number of alkaloids.[5] The importance of enantiopure 3-arylpiperidines lies in their interesting dopaminergic activity[6] and their use in the treatment of various central nervous system disorders.[7] Despite the impressive advances in the enantioselective synthesis of piperidine derivatives over the last years,[3] the preparation of enantiopure 3-arylpiperidines, has received very little attention.[8] While most enantiopure 3-arylpiperidines reported so far have been obtained by routes involving the conventional resolution of a racemate,[8a,9] Amat et al. reported recently an efficient and straightforward procedure for the enantioselective synthesis of 3-arylpiperidines, involving a reduction of bicyclic δ-lactams, formed via cyclodehydration of racemic γ-aryl-δ-oxoesters with (*R*)- or (*S*)-phenylglycinol, a process that involves a dynamic kinetic resolution.[10] However, previously reported methods for the preparation of enantiopure 3-alkylpiperidines, via alkylation of a postulated rigid amide enolate derived from bicyclic δ-lactams, could not be extended to the synthesis of 3-arylpiperidines.[11] On the other hand, the α-alkylation of *N*-sulfinyl imidates with $X^1(CH_2)_3X^2$ could afford a new general synthetic pathway for the synthesis of enantiopure 3-alkylated and 3-arylated piperidines. Very recently, the synthesis of chiral 3-alkyl- and 3-aryl-*N*-tosylpiperidines was performed via iridium-catalyzed hydrogenation of the corresponding *N*-tosyl-1,2,3,6-tetrahydropyridines in good to excellent enantiomeric excess.[12] In contrast to chiral 2-substituted *N*-sulfinyl piperidines,[13] no enantiopure 3-substituted *N*-sulfinyl piperidines are known in literature, unless some specific trisubstituted bicyclic examples.[14] Also 4-substituted *N*-sulfinyl piperidines are scarce in literature.[15] Hence, the first synthesis of chiral *N*-sulfinyl 3-alkyl- and 3-arylpiperidines is described herein.

Results and Discussion

The α-alkylation of *N*-*tert*-butanesulfinyl imidates **1** with $X^1(CH_2)_3X^2$ was optimized by systematically changing the reaction conditions in the α-alkylation of *N*-sulfinyl imidate (***R*****$_s$)-1a** and (***S*****$_s$)-4** with $X^1(CH_2)_3X^2$ for the synthesis of 2-substituted *N*-sulfinyl-5-chloropentanimidates (***R*****)-2a** and (***S*****)-2a** (Table 1). The synthesis of *N*-*tert*-butanesulfinyl imidate (***R*****$_s$)-1a** was performed according to a literature procedure via condensation of (*R*$_s$)-*tert*-butanesulfinamide and the corresponding ortho ester with a catalytic amount of *p*-TsOH without solvent.[4,16] Using the optimized conditions found in our previous reported work on the α-alkylation of *N*-sulfinyl imidates,[4] namely treating *N*-*tert*-butanesulfinyl imidate (***R*****$_s$)-1a** with 1.2 equivalents of KHMDS for 45 min at −78 °C followed by reaction with 1.3 equivalents of $Cl(CH_2)_3Br$ at −78 °C for 1.5 h during which the temperature was allowed to increase to room temperature, *N*-sulfinyl imidate (***R*****$_s$)-1a**

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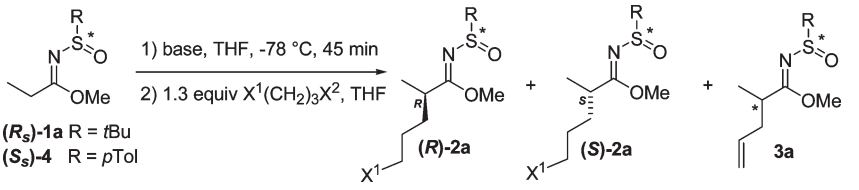
TABLE 1. Optimization of the α-Alkylation of *N*-Sulfinyl Imidates (R_s)-1a and (S_s)-4 with $X^1(CH_2)_3X^2$



entry	R	X^1	X^2	base (equiv)	temp (°C)/ time (h)	conversion of **1a** into **2a** and **3a** (%)[a]	**2a**/**3a**[a]	dr[a] (***R***)-**2a**/ (***S***)-**2a**
1	*t*Bu	Cl	Br	KHMDS (1.2)	−78 to rt/1.5	27	74/26	−
2	*t*Bu	Cl	I	KHMDS (1.2)	−78 to rt/1.5	60	100/0	72/28
3	*t*Bu	I	I	KHMDS (1.2)	−78 to rt/1.5	54	29/71	−
4	*t*Bu	Cl	I	KHMDS (2.0)	−78 to rt/1.5	71	100/0	73/27
5	*t*Bu	Cl	I	LDA (1.2)[b]	0/0.5	100	94/6	47/53[c]
6	*t*Bu	Cl	I	LDA (1.2)[b]	−78/1	91	100/0	60/40
7	*t*Bu	Cl	I	LDA (1.5)[b]	−78/1	100	99/1	59/41
8	*t*Bu	Cl	I	LiHMDS (1.2)	−78/4	85	100/0	70/30
9	*t*Bu	Cl	I	LiHMDS (1.2)	0/1	100	96/4	58/42
10	*t*Bu	Cl	I	LiHMDS (2.0)	−78/4	88	100/0	70/30
11	*t*Bu	Cl	I	LiHMDS (2.0)	−78/3 + 0/2	100	97/3	70/30[d]
12	*t*Bu	Cl	I	LiHMDS (2.0)[e]	−78/3 + 0/2	38	100/0	47/53
13	*p*Tol	Cl	I	LiHMDS (2.0)	−78/3 + 0/2	74	−	43/57
14	*t*Bu	OTHP	Cl	LiHMDS (2.0)	−78/3 + 0/2	−	−	−

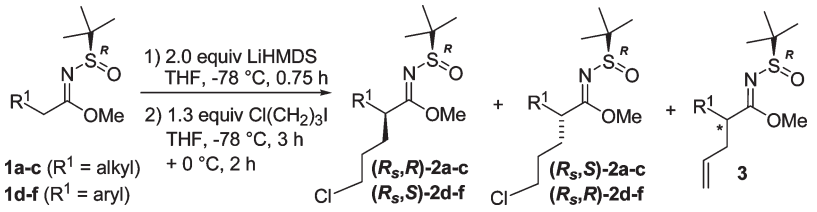
[a]Determined via ^{1}H NMR analysis of the crude reaction mixture. [b]Deprotonation was performed at 0 °C. [c]After flash chromatography (***R*$_s$,*R***)-**2a** was isolated in 25% yield, (***R*$_s$,*S***)-**2a** in 29% yield and a mixture of (***R*$_s$,*R***)-**2a**/(***R*$_s$,*S***)-**2a** 22/78 in 14% yield. [d]After flash chromatography (***R*$_s$,*R***)-**2a** was isolated in 47% yield (97% purity, 3% **3a**), (***R*$_s$,*S***)-**2a** in 22% yield, a mixture of (***R*$_s$,*R***)-**2a**/(***R*$_s$,*S***)-**2a** 57/43 in 2% yield and a mixture of (***R*$_s$,*R***)-**2a**/(***R*$_s$,*S***)-**2a** 19/81 in 6% yield. [e]After deprotonation, 2.0 equiv $ZnCl_2$ was added at −78 °C for 15 min.

was only for 27% converted to the desired 2-substituted *N*-*tert*-butanesulfinyl-5-chloropentanimidates **2a** and to methyl *N*-*tert*-butanesulfinyl-2-methylpent-4-enimidate **3a** (Table 1, entry 1). *N*-Sulfinyl imidate **3a** was formed as byproduct due to the base-induced dehydrochlorination of *N*-sulfinyl imidates **2a**; **2a**/**3a** 74/26. When changing the electrophile to $Cl(CH_2)_3I$, the conversion of (***R*$_s$**)-**1a** into **2a** and **3a** was increased to 60% using the same reaction conditions and no formation of elimination product **3a** was observed (Table 1, entry 2). Via ^{1}H NMR analysis of the crude reaction mixture a diastereomeric ratio of (***R*$_s$,*R***)-**2a**/(***R*$_s$,*S***)-**2a** 72/28 was observed. When switching the electrophile to $I(CH_2)_3I$ the conversion of (***R*$_s$**)-**1a** into **2a** and **3a** decreased to 54%, while *N*-sulfinyl imidate **3a** was formed as major product (**2a**/**3a** 29/71) (Table 1, entry 3). The use of 2.0 equivalents of KHMDS resulted in a slightly increased conversion of (***R*$_s$**)-**1a** into **2a** and **3a** of 71%, while the diastereomeric ratio was unchanged (Table 1, entry 4).

The use of LDA as base led overall to a better or complete conversion of (***R*$_s$**)-**1a** into **2a** and **3a**, but the diastereoselectivity decreased (Table 1, entry 5−7). When the reaction was performed with LiHMDS as base, after 4 h at −78 °C, (***R*$_s$**)-**1a** was converted for 85% in **2a** (no formation of **3a**) in an acceptable diastereomeric ratio of 70/30 (Table 1, entry 8). Applying these conditions at higher temperature led to full conversion of (***R*$_s$**)-**1a** into **2a** and **3a**, but not surprisingly the diastereoselectivity was lowered to 58/42 and the formation of the elimination product **3a** was observed in small amounts (Table 1, entry 9). The use of 2.0 equivalents LiHMDS improved the conversion slightly when the reaction was performed at −78 °C for 4 h (Table 1, entry 10). Therefore, the reaction was repeated at −78 °C for 3 h, followed by 2 h at 0 °C, leading to a complete conversion of (***R*$_s$**)-**1a** into **2a** and **3a**, while the diastereoselectivity was maintained and only a trace amount of the elimination product **3a** was formed (Table 1, entry 11). In order to improve the diastereoselectivity of the reaction, several Lewis acids were tested. When $ZnCl_2$ was added after deprotonation only a 38% conversion was observed, while the diastereoselectivity was lowered to 47/53 (Table 1, entry 12). The addition of $BF_3.OEt_2$ afforded a complex mixture, and the addition of $MgBr_2$ gave no reaction. Also the addition of HMPA led to an unreacted mixture of *N*-sulfinyl imidate (***R*$_s$**)-**1a** and $Cl(CH_2)_3I$ after workup. Subsequently, with a view to improving the diastereoselectivity, (S_S)-methyl *N*-*p*-toluenesulfinylpropanimidate (***S*$_S$**)-**4** was synthesized[4,16] and used instead of (***R*$_s$**)-**1a** (Table 1, entry 13). Unfortunately, this resulted in a large decrease of conversion (74%) and diastereoselectivity (43/57). In a last attempt, $Cl(CH_2)_3OTHP$ was used instead of $Cl(CH_2)_3I$, unfortunately giving rise to a complex mixture (Table 1, entry 14). Therefore, the best result was obtained upon treating *N*-sulfinyl imidate (***R*$_s$**)-**1a** with 2.0 equivalents of LiHMDS for 45 min at −78 °C followed by reaction with 1.3 equivalents of $Cl(CH_2)_3I$ at −78 °C for 3 h, followed by 2 h at 0 °C, affording 2-substituted *N*-*tert*-butanesulfinyl-5-chloropentanimidates (***R*$_s$,*R***)-**2a** and (***R*$_s$,*S***)-**2a** in an acceptable diastereomeric ratio of 70/30 and a trace amount of elimination product **3a** (**2a**/**3a** 97/3). After flash chromatography, compound (***R*$_s$,*R***)-**2a** was isolated in 47% yield (97% purity, 3% **3a**), (***R*$_s$,*S***)-**2a** in 22% yield, besides a mixture of (***R*$_s$,*R***)-**2a**/(***R*$_s$,*S***)-**2a** 57/43 in 2% yield and a mixture of (***R*$_s$,*R***)-**2a**/(***R*$_s$,*S***)-**2a** 19/81 in 6% yield.

Analogously, a variety of new chiral 2-substituted *N*-*tert*-butanesulfinyl-5-chloropentanimidates **2** was prepared in acceptable diastereomeric ratios (dr 67/33 to 72/28) and good yields (74−86%) using the optimized reaction conditions (Table 2). When the reaction was performed with R_s-methyl *N*-*tert*-butanesulfinylbutanimidate **1b** (R^1 = Et) and pentanimidate **1c** (R^1 = *n*-Pr), imidates **2b** and **2c** were obtained in a diastereomeric ratio of 67/33 and 71/29 respectively (Table 2, entries 2 and 3). Unfortunately, the diastereomers

TABLE 2. Asymmetric α-Alkylation of *N*-Sulfinyl Imidates 1 with $Cl(CH_2)_3I$



entry	R^1	**2**/**3**[a]	dr[a] (***R*****ₛ,*R*)-2**/(***R*****ₛ,*S*)-2**	yield (%)[b]
1	Me	97/3	70/30	(***R*****ₛ,*R*)-2a** (47)[c], (***R*****ₛ,*S*)-2a** (22)[d]
2	Et	97/3	67/33	**2b** (86)[c,e]
3	*n*-Pr	97/3	71/29	**2c** (74)[c,f]
4	C_6H_5	95/5	68/32	(***R*****ₛ,*R*)-2d** (54)[g], (***R*****ₛ,*S*)-2d** (23)
5	4-FC_6H_4	92/8	72/28	(***R*****ₛ,*R*)-2e** (51), (***R*****ₛ,*S*)-2e** (24)
6	4-$MeOC_6H_4$	94/6	72/28	(***R*****ₛ,*R*)-2f** (54)[h]

[a]Determined via ^{1}H NMR analysis of the crude reaction mixture. [b]Isolated yield after flash chromatography. [c]Purity 97%, contains 3% **3**. [d]Additionally a mixture of (***R*****ₛ,*R*)-2a**/(***R*****ₛ,*S*)-2a** 57/43 and a mixture of (***R*****ₛ,*R*)-2a**/(***R*****ₛ,*S*)-2a** 19/81 was isolated respectively in 2% and 6% yield. [e]The diastereomers **2b** could not be separated via flash chromatography resulting in **2b** (22% dr 92/8, 38% dr 63/37, 16% dr 27/73 and 10% dr 24/76). [f]The diastereomers **2c** could not be separated via flash chromatography resulting in **2c** (74% dr 71/29). [g]Purity 94%, contains 6% **3d**. [h]First purification via flash chromatography: (***R*****ₛ,*R*)-2f** (46%, 95% purity, 5% **3f**) + (***R*****ₛ,*R*)-2f**/(***R*****ₛ,*S*)-2f** 39/61 (28%), second attempt for separation of the latter mixture: (***R*****ₛ,*R*)-2f** (8%) + (***R*****ₛ,*R*)-2f**/(***R*****ₛ,*S*)-2f** 18/82 (20%).

of **2b** and **2c** could not be separated via flash chromatography resulting in isolated diastereomeric mixtures with a yield of 86% and 74%, respectively. Noteworthy, the stereoselectivity obtained in the α-alkylation of *N*-*tert*-butanesulfinyl imidates **1a**−**c** (R^1 = alkyl) is in analogy with the previously reported stereoselective α-alkylation of *N*-sulfinyl imidates in the synthesis of chiral α-substituted *N*-sulfinyl imidates,[4] although the use of 1-chloro-3-iodopropane as electrophile clearly lowers the diastereoselectivity as compared to the use of monohalogenated electrophiles. The coordinating ability of the additional chlorine atom of the dihalogenated electrophile with the metal of the metalloenamine could be an important factor leading to a decrease in diastereoselectivity.

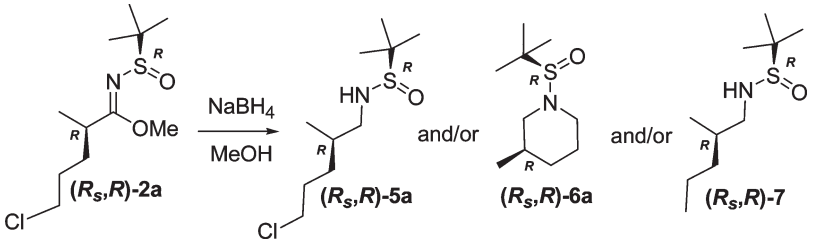
In the assumption that the diastereomers of (R_s)-methyl *N*-*tert*-butanesulfinyl-5-chloro-2-arylpentanimidates **2d**−**f** would be better separatable, R_s-methyl *N*-*tert*-butanesulfinylarylacetimidates **1d-f** were synthesized.[16a] When the reaction was performed with (R_s)-methyl *N*-*tert*-butanesulfinylphenylacetimidate **1d** (R^1 = C_6H_5), (R_s)-methyl *N*-*tert*-butanesulfinyl-5-chloro-2-phenylpentanimidates (***R*****ₛ,*R*)-2d** and (***R*****ₛ,*S*)-2d** were obtained in a diastereomeric ratio of 68/32 (Table 2, entry 4). In accordance with our assumption, the diastereomers (***R*****ₛ,*R*)-2d** and (***R*****ₛ,*S*)-2d** could be separated by flash chromatography, leading to the isolation of (***R*****ₛ,*R*)-2d** in 54% yield and (***R*****ₛ,*S*)-2d** in 23% yield. It has to be noted that the separation of (***R*****ₛ,*R*)-2d** and the elimination product **3d** could not be realized, leading to (***R*****ₛ,*R*)-2d** in a purity of 94% (contains 6% of **3d**). At this stage, little attention was payed to the presence of this trace impurity as its separation could be easily accomplished in further steps of the synthesis of chiral *N*-sulfinyl piperidines.

Repeating the reaction with (R_s)-methyl *N*-*tert*-butanesulfinyl(4-fluorophenyl)acetimidate **1e** (R^1 = 4-FC_6H_4), resulted in the isolation of (R_s,*R*)-methyl *N*-*tert*-butanesulfinyl-5-chloro-2-(4-fluorophenyl)pentanimidate (***R*****ₛ,*R*)-2e** in 51% yield and (R_s,*S*)-methyl *N*-*tert*-butanesulfinyl-5-chloro-2-(4-fluorophenyl)pentanimidate (***R*****ₛ,*S*)-2e** in 24% yield (Table 2, entry 5). Finally, the α-alkylation of (R_s)-methyl *N*-*tert*-butanesulfinyl(4-methoxyphenyl)acetimidate **1f** (R^1 = 4-$MeOC_6H_4$), afforded (R_s)-methyl *N*-*tert*-butanesulfinyl-5-chloro-2-(4-methoxy)phenylpentanimidates (***R*****ₛ,*R*)-2f** and (***R*****ₛ,*S*)-2f** in a diastereomeric ratio of 72/28 (Table 2, entry 6). After a first purification via flash chromatography, compound (***R*****ₛ,*R*)-2f** was isolated in 46% (95% purity, 5% **3f**) and additionally a mixture of diastereomers (***R*****ₛ,*R*)-2f** and (***R*****ₛ,*S*)-2f** in a ratio of 39/61 was isolated in 28% yield. In a second effort to separate the latter mixture via flash chromatography, compound (***R*****ₛ,*R*)-2f** was isolated in an additional 8% yield besides a mixture of diastereomers (***R*****ₛ,*R*)-2f** and (***R*****ₛ,*S*)-2f** in a ratio of 18/82 in 20% yield. Noteworthy, as compared to the α-alkylation of *N*-*tert*-butanesulfinyl imidates **1a**−**c** (R^1 = alkyl), a reversed stereoselectivity was obtained in the α-alkylation of R_s-methyl *N*-*tert*-butanesulfinylarylacetimidates **1d**−**f** (R^1 = aryl).[17]

In a next step, the conversion of *N*-sulfinyl imidate (***R*****ₛ,*R*)-2a** to the corresponding *N*-sulfinyl piperidine (***R*****ₛ,*R*)-6a** via reductive cyclization with $NaBH_4$ was investigated (Table 3). In a first attempt, *N*-sulfinyl imidate (***R*****ₛ,*R*)-2a** was treated with 2.0 mol equiv of $NaBH_4$ in MeOH/THF at reflux temperature for 6 h, leading to sulfinamide (***R*****ₛ,*R*)-5a** with 77% conversion (Table 3, entry 1). When the reaction time was increased, a mixture of sulfinamide (***R*****ₛ,*R*)-5a** and *N*-sulfinyl piperidine (***R*****ₛ,*R*)-6a** was observed in a ratio of 60/40, while still 20% of *N*-sulfinyl imidate (***R*****ₛ,*R*)-2a** remained unreacted. When 5.0 equivalents $NaBH_4$ were added to *N*-sulfinyl imidate (***R*****ₛ,*R*)-2a** in MeOH/THF at reflux temperature for 1 h a full conversion to sulfinamide (***R*****ₛ,*R*)-5a** was achieved and after flash chromatography sulfinamide (***R*****ₛ,*R*)-5a** was isolated in 78% yield (Table 3, entry 2). Noteworthy, the sulfinamide formed via reduction of elimination product **3a**, present as a small impurity in the starting imidate (***R*****ₛ,*R*)-2a**, was separated via flash chromatography, resulting in a high purity of sulfinamide (***R*****ₛ,*R*)-5a**. In a last attempt for reductive cyclization of *N*-sulfinyl imidate (***R*****ₛ,*R*)-2a** to the corresponding *N*-sulfinyl piperidine (***R*****ₛ,*R*)-6a**, *N*-sulfinyl imidate (***R*****ₛ,*R*)-2a** was treated with 10.0 equivalents of $NaBH_4$,

(17) It is speculated that the nature of the α-substituent of the imidates influences the E/Z-ratio of the lithium enolates and determines the diastereomeric ratio of the reaction products.

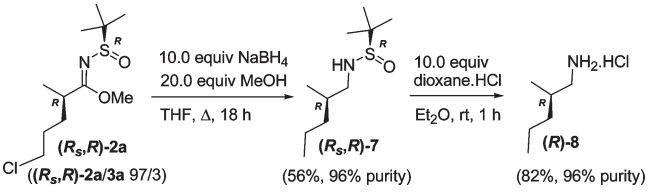
TABLE 3. Reaction of *N*-Sulfinyl Imidate (R_s,*R*)-2a with $NaBH_4$



entry	reaction conditions	**2a**/**5a**/**6a**/**7**[a]	yield (%)[b]
1	2.0 equiv $NaBH_4$, 4.0 equiv MeOH, THF, Δ, 6 h	23/77/0/0	–
	+ Δ, 13 h	20/48/32/0	–
2	5.0 equiv $NaBH_4$, 10.0 equiv MeOH, THF, Δ, 1 h	0/100/0/0	(R_s,*R*)-**5a** (78)
3	10.0 equiv $NaBH_4$, 20.0 equiv MeOH, THF, Δ, 18 h	0/0/0/100	(R_s,*R*)-**7** (56)[c]

[a]Determined via ^{1}H NMR analysis of the crude reaction mixture. [b]Isolated yields after flash chromatography. [c]Purity 96%, contains 4% of the amine resulting from the reduction of the trace amount of **3a**, present in the starting imidate (R_s,*R*)-**2a**.

SCHEME 1. Reduction of *N*-Sulfinyl Imidate (R_s,*R*)-2a to Sulfinamide (R_s,*R*)-7 and Subsequent Deprotection to (*R*)-2-Methylpentylamine Hydrochloride (*R*)-8



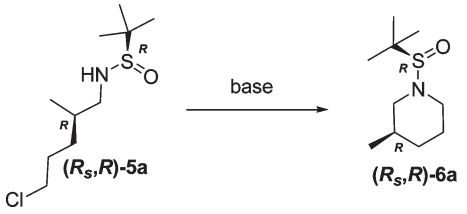
affording surprisingly sulfinamide (R_s,*R*)-**7** (Table 3, entry 3). After flash chromatography, sulfinamide (R_s,*R*)-**7** was isolated in 56% yield (96% purity).

After deprotection of sulfinamide (R_s,*R*)-**7** with an excess of dioxane·HCl, (*R*)-2-methylpentylamine hydrochloride (*R*)-**8** could be isolated in 82% yield (96% purity) (Scheme 1).

Since the reductive cyclization of *N*-sulfinyl imidate (R_s,*R*)-**2a** to the corresponding *N*-sulfinyl piperidine (R_s,*R*)-**6a** was not successful, the base-induced cyclization of sulfinamide (R_s,*R*)-**5a** toward *N*-sulfinyl piperidine (R_s,*R*)-**6a** was optimized (Table 4). In a first attempt, sulfinamide (R_s,*R*)-**5a** was treated with 3.0 equivalents of KOH in THF/H_2O (1:1) at reflux temperature for 24 h according to a procedure for the ring closure of sulfinamides to *N*-sulfinyl aziridines (Table 4, entry 1).[18] Unfortunately, this gave no reaction. When sulfinamide (R_s,*R*)-**5a** was treated with LiHMDS according to a procedure for the ring closure of fluorinated amines to fluoroaziridines,[19] also no reaction was observed (Table 4, entry 2).

In a next attempt, a Finkelstein reaction with NaI and subsequent base treatment was performed on sulfinamide (R_s,*R*)-**5a** according to a procedure for the synthesis of *N*-benzoyl (*R*)-coniine.[20] Unfortunately, a complex mixture was obtained after the reaction with NaI. Finally, sulfinamide (R_s,*R*)-**5a** was treated with 2.5 equivalents NaH in DMSO at 80 °C for 2 h,[21] leading to *N*-sulfinyl piperidine (R_s,*R*)-**6a**, which was isolated in 98% yield after flash chromatography (Table 4, entry 4).

TABLE 4. Investigation of the Base-Induced Ring Closure of Sulfinamide (R_s,*R*)-5a towards *N*-Sulfinyl Piperidine (R_s,*R*)-6a



entry	reaction conditions	yield (%)[a]
1	3.0 equiv KOH, THF/H_2O (1:1), Δ, 24 h	–
2	1.5 equiv LiHMDS, THF, 0 °C to rt, 7 h	–
3	1) 1.5 equiv NaI, 2-butanone, Δ, 24 h	
	2) 5.0 equiv NaH, THF/DMF (3:1), 0 °C	–
4	2.5 equiv NaH, DMSO, 80 °C, 2 h	(R_s,*R*)-**6a** (98)

[a]Isolated yield after flash chromatography.

Analogously, a variety of new chiral 3-substituted *N*-sulfinyl piperidines **6** was prepared in good to excellent yields via the developed reaction conditions for the base-induced cyclization of sulfinamides **5** (Scheme 2).

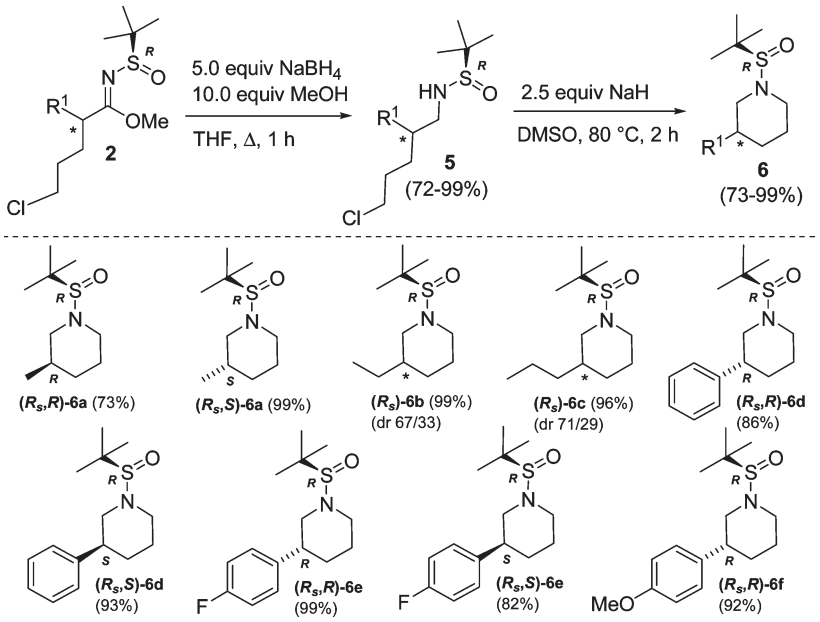
These sulfinamides **5** were obtained in good to excellent yields via reduction of the corresponding *N*-sulfinyl imidates **2** with $NaBH_4$. Noteworthy, during flash chromatography of the sulfinamides **5** (R^1 = alkyl) or *N*-sulfinyl piperidines **6** (R^1 = aryl), the amine obtained via reduction of elimination product **3** (if present as a side product with compounds **2**) was removed, resulting in a very high purity for all chiral 3-substituted *N*-sulfinyl piperidines **6**. Several efforts to separate the diastereomers of **5b**, **5c**, **6b** and **6c** were not successful, leading to a mixture of diastereomers **6b** and **6c** in a diastereomeric ratio of 67/33 and 71/29, respectively.

Finally, the 3-substituted *N*-sulfinyl piperidines **6** were *N*-deprotected by simple treatment with a 4.0 N solution of anhydrous HCl (10.0 equiv HCl) in dioxane for 1 h at room temperature in Et_2O. In this way the enantiopure piperidine hydrochlorides **9a** and **9d**−**f** were obtained in good yield (66−99%) after precipitation from diethyl ether (Scheme 3). Piperidine hydrochlorides **9b** and **9c** were obtained in an enantiomeric ratio of 67/33 and 71/29 (based on dr of **6b** and **6c**), respectively.

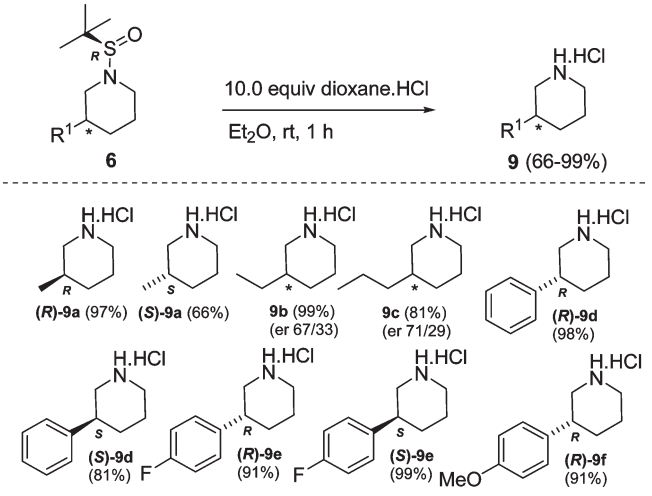
Piperidine hydrochloride (*S*)-**9a** is a known compound in the literature, prepared by the asymmetric hydrogenation of

(18) Denolf, B.; Leemans, E.; De Kimpe, N. *J. Org. Chem.* **2007**, *72*, 3211.
(19) Verniest, G.; Colpaert, F.; Van Hende, E.; De Kimpe, N. *J. Org. Chem.* **2007**, *72*, 8569.
(20) Friestad, G. K.; Marié, J.-C.; Suh, Y.; Qin, J. *J. Org. Chem.* **2006**, *71*, 7016.
(21) Dejaegher, Y.; Mangelinckx, S.; De Kimpe, N. *J. Org. Chem.* **2002**, *67*, 2075.

SCHEME 2. Reduction of *N*-Sulfinyl Imidates 2 to Sulfinamides 5 and Subsequent Ring Closure to *N*-Sulfinyl Piperidines 6



SCHEME 3. Deprotection of *N*-Sulfinyl Piperidines 6 to Piperidine Hydrochlorides 9



pyridines,[5i] and also prepared starting from a chiral lactam involving a postulated rigid amide enolate.[5l] The comparison of the optical rotations of the newly prepared piperidine hydrochloride (*R*)-**9a** ($[\alpha]_D$ +3.0 (c 0.9, MeOH) vs (*S*)-**9a** −3.0 (c 0.6, MeOH) in lit.[5i]) and piperidine hydrochloride (*S*)-**9a** ($[\alpha]_D$ −2.6 (c 0.5, MeOH) vs (*S*)-**9a** -3.0 (c 0.6, MeOH) in lit.[5i]) afforded proof of the stereochemical outcome of the asymmetric α-alkylation of *N*-sulfinyl imidates **1a**−**c** (R^1 = alkyl) with $Cl(CH_2)_3I$. Piperidine hydrochlorides (*R*)-**9d** and (*S*)-**9d** are also known compounds in the literature,[10a,22] and comparing the optical rotations of the newly prepared piperidine hydrochloride (*R*)-**9d** ($[\alpha]_D$ −10.7 (c 0.3, MeOH) vs −10.3 (c 0.5, MeOH) in lit.[10a]) and piperidine hydrochloride (*S*)-**9d** ($[\alpha]_D$ +11.5 (c 0.3, MeOH) vs +12.2 (c 0.5, MeOH) in lit.[22]) afforded proof of the stereochemical outcome of the asymmetric α-alkylation of *N*-sulfinyl imidates **1d**−**f** (R^1 = aryl) with $Cl(CH_2)_3I$. In view of the strong correspondence of the optical rotations of compounds **9a** and **9d** with literature data, together with an enatiomeric excess of >98% for the commercially available starting material (R_S)-*tert*-butanesulfinamide, an enantiomeric excess of >98% can be concluded for all synthesized piperidine hydrochlorides **9**, except for compounds **9b** and **9c**, obtained in an enantiomeric ratio of 67/33 and 71/29, respectively.

(22) Morlacchi, F.; D'Ambruoso, M.; Tortorella, V. *Chim. Ind.* (*Milan*) **1974**, *56*, 465.

Conclusions

It was demonstrated that chiral 2-substituted *N*-*tert*-butanesulfinyl-5-chloropentanimidates are formed in acceptable diastereomeric ratios (dr 67/33 to 72/28) and good yields (74−86%) via α-alkylation of *N*-sulfinyl imidates with 1-chloro-3-iodopropane. Subsequent reduction with $NaBH_4$, followed by cyclization of the obtained chiral 2-substituted *N*-*tert*-butanesulfinyl-5-chloropentylamines using NaH in DMSO, afforded the first synthesis of chiral *N*-sulfinyl 3-alkyl- and 3-arylpiperidines. Finally, deprotection of the 3-substituted *N*-sulfinyl piperidines with dioxane·HCl gave rise to a new and general synthetic pathway for the synthesis of enantiomerically pure 3-substituted piperidine hydrochlorides. By comparing the optical rotations of the synthesized piperidine hydrochlorides with literature data from known compounds, evidence was obtained about the stereochemical outcome of the alkylation reaction.

Experimental Section

Synthesis of *N*-*tert*-Butanesulfinylphenylacetimidates 1d−f. The synthesis of *N*-*tert*-butanesulfinyl imidates **1d**−**f** was performed according to a literature procedure via condensation of (R_s)-*tert*-butanesulfinamide and the corresponding ortho ester with a catalytic amount of *p*-TsOH without solvent.[16a]

(R_s)-Methyl *N*-*tert*-butanesulfinylphenylacetimidate 1d. R_f = 0.32 (petroleum ether/Et_2O 6:4). Yellow oil, yield 88%. $[\alpha]_D$ −171.7 (c 0.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 1.20 (9H, s), 3.75 (3H, s), 3.96 (1H, d, *J* = 14.3 Hz), 4.09 (1H, d, *J* = 14.3 Hz),

7.21−7.34 (5H, m). Anal. calcd for $C_{13}H_{19}NO_2S$: C 61.63; H 7.56; N 5.53. Found: C 61.42; H 7.76; N 5.41. All spectroscopic data were in good agreement with reported data.[16a]

(R_s)-Methyl *N*-*tert*-Butanesulfinyl(4-fluorophenyl)acetimidate 1e. R_f = 0.29 (petroleum ether/Et_2O 6:4). Yellow oil, yield 97%. $[\alpha]_D$ −136.8 (c 1.0, $CHCl_3$). IR (cm^{-1}): ν_{max} 1173, 1158, 1221, 1273, 1508, 1614, 2948. ^1H NMR (300 MHz, $CDCl_3$): δ 1.21 (9H, s), 3.75 (3H, s), 3.96 (1H, d, J = 14.3 Hz), 4.02 (1H, d, J = 14.3 Hz), 6.94−7.05 (2H, m), 7.25−7.37 (2H, m). ^{19}F NMR (282 MHz, $CDCl_3$): δ −115.43 to −115.54 (1F, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.0, 37.7, 54.5, 56.3, 115.5 (2C, d, J = 21.9 Hz), 130.2 (d, J = 3.5 Hz), 131.0 (2C, d, J = 8.1 Hz), 162.0 (d, J = 245.8 Hz), 173.3. MS (ES, pos. mode) m/z (%): 272 ($M + H^+$, 100). Anal. calcd for $C_{13}H_{18}FNO_2S$: C 57.54; H 6.69; N 5.16. Found: C 57.24; H 6.85; N 5.28.

(R_s)-Methyl *N*-*tert*-Butanesulfinyl(4-methoxyphenyl)acetimidate 1f. R_f = 0.16 (petroleum ether/Et_2O 6:4). Yellow oil, yield 95%. $[\alpha]_D$ −154.2 (c 1.2, $CHCl_3$). IR (cm^{-1}): ν_{max} 751, 1033, 1074, 1246, 1510, 1611, 2948. ^1H NMR (300 MHz, $CDCl_3$): δ 1.20 (9H, s), 3.75 (3H, s), 3.78 (3H, s), 3.89 (1H, d, J = 14.3 Hz), 4.01 (1H, d, J = 14.3 Hz), 6.81−6.90 (2H, m), 7.18−7.27 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.0, 37.8, 54.5, 55.3, 56.2, 114.1 (2C), 126.4, 130.5 (2C), 158.7, 174.3. MS (ES, pos. mode) m/z (%): 284 ($M + H^+$, 100). Anal. calcd for $C_{14}H_{21}NO_3S$: C 59.34; H 7.47; N 4.94. Found: C 59.51; H 7.59; N 4.96.

Synthesis of (S_S)-methyl *N*-*p*-toluenesulfinylpropanimidate (S_S)-4. The synthesis of (S_S)-methyl *N*-*p*-toluenesulfinylpropanimidate (**S_S)-4** was performed according to a previous reported procedure via condensation of (S_s)-*p*-toluenesulfinamide and the corresponding ortho ester with a catalytic amount of *p*-TsOH without solvent.[4]

(S_S)-Methyl *N*-*p*-Toluenesulfinylpropanimidate (S_S)-4. R_f = 0.17 (petroleum ether/Et_2O 7:3). Yellow oil, 82%. $[\alpha]_D$ +26.7 (c 0.3, $CHCl_3$). IR (cm^{-1}): ν_{max} 1069, 1294, 1593, 2946. ^1H NMR (300 MHz, $CDCl_3$): δ 1.24 (3H, t, J = 7.2 Hz), 2.41 (3H, s), 2.74 (1H, d × q, J = 14.6, 7.2 Hz), 2.80 (1H, d × q, J = 14.6, 7.2 Hz), 3.77 (3H, s), 7.31 (2H, d, J = 8.3 Hz), 7.65 (2H, d, J = 8.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.9, 21.5, 26.5, 54.6, 125.0 (2C), 129.8 (2C), 141.7, 144.6, 176.6. MS (ES, pos. mode) m/z (%): 226 ($M + H^+$, 100). Anal. calcd for $C_{11}H_{15}NO_2S$: C 58.64; H 6.71; N 6.22. Found: C 58.52; H 6.45; N 5.93.

Synthesis of 2-Substituted *N*-*tert*-Butanesulfinyl-5-chloropentanimidates 2. The synthesis of methyl *N*-*tert*-butanesulfinyl-5-chloro-2-methylpentanimidates **2a** is representative. A solution of R_s-methyl *N*-*tert*-butanesulfinylpropanimidate (1.0 equiv, 3.00 g, 15.71 mmol) in THF (70 mL) was cooled to −78 °C. A 1.0 M solution of LiHMDS (2.0 equiv, 31.42 mL, 31.42 mmol) in THF was slowly added and the resulting solution was stirred for 45 min at −78 °C. After deprotonation, 1-chloro-3-iodopropane (1.3 equiv, 2.15 mL, 20.42 mmol) was added dropwise and the reaction mixture was stirred for 3 h at −78 °C followed by stirring at 0 °C for 2 h. The reaction was quenched at this temperature by addition of a saturated solution of NH_4Cl (3 mL) and diluted with saturated aqueous $NaHCO_3$ (50 mL) at room temperature. The aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated in vacuo. The crude product was purified by flash chromatography to yield 1.98 g (7.38 mmol) of (R_s,*R*)-methyl *N*-*tert*-butanesulfinyl-5-chloro-2-methylpentanimidate (**R_s,*R*)-2a** (97% purity, 3% **3a**), 0.09 g (0.34 mmol) of a mixture of diastereomers (**R_s,*R*)-2a** and (**R_s,*S*)-2a** in a ratio 57:43, 0.25 g (0.93 mmol) of a mixture of diastereomers (**R_s,*R*)-2a** and (**R_s,*S*)-2a** in a ratio 19:81 and 0.92 g (3.46 mmol) of pure (R_s,*S*)-methyl *N*-*tert*-butanesulfinyl-5-chloro-2-methylpentanimidate (**R_s,*S*)-2a**.

(R_s,*R*)-Methyl *N*-*tert*-Butanesulfinyl-5-chloro-2-methylpentanimidate (R_s,*R*)-2a. R_f = 0.22 (petroleum ether/Et_2O 7:3). Yellow oil, yield 47% (97% purity, 3% **3a**). $[\alpha]_D$ −77.9 (c 1.4, $CHCl_3$). IR (cm^{-1}): ν_{max} 1071, 1604, 2869, 2947. ^1H NMR (300 MHz, $CDCl_3$): δ 1.19 (3H, d, J = 7.2 Hz), 1.22 (9H, s), 1.56−1.89 (4H, m), 3.38 (1H, sextet, J = 7.2 Hz), 3.49−3.61 (2H, m), 3.77 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.9, 21.9, 30.2, 31.3, 36.6, 44.8, 54.1, 55.7, 179.0. MS (ES, pos. mode) m/z (%): 268/270 ($M + H^+$, 100).

(R_s,*S*)-Methyl *N*-*tert*-Butanesulfinyl-5-chloro-2-methylpentanimidate (R_s,*S*)-2a. R_f=0.18 (petroleum ether/Et_2O 7:3). Yellow oil, yield 22%. $[\alpha]_D$ −110.8 (c 1.5, $CHCl_3$). IR (cm^{-1}): ν_{max} 1073, 1604, 2928, 2947. ^1H NMR (300 MHz, $CDCl_3$): δ 1.22 (9H, s), 1.24 (3H, d, J = 7.7 Hz), 1.53−1.83 (4H, m), 3.38 (1H, sextet, J = 7.7 Hz), 3.53 (2H, t, J = 6.6 Hz), 3.77 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.4, 22.0, 30.5, 31.3, 37.0, 44.6, 54.2, 55.8, 179.5. MS (ES, pos. mode) m/z (%): 268/270 ($M + H^+$, 100). Anal. calcd for $C_{11}H_{22}ClNO_2S$: C 49.33; H 8.28; N 5.23. Found: C 49.13; H 8.51; N 5.37.

(R_s)-Methyl *N*-*tert*-Butanesulfinyl-5-chloro-2-ethylpentanimidate (R_s)-2b. R_f = 0.23 (petroleum ether/Et_2O 7:3). Colorless oil, yield 86% (97% purity, 3% **3b**). The diastereomers **2b** could not be separated via flash chromatography resulting in **2b** (22% dr 92/8, 38% dr 63/37, 16% dr 27/73 and 10% dr 24/76). The spectral data of (**R_s,*R*)-2b** and (**R_s,*S*)-2b** were obtained from the mixture of diastereomers **2b** (dr 63/37). IR (cm^{-1}): ν_{max} 1073, 1603, 2961. ^1H NMR (300 MHz, $CDCl_3$): (**R_s,*R*)-2b** δ 0.74 (3H, t, J = 7.7 Hz), 1.07 (9H, s), 1.36−1.75 (6H, m), 3.08−3.21 (1H, m), 3.36−3.45 (2H, m), 3.61 (3H, s); (**R_s,*S*)-2b** δ 0.79 (3H, t, J = 7.7 Hz), 1.06 (9H, s), 1.36−1.75 (6H, m), 3.08−3.21 (1H, m), 3.36−3.45 (2H, m), 3.61 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): (**R_s,*R*)-2b** δ 12.0, 22.0, 26.2, 29.8, 30.2, 43.9, 44.9, 54.1, 55.6, 178.6; (**R_s,*S*)-2b** δ 11.9, 22.0, 26.0, 29.7, 30.6, 43.9, 44.6, 53.9, 55.7, 178.4. MS (ES, pos. mode) m/z (%): 282/284 ($M + H^+$, 100).

(R_s)-Methyl *N*-*tert*-Butanesulfinyl-5-chloro-2-propylpentanimidate (R_s)-2c. R_f = 0.22 (petroleum ether/Et_2O 7:3). Colorless oil, yield 74% (97% purity, 3% **3c**). The diastereomers **2c** could not be separated via flash chromatography resulting in **2c** (74% dr 71/29). The spectral data of (**R_s,*R*)-2c** and (**R_s,*S*)-2c** were obtained from the mixture of diastereomers **2c** (dr 71/29). IR (cm^{-1}): ν_{max} 1074, 1603, 1623, 2931, 2957. ^1H NMR (300 MHz, $CDCl_3$): (**R_s,*R*)-2c** δ 0.92 (3H, t, J = 7.7 Hz), 1.14−1.88 (8H, m), 1.22 (9H, s), 3.28−3.39 (1H, m), 3.49−3.59 (2H, m), 3.76 (3H, s). (**R_s,*S*)-2c** δ 0.90 (3H, t, J = 7.2 Hz), 1.14−1.88 (8H, m), 1.20 (9H, s), 3.28−3.39 (1H, m), 3.49−3.59 (2H, m), 3.75 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): (**R_s,*R*)-2c** δ 14.1, 20.7, 22.0, 30.1, 30.2, 35.3, 42.2, 44.9, 54.0, 55.6, 178.7; (**R_s,*S*)-2c** δ 14.1, 20.6, 22.0, 30.0, 30.5, 35.1, 42.1, 44.6, 53.9, 55.7, 178.6. MS (ES, pos. mode) m/z (%): 296/298 ($M + H^+$, 100).

(R_s,*R*)-Methyl *N*-*tert*-Butanesulfinyl-5-chloro-2-phenylpentanimidate (R_s,*R*)-2d. R_f = 0.31 (petroleum ether/Et_2O 7:3). Yellow oil, yield 54% (94% purity, 6% **3d**). $[\alpha]_D$ +33.9 (c 0.3, $CHCl_3$). IR (cm^{-1}): ν_{max} 753, 1074, 1244, 1455, 1596, 1604, 1628. ^1H NMR (300 MHz, $CDCl_3$): δ 1.21 (9H, s), 1.66−1.82 (2H, m), 1.99−2.11 (1H, m), 2.15−2.27 (1H, m), 3.54 (2H, t, J = 6.4 Hz), 3.73 (3H, s), 4.62 (1H, t, J = 7.7 Hz), 7.19−7.37 (3H, m), 7.41−7.48 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.1, 30.1, 30.5, 44.6, 47.7, 54.5, 56.4, 127.4, 128.6 (4C), 138.1, 175.1. MS (ES, pos. mode) m/z (%): 330/332 ($M + H^+$, 100).

(R_s,*S*)-Methyl *N*-*tert*-Butanesulfinyl-5-chloro-2-phenylpentanimidate (R_s,*S*)-2d. R_f = 0.24 (petroleum ether/Et_2O 7:3). Yellow oil, yield 23%. $[\alpha]_D$ −210.4 (c 0.3, $CHCl_3$). IR (cm^{-1}): ν_{max} 754, 1071, 1283, 1455, 1596, 1605, 1624. ^1H NMR (300 MHz, $CDCl_3$): δ 1.12 (9H, s), 1.66−1.81 (2H, m), 1.94−2.07 (1H, m), 2.15−2.27 (1H, m), 3.53 (2H, t, J = 6.4 Hz), 3.80 (3H, s), 4.60 (1H, t, J = 7.7 Hz), 7.22−7.40 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.9, 30.4, 30.6, 44.7, 47.9, 54.6, 56.2, 127.6, 128.4 (2C), 128.9 (2C), 138.7, 175.2. MS (ES, pos. mode) m/z (%): 330/332 ($M + H^+$, 100). Anal. calcd for $C_{16}H_{24}ClNO_2S$: C 58.25; H 7.33; N 4.25. Found: C 58.02; H 7.42; N 4.46.

(R_s,*R*)-Methyl *N-tert*-Butanesulfinyl-5-chloro-2-(4-fluorophenyl)-pentanimidate (R_s,*R*)-2e. R_f = 0.33 (petroleum ether/Et_2O 7:3). Yellow oil, yield 51%. $[\alpha]_D$ +30.9 (c 0.5, $CHCl_3$). IR (cm^{-1}): ν_{max} 752, 1073, 1223, 1508, 1606, 1628, 2949. ^1H NMR (300 MHz, $CDCl_3$): δ 1.21 (9H, s), 1.65−1.82 (2H, m), 1.95−2.08 (1H, m), 2.13−2.26 (1H, m), 3.55 (2H, t, J = 6.6 Hz), 3.75 (3H, s), 4.62 (1H, t, J = 8.0 Hz), 6.94−7.04 (2H, m), 7.39−7.47 (2H, m). ^{19}F NMR (282 MHz, $CDCl_3$): δ −115.14 to −115.25 (1F, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.1, 30.3, 30.5, 44.5, 46.7, 54.6, 56.5, 115.4 (2C, d, J = 21.9 Hz), 130.3 (2C, d, J = 8.1 Hz), 133.8 (d, J = 2.3 Hz), 162.1 (d, J = 245.8 Hz), 174.7. MS (ES, pos. mode) m/z (%): 348/350 (M + H^+, 100). Anal. calcd for $C_{16}H_{23}ClFNO_2S$: C 55.24; H 6.66; N 4.03. Found: C 54.97; H 6.38; N 3.88.

(R_s,*S*)-Methyl *N-tert*-Butanesulfinyl-5-chloro-2-(4-fluorophenyl)-pentanimidate (R_s,*S*)-2e. R_f = 0.23 (petroleum ether/Et_2O 7:3). Yellow oil, yield 24%. $[\alpha]_D$ −199.5 (c 0.3, $CHCl_3$). IR (cm^{-1}): ν_{max} 752, 1072, 1224, 1508, 1607, 2949. ^1H NMR (300 MHz, $CDCl_3$): δ 1.15 (9H, s), 1.65−1.80 (2H, m), 1.89−2.03 (1H, m), 2.12−2.27 (1H, m), 3.54 (2H, t, J = 6.6 Hz), 3.79 (3H, s), 4.61 (1H, t, J = 7.7 Hz), 6.97−7.06 (2H, m), 7.30−7.38 (2H, m). ^{19}F NMR (282 MHz, $CDCl_3$): δ −114.54 to −114.64 (1F, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.0, 30.3, 30.7, 44.7, 47.0, 54.6, 56.3, 115.7 (2C, d, J = 21.9 Hz), 130.0 (2C, d, J = 8.1 Hz), 134.4 (d, J = 3.5 Hz), 162.2 (d, J = 245.8 Hz), 174.6. MS (ES, pos. mode) m/z (%): 348/350 (M + H^+, 100). Anal. calcd for $C_{16}H_{23}ClFNO_2S$: C 55.24; H 6.66; N 4.03. Found: C 55.01; H 6.52; N 3.79.

(R_s,*R*)-Methyl *N-tert*-Butanesulfinyl-5-chloro-2-(4-methoxyphenyl)pentanimidate (R_s,*R*)-2f. R_f = 0.32 (petroleum ether/Et_2O 5:5). Yellow oil, yield 54% (46%, 95% purity, 5% **3f** + 8%, 100% purity). The spectral data of (R_s,*R*)-**2f** were obtained from (R_s,*R*)-**2f** (8%, 100% purity). $[\alpha]_D$ +55.1 (c 0.4, $CHCl_3$). IR (cm^{-1}): ν_{max} 750, 1035, 1072, 1179, 1249, 1511, 1598, 2958. ^1H NMR (300 MHz, $CDCl_3$): δ 1.21 (9H, s), 1.66−1.81 (2H, m), 1.94−2.07 (1H, m), 2.11−2.24 (1H, m), 3.53 (2H, t, J = 6.4 Hz), 3.73 (3H, s), 3.77 (3H, s), 4.55 (1H, t, J = 7.7 Hz), 6.83 (2H, d, J = 8.8 Hz), 7.36 (2H, d, J = 8.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.1, 30.2, 30.5, 44.6, 46.7, 54.5, 55.3, 56.3, 114.0 (2C), 126.7 (2C), 130.0, 158.9, 175.6. MS (ES, pos. mode) m/z (%): 360/362 (M + H^+, 100). Anal. calcd for $C_{17}H_{26}ClNO_3S$: C 56.73; H 7.28; N 3.89. Found: C 56.86; H 7.44; N 3.93.

(R_s,*S*)-Methyl *N-tert*-Butanesulfinyl-5-chloro-2-(4-methoxyphenyl)pentanimidate (R_s,*S*)-2f. R_f = 0.37 (petroleum ether/Et_2O 35:65). Yellow oil, yield 20% (dr (R_s,*S*)-**2f**/(R_s,*R*)-**2f** 82:18). The diastereomer (R_s,*S*)-**2f** could not be separated via flash chromatography from (R_s,*R*)-**2f** resulting in (R_s,*S*)-**2f**/(R_s,*R*)-**2f** 82:18. The spectral data of (R_s,*S*)-**2f** were obtained from the mixture of diastereomers **2f** (dr 82:18). IR (cm^{-1}): ν_{max} 752, 1034, 1072, 1178, 1248, 1510, 1600, 2951. ^1H NMR (300 MHz, $CDCl_3$): δ 1.13 (9H, s), 1.73 (2H, quintet, J = 7.2 Hz), 1.89−2.06 (1H, m), 2.10−2.24 (1H, m), 3.53 (2H, t, J = 6.6 Hz), 3.78 (3H, s), 3.79 (3H, s), 4.53 (1H, t, J = 7.7 Hz), 6.80−6.88 (2H, m), 7.24−7.30 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.9, 30.4, 30.6, 44.7, 47.0, 54.5, 55.3, 56.1, 114.2 (2C), 129.4 (2C), 130.6, 159.0, 175.5. MS (ES, pos. mode) m/z (%): 360/362 (M + H^+, 100). Anal. calcd for $C_{17}H_{26}ClNO_3S$: C 56.73; H 7.28; N 3.89. Found: C 56.48; H 7.02; N 3.70.

Synthesis of 2-Substituted *N-tert*-Butanesulfinyl-5-chloropentylamines 5. The synthesis of (R_s,*R*)-*N-tert*-butanesulfinyl-5-chloro-2-methylpentylamine (R_s,*R*)-**5a** is representative. To a solution of (R_s,*R*)-methyl *N-tert*-butanesulfinyl-5-chloro-2-methylpentanimidate (R_s,*R*)-**2a** (1.0 equiv, 1.50 g, 5.61 mmol) in THF (30 mL) was added methanol (10.0 equiv, 1.80 g, 56.10 mmol), followed by $NaBH_4$ (5.0 equiv, 1.06 g, 28.05 mmol). The resulting solution was stirred for 1 h at reflux temperature and subsequently poured into a saturated aqueous solution of $NaHCO_3$ (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated in vacuo. The crude product was purified by flash chromatography to yield 1.05 g (4.39 mmol) of pure (R_s,*R*)-*N-tert*-butanesulfinyl-5-chloro-2-methylpentylamine (R_s,*R*)-**5a**. *N-tert*-butanesulfinyl-5-chloropentylamines (R_s,*R*)-**5d-f** were purified by recrystallization from diethyl ether.

(R_s,*R*)-*N-tert*-Butanesulfinyl-5-chloro-2-methylpentylamine (R_s,*R*)-5a. R_f = 0.26 (petroleum ether/EtOAc 2:8). Yellow crystals, yield 78%. Mp 54.1−55.2 °C. $[\alpha]_D$ −49.6 (c 1.1, $CHCl_3$). IR (cm^{-1}): ν_{max} 1052, 1458, 2870, 2926, 2956, 3209. ^1H NMR (300 MHz, $CDCl_3$): δ 0.94 (3H, d, J = 6.6 Hz), 1.21−1.39 and 1.50−1.92 (5H, m), 1.23 (9H, s), 2.92−3.11 (2H, m), 3.23 (1H, t, J = 6.6 Hz), 3.54 (2H, t, J = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.6, 22.7, 29.9, 31.3, 34.0, 45.3, 51.6, 55.8. MS (ES, pos. mode) m/z (%): 240/242 (M + H^+, 100). Anal. calcd for $C_{10}H_{22}ClNOS$: C 50.09; H 9.25; N 5.84. Found: C 49.72; H 9.55; N 5.69.

(R_s,*S*)-*N-tert*-Butanesulfinyl-5-chloro-2-methylpentylamine (R_s,*S*)-5a. R_f = 0.33 (petroleum ether/EtOAc 3:7). Yellow oil, yield 72%. $[\alpha]_D$ −58.4 (c 1.5, $CHCl_3$). IR (cm^{-1}): ν_{max} 1053, 1458, 2868, 2925, 2954, 3199. ^1H NMR (300 MHz, $CDCl_3$): δ 0.95 (3H, d, J = 7.2 Hz), 1.17−1.33 and 1.50−1.89 (5H, m), 1.23 (9H, s), 2.84−2.96 (1H, m), 3.12−3.21 (1H, m), 3.13 (1H, t, J = 5.5 Hz), 3.53 (2H, t, J = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.6, 22.7, 30.0, 31.4, 34.0, 45.3, 51.5, 55.9. MS (ES, pos. mode) m/z (%): 240/242 (M + H^+, 100). Anal. calcd for $C_{10}H_{22}ClNOS$: C 50.09; H 9.25; N 5.84. Found: C 49.83; H 9.11; N 5.52.

(R_s)-*N-tert*-Butanesulfinyl-5-chloro-2-ethylpentylamine (R_s)-5b. R_f = 0.29 (petroleum ether/EtOAc 3:7). Colorless oil, yield 93%. The diastereomers **5b** could not be separated via flash chromatography resulting in **5b** (93%, dr 67/33). The spectral data of (R_s,*R*)-**5b** and (R_s,*S*)-**5b** were obtained from the mixture of diastereomers **5b** (dr 67/33). IR (cm^{-1}): ν_{max} 1052, 1459, 2972, 2927, 2958, 3209. ^1H NMR (300 MHz, $CDCl_3$): (R_s,*R*)-**5b** δ 0.90 (3H, t, J = 7.2 Hz), 1.22 (9H, s), 1.23−1.55 and 1.70−1.84 (7H, m), 2.90−3.06 (1H, m), 3.10−3.25 (2H, m), 3.54 (2H, t, J = 6.6 Hz); (R_s,*S*)-**5b** δ 0.87 (3H, t, J = 6.6 Hz), 1.22 (9H, s), 1.23−1.55 and 1.70−1.84 (7H, m), 2.90−3.06 (1H, m), 3.10−3.25 (2H, m), 3.54 (2H, t, J = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): (R_s,*R*)-**5b** δ 10.9, 22.7, 24.0, 28.3, 29.6, 40.1, 45.4, 48.4, 55.8; (R_s,*S*)-**5b** δ 10.8, 22.7, 24.0, 28.2, 29.7, 40.0, 45.4, 48.2, 55.8. MS (ES, pos. mode) m/z (%): 254/256 (M + H^+, 100). Anal. calcd for $C_{11}H_{24}ClNOS$: C 52.05; H 9.53; N 5.52. Found: C 52.17; H 9.35; N 5.67.

(R_s)-*N-tert*-Butanesulfinyl-5-chloro-2-propylpentylamine (R_s)-5c. R_f = 0.27 (petroleum ether/EtOAc 3:7). Colorless oil, yield 97%. The diastereomers **5c** could not be separated via flash chromatography resulting in **5c** (97%, dr 71/29). The spectral data of (R_s,*R*)-**5c** and (R_s,*S*)-**5c** were obtained from the mixture of diastereomers **5c** (dr 71/29). IR (cm^{-1}): ν_{max} 1052, 1457, 2870, 2926, 2956, 3210. ^1H NMR (300 MHz, $CDCl_3$): (R_s,*R*)-**5c** and (R_s,*S*)-**5c** δ 0.90 (3H, t, J = 6.6 Hz), 1.16−1.86 (9H, m), 1.22 (9H, s), 2.89−3.05 (1H, m), 3.10−3.23 (2H, m), 3.53 (2H, t, J = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): (R_s,*R*)-**5c** δ 14.4, 19.8, 22.7, 28.8, 29.6, 33.8, 38.3, 45.4, 48.7, 55.9; (R_s,*S*)-**5c** δ 14.3, 19.7, 22.7, 28.7, 29.7, 33.8, 38.3, 45.4, 48.5, 55.9. MS (ES, pos. mode) m/z (%): 268/270 (M + H^+, 100). Anal. calcd for $C_{12}H_{26}ClNOS$: C 53.81; H 9.78; N 5.23. Found: C 53.59; H 9.63; N 5.02.

(R_s,*R*)-*N-tert*-Butanesulfinyl-5-chloro-2-phenylpentylamine (R_s,*R*)-5d. White crystals, yield 90% (96% purity). Mp 66.7−66.9 °C. $[\alpha]_D$ −19.5 (c 0.3, $CHCl_3$). IR (cm^{-1}): ν_{max} 1040, 1454, 2930, 3187. ^1H NMR (300 MHz, $CDCl_3$): δ 1.09 (9H, s), 1.56−1.81 (3H, m), 1.83−1.95 (1H, m), 2.81−2.93 (1H, m), 3.13 (1H, t, J = 6.6 Hz), 3.18−3.29 (1H, m), 3.39−3.51 (3H, m), 7.15−7.37 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.6, 30.3, 30.4, 45.0, 46.8, 52.0, 55.9, 127.0, 128.2 (2C), 128.8 (2C), 141.7. MS (ES, pos. mode) m/z (%): 302/304 (M + H^+, 100).

(R_s,*S*)-*N*-*tert*-Butanesulfinyl-5-chloro-2-phenylpentylamine (R_s,*S*)-5d. R_f=0.44 (petroleum ether/EtOAc 3:7). Yellow oil, yield 99%. $[\alpha]_D$ −40.7 (c 0.2, $CHCl_3$). IR (cm^{-1}): ν_{max} 731, 1055, 1454, 2957, 3220. ^1H NMR (300 MHz, $CDCl_3$): δ 1.12 (9H, s), 1.56−1.79 (3H, m), 1.84−1.98 (1H, m), 2.72−2.83 (1H, m), 3.11 (1H, d × d, J = 8.3, 5.0 Hz), 3.23−3.41 (2H, m), 3.47 (2H, t, J = 6.4 Hz), 7.21−7.37 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.7, 30.3, 30.7, 45.0, 46.8, 51.1, 55.8, 127.2, 128.0 (2C), 128.9 (2C), 141.7. MS (ES, pos. mode) m/z (%): 302/304 ($M + H^+$, 100). Anal. calcd for $C_{15}H_{24}ClNOS$: C 59.68; H 8.01; N 4.64. Found: C 59.77; H 8.15; N 4.39.

(R_s,*R*)-*N*-*tert*-Butanesulfinyl-5-chloro-2-(4-fluorophenyl)pentylamine (R_s,*R*)-5e. White crystals, yield 99%. Mp 94.3−94.6 °C. $[\alpha]_D$ −19.2 (c 0.4, $CHCl_3$). IR (cm^{-1}): ν_{max} 816, 1040, 1222, 1508, 2928, 3178. ^1H NMR (300 MHz, $CDCl_3$): δ 1.09 (9H, s), 1.53−1.76 (3H, m), 1.82−1.94 (1H, m), 2.82−2.94 (1H, m), 3.08−3.25 (2H, m), 3.38−3.44 (1H, m), 3.48 (2H, t, J = 6.1 Hz), 6.97−7.07 (2H, m), 7.13−7.20 (2H, m). ^{19}F NMR (282 MHz, $CDCl_3$): δ −115.71 to −115.81 (1F, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.6, 30.3, 30.6, 44.9, 46.2, 52.1, 55.9, 115.6 (2C, d, J = 21.9 Hz), 129.7 (2C, d, J = 6.9 Hz), 137.3 (d, J = 2.3 Hz), 161.8 (d, J = 244.6 Hz). MS (ES, pos. mode) m/z (%): 320/322 ($M + H^+$, 100). Anal. calcd for $C_{15}H_{23}ClFNOS$: C 56.32; H 7.25; N 4.38. Found: C 56.41; H 7.39; N 4.27.

(R_s,*S*)-*N*-*tert*-Butanesulfinyl-5-chloro-2-(4-fluorophenyl)pentylamine (R_s,*S*)-5e. R_f = 0.42 (petroleum ether/EtOAc 3:7). Yellow oil, yield 93%. $[\alpha]_D$ −60.2 (c 0.3, $CHCl_3$). IR (cm^{-1}): ν_{max} 754, 834, 1055, 1223, 1509, 2926, 3218. ^1H NMR (300 MHz, $CDCl_3$): δ 1.13 (9H, s), 1.52−1.75 (3H, m), 1.83−1.97 (1H, m), 2.73−2.85 (1H, m), 3.13 (1H, d × d, J = 7.7, 5.5 Hz), 3.22−3.38 (2H, m), 3.47 (2H, t, J = 6.1 Hz), 6.97−7.06 (2H, m), 7.09−7.16 (2H, m). ^{19}F NMR (282 MHz, $CDCl_3$): δ −115.39 to −115.49 (1F, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.6, 30.2, 30.8, 44.9, 46.0, 51.1, 55.9, 115.7 (2C, d, J = 21.9 Hz), 129.3 (2C, d, J = 8.1 Hz), 137.4 (d, J = 3.5 Hz), 161.8 (d, J = 245.8 Hz). MS (ES, pos. mode) m/z (%): 320/322 ($M + H^+$, 100). Anal. calcd for $C_{15}H_{23}ClFNOS$: C 56.32; H 7.25; N 4.38. Found: C 56.01; H 6.97; N 4.22.

(R_s,*R*)-*N*-*tert*-Butanesulfinyl-5-chloro-2-(4-methoxyphenyl)-pentylamine (R_s,*R*)-5f. Yellow crystals, yield 99% (95% purity). Mp 80.2−80.7 °C. $[\alpha]_D$ −17.8 (c 0.4, $CHCl_3$). IR (cm^{-1}): ν_{max} 812, 1039, 1245, 1513, 2926, 3200. ^1H NMR (300 MHz, $CDCl_3$): δ 1.10 (9H, s), 1.57−1.77 (3H, m), 1.79−1.93 (1H, m), 2.78−2.96 (1H, m), 3.05−3.28 (2H, m), 3.36−3.44 (1H, m), 3.47 (2H, t, J = 6.1 Hz), 3.80 (3H, s), 6.82−6.93 (2H, m), 7.06−7.16 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.6, 30.3, 30.5, 45.1, 46.0, 52.2, 55.3, 55.9, 114.2 (2C), 129.2 (2C), 133.5, 158.5. MS (ES, pos. mode) m/z (%): 332/334 ($M + H^+$, 100).

Synthesis of 3-Substituted *N*-*tert*-Butanesulfinylpiperidines 6. The synthesis of (R_s,*R*)-*N*-*tert*-butanesulfinyl-3-methylpiperidine (**R_s,*R*)-6a** is representative. To sodium hydride (2.5 equiv, 0.25 g, 10.44 mmol) was added DMSO (5 mL) and the mixture was stirred at room temperature for 15 min. Subsequently, a solution of (R_s,*R*)-*N*-*tert*-butanesulfinyl-5-chloro-2-methylpentylamine (**R_s,*R*)-5a** (1.0 equiv, 1.00 g, 4.18 mmol) in DMSO (3 mL) was added dropwise and the reaction mixture was stirred for 2 h at 80 °C. After cooling to room temperature, the reaction mixture was poured into water (10 mL) and extracted with diethyl ether (3 × 15 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), filtered and evaporated in vacuo. The crude product was purified by flash chromatography to yield 0.83 g (4.09 mmol) of pure (R_s,*R*)-*N*-*tert*-butanesulfinyl-3-methylpiperidine (**R_s,*R*)-6a**.

(R_s,*R*)-*N*-*tert*-Butanesulfinyl-3-methylpiperidine (R_s,*R*)-6a. R_f = 0.35 (petroleum ether/Et_2O 3:7). Yellow oil, yield 98%. $[\alpha]_D$ −11.0 (c 1.0, $CHCl_3$). IR (cm^{-1}): ν_{max} 750, 1069, 1457, 2928, 2951. ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (3H, d, J = 6.6 Hz), 0.90−1.11 and 1.52−1.83 (5H, m), 1.17 (9H, s), 2.32 (1H, d × d, J = 12.7, 10.5 Hz), 2.83 (1H, t × d, J = 11.8, 2.9 Hz), 3.26−3.36 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.3, 23.2, 26.1, 31.3, 33.0, 48.1, 53.7, 58.4. MS (ES, pos. mode) m/z (%): 204 ($M + H^+$, 100). Anal. calcd for $C_{10}H_{21}NOS$: C 59.07; H 10.41; N 6.89. Found: C 58.79; H 10.61; N 6.67.

(R_s,*S*)-*N*-*tert*-Butanesulfinyl-3-methylpiperidine (R_s,*S*)-6a. R_f = 0.25 (petroleum ether/Et_2O 3:7). Yellow oil, yield 99%. $[\alpha]_D$ +6.2 (c 1.2, $CHCl_3$). IR (cm^{-1}): ν_{max} 750, 1072, 1458, 2849, 2927. ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (3H, d, J = 6.6 Hz), 0.92−1.10 and 1.46−1.84 (5H, m), 1.17 (9H, s), 2.52 (1H, d × d, J = 11.4, 10.5 Hz), 2.65 (1H, t × d, J = 12.3, 3.3 Hz), 3.26−3.38 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.3, 23.3, 25.5, 31.9, 33.0, 46.6, 55.3, 58.4. MS (ES, pos. mode) m/z (%): 204 ($M + H^+$, 100). Anal. calcd for $C_{10}H_{21}NOS$: C 59.07; H 10.41; N 6.89. Found: C 59.25; H 10.56; N 6.96.

(R_s)-*N*-*tert*-Butanesulfinyl-3-ethylpiperidine (R_s)-6b. R_f = 0.42 (petroleum ether/Et_2O 3:7). Colorless oil, yield 99%. The diastereomers **6b** could not be separated via flash chromatography resulting in **6b** (99%, dr 67/33). The spectral data of (**R_s,*R*)-6b** and (**R_s,*S*)-6b** were obtained from the mixture of diastereomers **6b** (dr 67/33). IR (cm^{-1}): ν_{max} 1077, 1458, 2854, 2929. ^1H NMR (300 MHz, $CDCl_3$): (**R_s,*R*)-6b** δ 0.89 (3H, t, J = 7.2 Hz), 0.92−1.90 (7H, m), 1.17 (9H, s), 2.31 (1H, d × d, J = 12.4, 10.5 Hz), 2.87 (1H, t × d, J = 11.8, 3.3 Hz), 3.28−3.43 (2H, m); (**R_s,*S*)-6b** δ 0.89 (3H, t, J = 7.2 Hz), 0.92−1.90 (7H, m), 1.17 (9H, s), 2.54 (1H, d × d, J = 12.4, 10.5 Hz), 2.65 (1H, t × d, J = 11.8, 3.3 Hz), 3.28−3.43 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$): (**R_s,*R*)-6b** δ 11.3, 23.3, 26.1, 26.8, 31.0, 38.2, 48.9, 52.0, 58.4; (**R_s,*S*)-6b** δ 11.3, 23.3, 25.4, 26.8, 30.6, 38.5, 46.7, 54.2, 58.4. MS (ES, pos. mode) m/z (%): 218 ($M + H^+$, 100). Anal. calcd for $C_{11}H_{23}NOS$: C 60.78; H 10.66; N 6.44. Found: C 60.64; H 10.43; N 6.22.

(R_s)-*N*-*tert*-Butanesulfinyl-3-propylpiperidine (R_s)-6c. R_f = 0.42 (petroleum ether/Et_2O 3:7). Colorless oil, yield 96%. The diastereomers **6c** could not be separated via flash chromatography resulting in **6c** (96%, dr 71/29). The spectral data of (**R_s,*R*)-6c** and (**R_s,*S*)-6c** were obtained from the mixture of diastereomers **6c** (dr 71/29). IR (cm^{-1}): ν_{max} 1078, 1457, 2920. ^1H NMR (300 MHz, $CDCl_3$): (**R_s,*R*)-6c** δ 0.89 (3H, t, J = 7.2 Hz), 0.93−1.87 (9H, m), 1.17 (9H, s), 2.31 (1H, d × d, J = 12.4, 10.5 Hz), 2.86 (1H, t × d, J = 11.8, 3.3 Hz), 3.27−3.41 (2H, m); (**R_s,*S*)-6c** δ 0.89 (3H, t, J = 7.2 Hz), 0.93−1.87 (9H, m), 1.17 (9H, s), 2.54 (1H, d × d, J = 11.6, 10.5 Hz), 2.65 (1H, t × d, J = 12.4, 3.3 Hz), 3.27−3.41 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$): (**R_s,*R*)-6c** δ 14.3, 19.9, 23.3, 26.2, 31.3, 36.2, 36.3, 48.8, 52.3, 58.4; (**R_s,*S*)-5c** δ 14.3, 19.9, 23.3, 25.5, 31.1, 36.3, 36.6, 46.7, 54.5, 58.4. MS (ES, pos. mode) m/z (%): 232 ($M + H^+$, 100). Anal. calcd for $C_{12}H_{25}NOS$: C 62.29; H 10.89; N 6.05. Found: C 62.15; H 10.63; N 5.97.

(R_s,*R*)-*N*-*tert*-Butanesulfinyl-3-phenylpiperidine (R_s,*R*)-6d. R_f = 0.49 (petroleum ether/Et_2O 3:7). Colorless oil, yield 86%. $[\alpha]_D$ +25.8 (c 0.2, $CHCl_3$). IR (cm^{-1}): ν_{max} 697, 757, 944, 1073, 1360, 1454, 2929. ^1H NMR (300 MHz, $CDCl_3$): δ 1.17 (9H, s), 1.50−1.86 and 1.93−2.06 (4H, m), 2.67−2.85 (2H, m), 2.92 (1H, t × d, J = 11.6, 2.2 Hz), 3.38−3.57 (2H, m), 7.13−7.34 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.2, 25.8, 31.6, 43.6, 46.9, 54.4, 58.6, 126.7, 127.2 (2C), 128.6 (2C), 143.7. MS (ES, pos. mode) m/z (%): 266 ($M + H^+$, 100). Anal. calcd for $C_{15}H_{23}NOS$: C 67.88; H 8.73; N 5.28. Found: C 67.71; H 8.58; N 5.09.

(R_s,*S*)-*N*-*tert*-Butanesulfinyl-3-phenylpiperidine (R_s,*S*)-6d. R_f = 0.41 (petroleum ether/Et_2O 3:7). Yellow oil, yield 93%. $[\alpha]_D$ −37.9 (c 0.2, $CHCl_3$). IR (cm^{-1}): ν_{max} 698, 757, 949, 1072, 1454, 2856, 2929. ^1H NMR (300 MHz, $CDCl_3$): δ 1.18 (9H, s), 1.54−1.84 and 1.98−2.08 (4H, m), 2.78 (1H, t × d, J = 11.0, 8.8 Hz), 2.79−2.84 (1H, m), 2.92 (1H, t × d, J = 12.1, 3.3 Hz), 3.46−3.55 (2H, m), 7.13−7.36 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.2, 26.6, 31.8, 43.1, 47.6, 53.6, 58.6, 126.8, 127.1 (2C), 128.6 (2C), 143.6. MS (ES, pos. mode) m/z (%): 266 ($M + H^+$, 100). Anal. calcd for $C_{15}H_{23}NOS$: C 67.88; H 8.73; N 5.28. Found: C 67.97; H 8.89; N 5.22.

(R_s,R)-*N*-*tert*-Butanesulfinyl-3-(4-fluorophenyl)piperidine (R_s,R)-6e. R_f = 0.36 (petroleum ether/Et_2O 3:7). Yellow oil, yield 99%. $[\alpha]_D$ +18.3 (c 0.6, $CHCl_3$). IR (cm^{-1}): ν_{max} 751, 833, 1070, 1221, 1510, 2933. ^1H NMR (300 MHz, $CDCl_3$): δ 1.18 (9H, s), 1.56 (1H, q × d, J = 12.1, 3.9 Hz), 1.67−1.87 (2H, m), 1.94−2.05 (1H, m), 2.71−2.92 (3H, m), 3.40−3.55 (2H, m), 6.94−7.04 (2H, m), 7.13−7.21 (2H, m). ^{19}F NMR (282 MHz, $CDCl_3$): δ −116.20 to −116.30 (1F, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.2, 25.8, 31.8, 42.9, 47.0, 54.2, 58.7, 115.3 (2C, d, J = 20.8 Hz), 128.6 (2C, d, J = 8.1 Hz), 139.3 (d, J = 3.5 Hz), 161.7 (d, J = 244.6 Hz). MS (ES, pos. mode) m/z (%): 284 ($M + H^+$, 100). Anal. calcd for $C_{15}H_{22}FNOS$: C 63.57; H 7.82; N 4.94. Found: C 63.72; H 7.99; N 4.97.

(R_s,S)-*N*-*tert*-Butanesulfinyl-3-(4-fluorophenyl)piperidine (R_s,S)-6e. R_f = 0.33 (petroleum ether/Et_2O 3:7). Yellow oil, yield 82%. $[\alpha]_D$ −44.0 (c 0.3, $CHCl_3$). IR (cm^{-1}): ν_{max} 833, 1072, 1221, 1510, 2868, 2932. ^1H NMR (300 MHz, $CDCl_3$): δ 1.18 (9H, s), 1.56 (1H, q × d, J = 11.6, 3.9 Hz), 1.65−1.86 (2H, m), 1.96−2.05 (1H, m), 2.74 (1H, t × d, J = 11.6, 11.6 Hz), 2.75−2.86 (1H, m), 2.92 (1H, t × d, J = 12.0, 3.0 Hz), 3.43−3.54 (2H, m), 6.93−7.03 (2H, m), 7.10−7.19 (2H, m). ^{19}F NMR (282 MHz, $CDCl_3$): δ −116.15 to −116.25 (1F, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.2, 26.5, 31.9, 42.4, 47.6, 53.6, 58.6, 115.4 (2C, d, J = 20.8 Hz), 128.5 (2C, d, J = 6.9 Hz), 139.3 (d, J = 3.5 Hz), 161.7 (d, J = 244.6 Hz). MS (ES, pos. mode) m/z (%): 284 ($M + H^+$, 100). Anal. calcd for $C_{15}H_{22}FNOS$: C 63.57; H 7.82; N 4.94. Found: C 63.59; H 7.79; N 4.89.

(R_s,R)-*N*-*tert*-Butanesulfinyl-3-(4-methoxyphenyl)piperidine (R_s,R)-6f. R_f = 0.28 (petroleum ether/Et_2O 3:7). Yellow crystals, yield 92%. Mp 71.4−71.6 °C. $[\alpha]_D$ +30.4 (c 0.4, $CHCl_3$). IR (cm^{-1}): ν_{max} 751, 828, 1037, 1071, 1245, 1513, 2852, 2932. ^1H NMR (300 MHz, $CDCl_3$): δ 1.18 (9H, s), 1.56 (1H, q × d, J = 12.1, 3.9 Hz), 1.65−1.85 (2H, m), 1.94−2.03 (1H, m), 2.68−2.81 (2H, m), 2.85 (1H, t × d, J = 11.6, 11.6 Hz), 3.41−3.54 (2H, m), 3.78 (3H, s), 6.81−6.88 (2H, m), 7.10−7.17 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.3, 25.8, 31.8, 42.7, 46.8, 54.7, 55.3, 58.6, 114.0 (2C), 128.1 (2C), 135.8, 158.4. MS (ES, pos. mode) m/z (%): 296 ($M + H^+$, 100). Anal. calcd for $C_{16}H_{25}NO_2S$: C 65.05; H 8.53; N 4.74. Found: C 64.88; H 8.26; N 4.58.

Synthesis of (R_s,R)-*N*-*tert*-butanesulfinyl-2-methylpentylamine (R_s,R)-7. To a solution of (R_s,R)-methyl *N*-*tert*-butanesulfinyl-5-chloro-2-methylpentanimidate (**R_s,R)-2a** (97% purity, 3% **3a**) (1.0 equiv, 0.30 g, 1.12 mmol) in THF (6 mL) was added methanol (20.0 equiv, 0.72 g, 22.44 mmol), followed by $NaBH_4$ (10.0 equiv, 0.42 g, 11.22 mmol). The resulting solution was stirred for 17 h at reflux temperature and subsequently poured into a saturated aqueous solution of $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated in vacuo. The crude product was purified by flash chromatography to yield 0.13 g (0.63 mmol) of (R_s,R)-*N*-*tert*-butanesulfinyl-2-methylpentylamine (**R_s,R)-7** (96% purity).

(R_s,R)-*N*-*tert*-Butanesulfinyl-2-methylpentylamine (R_s,R)-7. R_f = 0.09 (petroleum ether/EtOAc 4:6). Colorless oil, yield 56% (96% purity). $[\alpha]_D$ −55.4 (c 0.9, $CHCl_3$). IR (cm^{-1}): ν_{max} 1053, 1458, 2871, 2927, 2955, 3204. ^1H NMR (300 MHz, $CDCl_3$): δ 0.84−0.95 (3H, m), 0.91 (3H, d, J = 6.6 Hz), 1.04−1.17 (2H, m), 1.22 (9H, s), 1.24−1.43 (2H, m), 1.57−1.70 (1H, m), 2.92−3.06 (2H, m), 3.23 (1H, t, J = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3, 17.6, 19.9, 22.7, 34.1, 36.4, 51.7, 55.7. MS (ES, pos. mode) m/z (%): 206 ($M + H^+$, 100).

Synthesis of (*R*)-2-Methylpentylamine Hydrochloride (*R*)-8. To a solution of (R_s,R)-*N*-*tert*-butanesulfinyl-2-methylpentylamine (**R_s,R)-7** (96% purity) (0.10 g, 0.49 mmol) in diethyl ether (2 mL) was added dropwise a 4.0 M solution of dioxane·HCl (10.0 equiv, 1.22 mL, 4.88 mmol) at room temperature. The mixture was allowed to stir for 1 h. Then the reaction mixture was concentrated in vacuo. Precipitation in diethyl ether afforded 0.055 g (0.40 mmol) of (*R*)-2-methylpentylamine hydrochloride (**(*R*)-8** (96% purity).

(*R*)-2-Methylpentylamine Hydrochloride (*R*)-8. White crystals, yield 82% (96% purity). Mp 137.2−137.5 °C. $[\alpha]_D$ +5.7 (c 0.3, MeOH). IR (cm^{-1}): ν_{max} 1509, 1610, 2972, 2913, 2957, 2993. ^1H NMR (300 MHz, $CDCl_3$): δ 0.90 (3H, t, J = 6.6 Hz), 1.06 (3H, d, J = 6.6 Hz), 1.14−1.47 (4H, m), 1.82−1.97 (1H, m), 2.66−2.82 (1H, m), 2.87−3.02 (1H, m), 8.34 (3H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 17.5, 19.7, 31.5, 36.2, 45.6. MS (ES, pos. mode) m/z (%): 102 ($M + H^+$ − HCl, 100).

Synthesis of 3-Substituted Piperidine Hydrochlorides 9. The synthesis of (*R*)-3-methylpiperidine hydrochloride (**(*R*)-9a** is representative. To a solution of (R_s,R)-*N*-*tert*-butanesulfinyl-3-methylpiperidine (**R_s,R)-6a** (0.50 g, 2.46 mmol) in diethyl ether (10 mL) was added dropwise a 4.0 M solution of dioxane·HCl (10.0 equiv, 6.16 mL, 24.63 mmol) at room temperature. The mixture was allowed to stir for 1 h. Then the reaction mixture was concentrated in vacuo. Precipitation in diethyl ether afforded 0.32 g (2.39 mmol) of pure (*R*)-3-methylpiperidine hydrochloride (**(*R*)-9a**.

(*R*)-3-Methylpiperidine Hydrochloride (*R*)-9a. White crystals, yield 97%. Mp 192.8−193.0 °C. $[\alpha]_D$ (**(*R*)-9a** +3.0 (c 0.9, MeOH) vs (**(*S*)-9a** −3.0 (c 0.6, MeOH) in lit.[5i] IR (cm^{-1}): ν_{max} 1453, 2422, 2536, 2763, 2871, 2934. ^1H NMR (300 MHz, $CDCl_3$): δ 0.97 (3H, d, J = 6.6 Hz), 1.02−1.20 (1H, m), 1.79−2.03 (3H, m), 2.03−2.20 (1H, m), 2.46 (1H, t × d, J = 11.6, 11.6 Hz), 2.76 (1H, t × d, J = 11.0, 11.0 Hz), 3.36 (1H, d, J = 12.1 Hz), 3.44 (1H, d, J = 12.7 Hz), 9.37 (1H, br s), 9.55 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.0, 22.2, 28.5, 31.0, 43.9, 50.3. MS (ES, pos. mode) m/z (%): 100 ($M + H^+$ − HCl, 100). Anal. calcd for $C_6H_{14}ClN$: C 53.13; H 10.40; N 10.33. Found: C 53.47; H 10.72; N 10.63. **(*R*)-9a** is a known compound in literature, but no spectral data were available.[5f,23]

(*S*)-3-Methylpiperidine Hydrochloride (*S*)-9a. White crystals, yield 66%. Mp 193.1−193.3 °C. $[\alpha]_D$ −2.6 (c 0.5, MeOH) vs −3.0 (c 0.6, MeOH) in lit.[5i,l] ^1H NMR (300 MHz, $CDCl_3$): δ 0.97 (3H, d, J = 6.6 Hz), 1.02−1.19 (1H, m), 1.78−2.20 (4H, m), 2.45 (1H, t × d, J = 11.6, 11.0 Hz), 2.75 (1H, t × d, J = 11.0, 11.0 Hz), 3.36 (1H, d, J = 12.1 Hz), 3.44 (1H, d, J = 12.1 Hz), 9.38 (1H, br s), 9.59 (1H, br s). Anal. calcd for $C_6H_{14}ClN$: C 53.13; H 10.40; N 10.33. Found: C 52.93; H 10.22; N 10.08. All spectroscopic data were in good agreement with reported data.[5i,l]

3-Ethylpiperidine Hydrochloride 9b. White crystals, yield 99%. Mp 147.1−147.4 °C. er 67/33 (based on dr of **6b**). ^1H NMR (300 MHz, $CDCl_3$): δ 0.92 (3H, d, J = 7.2 Hz), 0.99−1.17 (1H, m), 1.19−1.42 (2H, m), 1.79−2.07 (4H, m), 2.48 (1H, t × d, J = 11.0, 11.0 Hz), 2.76 (1H, t × d, J = 11.0, 9.9 Hz), 3.40 (1H, d, J = 13.2 Hz), 3.45 (1H, d, J = 12.2 Hz), 9.34 (1H, br s), 9.61 (1H, br s). Anal. calcd for $C_7H_{16}ClN$: C 56.18; H 10.78; N 9.36. Found: C 56.32; H 10.95; N 9.57. All spectroscopic data were in good agreement with reported data.[5e−g,11e]

3-Propylpiperidine Hydrochloride 9c. White crystals, yield 81%. Mp 122.5−122.7 °C. er 71/29 (based on dr of **6c**). IR (cm^{-1}): ν_{max} 1060, 1464, 2572, 2735, 2845, 2953. ^1H NMR (300 MHz, $CDCl_3$): δ 0.90 (3H, d, J = 7.2 Hz), 1.00−1.14 (1H, m), 1.16−1.42 (4H, m), 1.75−2.13 (4H, m), 2.46 (1H, t × d, J = 10.5, 10.5 Hz), 2.75 (1H, t × d, J = 11.0, 9.9 Hz), 3.39 (1H, d, J = 14.3 Hz), 3.44 (1H, d, J = 14.3 Hz), 9.29 (1H, br s), 9.59 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 19.4, 22.3, 29.1, 33.2, 36.0, 44.4, 49.3. MS (ES, pos. mode) m/z (%): 128 ($M + H^+$ − HCl, 100). Anal. calcd for $C_8H_{18}ClN$: C 58.70; H 11.08; N 8.56. Found: C 58.87; H 11.11; N 8.59. **9c** is a known compound in literature, but no spectral data were available.[24]

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(*R*)-3-Phenylpiperidine Hydrochloride (*R*)-9d. White crystals, yield 98%. Mp 179.2−179.5 °C. $[\alpha]_D$ −10.7 (c 0.3, MeOH) vs −10.3 (c 0.5, MeOH) in lit.[10a] ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.66 (1H, q × d, J = 12.8, 3.3 Hz), 1.94−2.25 (3H, m), 2.80−3.00 (1H, m), 2.90 (1H, t, J = 11.6 Hz), 3.26 (1H, t × m, J = 12.1 Hz), 3.47−3.62 (2H, m), 7.16−7.36 (5H, m), 9.67 (1H, br s), 9.88 (1H, br s). Anal. calcd for $C_{11}H_{16}ClN$: C 66.83; H 8.16; N 7.08. Found: C 66.96; H 8.33; N 7.06. All spectroscopic data were in good agreement with reported data.[10a]

(*S*)-3-Phenylpiperidine Hydrochloride (*S*)-9d. White crystals, yield 81%. Mp 178.2−178.4 °C. $[\alpha]_D$ +11.5 (c 0.3, MeOH) vs +12.2 (c 0.5, MeOH) in lit.[22] ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.66 (1H, q × d, J = 12.8, 3.3 Hz), 1.91−2.25 (3H, m), 2.79−3.00 (1H, m), 2.90 (1H, t, J = 11.8 Hz), 3.25 (1H, t × m, J = 12.1 Hz), 3.48−3.65 (2H, m), 7.11−7.46 (5H, m), 9.62 (1H, br s), 9.81 (1H, br s). Anal. calcd for $C_{11}H_{16}ClN$: C 66.83; H 8.16; N 7.08. Found: C 66.57; H 7.97; N 7.03. All spectroscopic data were in good agreement with reported data.[22]

(*R*)-3-(4-Fluorophenyl)piperidine Hydrochloride (*R*)-9e. White crystals, yield 91%. Mp 219.8−220.0 °C. $[\alpha]_D$ −14.7 (c 0.5, MeOH). IR (cm^{-1}): ν_{max} 840, 1212, 1511, 2705, 2926. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.54−1.75 (1H, m), 1.93−2.27 (3H, m), 2.76−3.01 (2H, m), 3.26 (1H, t, J = 11.0 Hz), 3.45−3.65 (2H, m), 6.97−7.11 (2H, m), 7.12−7.23 (2H, m), 9.66 (1H, br s), 9.87 (1H, br s). ^{19}F NMR (282 MHz, $CDCl_3$): δ −114.57 to −114.68 (1F, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.7, 30.4, 38.9, 44.0, 49.4, 115.9 (2C, d, J = 20.8 Hz), 128.5 (2C, d, J = 8.1 Hz), 136.5 (d, J = 3.5 Hz), 162.1 (d, J = 246.9 Hz). MS (ES, pos. mode) m/z (%): 180 (M + H$^+$ − HCl, 100). Anal. calcd for $C_{11}H_{15}ClFN$: C 61.25; H 7.01; N 6.49. Found: C 61.37; H 7.15; N 6.59.

(*S*)-3-(4-Fluorophenyl)piperidine Hydrochloride (*S*)-9e. White crystals, yield 99%. Mp 218.5−218.8. $[\alpha]_D$ +14.9 (c 0.3, MeOH). IR (cm^{-1}): ν_{max} 840, 1212, 1511, 2706, 2926. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55−1.72 (1H, m), 1.94−2.33 (3H, m), 2.78−2.99 (2H, m), 3.26 (1H, t, J = 11.6 Hz), 3.44−3.63 (2H, m), 7.01 (2H, t, J = 8.3 Hz), 7.17 (2H, d × d, J = 8.3, 5.5 Hz), 9.66 (1H, br s), 9.85 (1H, br s). ^{19}F NMR (282 MHz, $CDCl_3$): δ −114.59 to −114.70 (1F, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.6, 30.3, 38.8, 43.9, 49.4, 115.8 (2C, d, J = 21.9 Hz), 128.5 (2C, d, J = 8.1 Hz), 136.5 (d, J = 3.5 Hz), 162.0 (d, J = 245.8 Hz). MS (ES, pos. mode) m/z (%): 180 (M + H$^+$ − HCl, 100). Anal. calcd for $C_{11}H_{15}ClFN$: C 61.25; H 7.01; N 6.49. Found: C 61.47; H 7.22; N 6.52.

(*R*)-3-(4-Methoxyphenyl)piperidine Hydrochloride (*R*)-9f. White crystals, yield 91%. Mp 187.6−188.0. $[\alpha]_D$ −12.3 (c 0.4, MeOH). IR (cm^{-1}): ν_{max} 834, 1033, 1246, 1444, 1514, 2722, 2931. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.54−1.71 (1H, m), 1.93−2.31 (3H, m), 2.87 (2H, t × d, J = 11.6, 11.6 Hz), 3.20 (1H, t × m, J = 12.1 Hz), 3.52 (2H, t × m, J = 12.4 Hz), 3.79 (3H, s), 6.85 (2H, d, J = 8.8 Hz), 7.11 (2H, d, J = 8.8 Hz), 9.63 (1H, br s), 9.82 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.7, 30.4, 38.7, 43.9, 49.5, 55.3, 114.2 (2C), 127.9 (2C), 132.8, 158.8. MS (ES, pos. mode) m/z (%): 192 (M + H$^+$ − HCl, 100). Anal. calcd for $C_{12}H_{18}ClNO$: C 63.29; H 7.97; N 6.15. Found: C 63.42; H 8.04; N 6.22.

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Supporting Information Available: General experimental conditions and copies of ^{1}H NMR and ^{13}C NMR spectra for *N*-sulfinyl imidates **1d**−**f**, α-alkylated *N*-sulfinyl imidates **2**, (S_S)-methyl-*N*-*p*-toluenesulfinylpropanimidate (***S*$_S$)-4**, sulfinamides **5**, *N*-sulfinyl piperidines **6**, sulfinamide (***R*$_s$,*R*)-7a**, (*R*)-2-methylpentylamine hydrochloride (***R*)-8**, and piperidine hydrochlorides **9**. This material is available free of charge via the Internet at http://pubs.acs.org.