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Asymmetric Synthesis of Aziridines by Reduction of *N*-*tert*-Butanesulfinyl α-Chloro Imines

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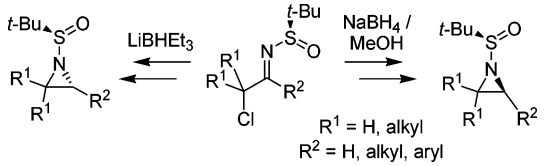

Reduction of (R_S)-*N*-*tert*-butanesulfinyl α-halo imines afforded chiral aziridines in good to excellent yields. Upon reduction of (R_S)-*N*-*tert*-butanesulfinyl α-halo imines with $NaBH_4$ in THF, in the presence of 10 equiv of MeOH, (R_S,*S*)-*β*-halo sulfinamides were formed in excellent yield (up to 98%) with very good stereoselectivity (>98:2). Simple treatment of the latter (R_S,*S*)-*β*-halo-*tert*-butanesulfinamides with KOH afforded the corresponding (R_S,*S*)-*N*-(*tert*-butylsulfinyl)aziridines in quantitative yields. On the contrary, its epimer, (R_S,*R*)-*N*-(*tert*-butylsulfinyl)aziridine was synthesized by switchover of the reducing agent from $NaBH_4$ to $LiBHEt_3$. (R_S,*R*)-*N*-(*tert*-Butylsulfinyl)aziridines were synthesized in good yields (up to 85%) and diastereoselectivity (up to 92:8) by reduction of (R_S)-*N*-*tert*-butanesulfinyl α-halo imines with $LiBHEt_3$ in dry THF and subsequent treatment with KOH. All chiral aziridines were obtained as a single diastereomer after recrystallization (overall yield up to 91%) or after flash chromatography.

Introduction

Aziridines are versatile synthetic intermediates for the synthesis of a variety of attractive compounds via regio- and stereoselective ring opening reaction with nucleophiles.[1] In recent years chiral aziridines have received an increasing amount of attention since they are key substrates in the synthesis of a number of useful alkaloids, amino acids, or *β*-lactam antibiotics or are used as chiral auxiliaries and ligands.[1,2] Noteworthy, while the synthesis of aziridines has been well described, the stereoselective synthesis remains more limited.[1,2] Main routes toward chiral aziridines include an asymmetric aza-Darzens reaction,[3] stereoselective nitrene addition to olefins,[4] asymmetric additions to azirines,[5] or aza-Payne rearrangement of 2,3-epoxy amines.[6] Also the chiral aziridine synthesis starting from *N*-sulfinyl imines has proven to be a good alternative to known procedures.[7−10] Activation of the imino function by a chiral *N*-sulfinyl group is borne out in high yields and diastereoselectivities of the aziridines synthesized. Diverse strategies, utilizing the Corey−Chaykovsky-type reaction with sulfur or tellurium ylides,[7] the aza-Darzens-type addition with α-halo enolates,[8] or allenylzinc

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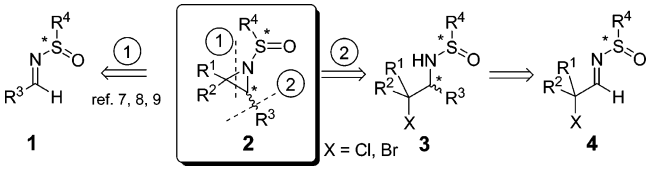
SCHEME 1. Asymmetric Aziridine Synthesis from *N*-Sulfinyl Imines

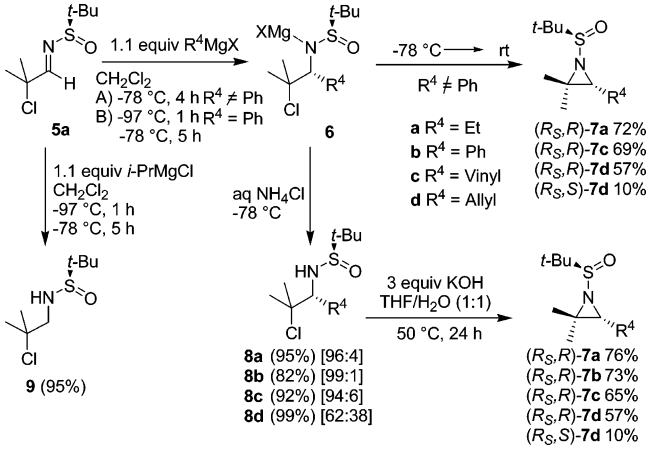


reactions[9] with nonfunctionalized *N*-sulfinyl imines are described to afford chiral aziridines. As a result, the nucleophile is incorporated as part of the backbone of the ring (Scheme 1, pathway 1).

Via an alternative strategy, the stereoselective aziridine synthesis has already been described by us, starting from *N*-sulfinyl α-halo aldimines **4** (Scheme 1, pathway 2).[10] Given the interest in and synthetic potential of α-halo imines[11] in combination with the enhanced reactivity of *N*-sulfinyl imines reported by Davis[12] and Ellman,[13] a more profound research of *N*-sulfinyl α-halo ketimines is highly desirable. The simple synthesis of *N*-sulfinyl α-halo imines **4** and the subsequent cyclization after an addition reaction, toward aziridines **2**, make the α-halo imino moiety an interesting building block. Needless to say, the chemistry of such imines might differ substantially from that of nonfunctionalized *N*-sulfinyl imines by virtue of other possible reactions, e.g., substitution, dehydrohalogenation, enhanced reactivity, etc.

Upon Grignard addition (EtMgBr, PhMgCl, vinyl-MgBr) to *N*-*tert*-butanesulfinyl α-chloro aldimine **5a**, *N*-(*tert*-butylsulfinyl)aziridines **7** have been synthesized in good to excellent yield with high stereoselectivity (Scheme 2),[10] though it has to be reported that the steric bulk of both the substrate and Grignard reagent, in combination with its electronic properties, had its limitations. For example, *N*-sulfinyl α-chloro aldimine **5a** was

SCHEME 2. Aziridine Synthesis from *N*-*tert*-Butanesulfinyl α-Chloro Aldimine 5a



reduced to β-chloro sulfinamide **9** at −78 °C in CH_2Cl_2 if 1.1 equiv of *i*-PrMgCl was added at −97 °C.[10] The addition of PhMgCl to *N*-*tert*-butanesulfinyl α-chloro aldimine **5a** in CH_2Cl_2 afforded 2-phenylaziridine **7b** only when performed at well-controlled reaction conditions to avoid competitive side reactions (Scheme 2).

Therefore, it was considered that the steric hindrance could be anticipated by reduction of *N*-*tert*-butanesulfinyl α-halo ketimines followed by ring closure of the resulting β-halo sulfinamide intermediates in a complementary, simple, and straightforward strategy. For many synthetic targets a ketone precursor is readily accessible. The hydride addition to nonfunctionalized *N*-sulfinyl imines has been described to proceed in high yields and with excellent diastereofacial control in some cases.[14] At the start of our research a thoroughly elaborated study of hydride addition across *N*-sulfinyl imines seemed to be lacking in the literature, yet very recently a profound study of hydride reduction of nonfunctionalized *N*-sulfinyl imines toward chiral secondary amines has been reported,[15] but the reduction of functionalized *N*-sulfinyl imines and *N*-sulfinyl α-halo imines specifically, allowing further elaboration after reaction, was not incorporated. This study will fill this gap by the development of a synthetic method for chiral aziridines from *N*-*tert*-butanesulfinyl α-halo ketimines.

Results and Discussion

New *N*-*tert*-butanesulfinyl α-halo imines (R_S)-**5** and -**12** were prepared by condensation of α-halo ketones (1−1.1 equiv) or α-chloro aldehydes (1.05 equiv) with (R_S)-*tert*-butanesulfinamide in the presence of 2 equiv of $Ti(OEt)_4$ in 82−92% yield (the reaction conditions and yields are reported in the Supporting Information).

As compared to the hydride reduction of nonfunctionalized *N*-sulfinyl imines, the incorporation of a vicinal chlorine atom next to the imino bond was expected to influence the reaction rate of the reduction reaction by hydride. Complete reduction of *N*-*tert*-butanesulfinyl α-chloro imine (R_S)-**5a** was achieved with 2 equiv of $NaBH_4$ with stirring for 12 h in THF at room temperature (Table 1, entry 1). To further elaborate these

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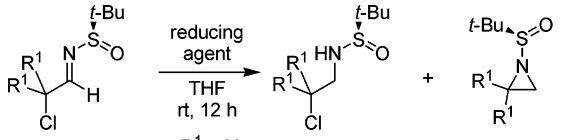
TABLE 1. Reduction of *N*-Sulfinyl α-Chloro Imines (R_S)-5a,b in THF Using Various Metal Hydrides



entry	reducing agent	R^1	amt, equiv	conversion of (R_S)-**5**,[a] %	(R_S)-**10**:(R_S)-**11**
1	$NaBH_4$	Me	2	100	1:0
2		Et	2	100	1:0
3	$NaCNBH_3$	Me	2	49	1:0
4		Et	2	34	1:0
5	$LiBH_4$	Me	2	100[b]	4:1
6		Et	2	100[b]	4.5:1
7	9-BBN	Me	2	100	1:0
8		Et	2	100	1:0
8	$LiBHEt_3$	Me	1.1	100[b]	1:2
9		Et	1.1	100[b]	1:2
10	$LiAlH_4$	Me	1.1	100[b]	1:4
11		Et	1.1	100[b]	1:3
12	DIBAL-H	Me	1.1	100[b]	1:1
13		Et	1.1	100[b]	1:1

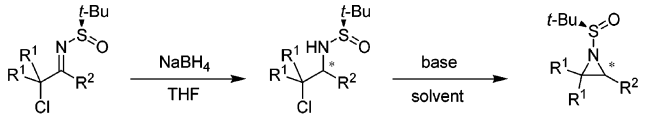
[a] Determined by TLC and by ^{1}H NMR. [b] Partial ring closure and subsequent *N*-sulfinyl deprotection occurred.

reductions in detail, the reaction conditions were systematically changed. Therefore, addition of a series of reducing agents, such as $NaBH_4$, $LiBH_4$, 9-BBN, $NaCNBH_3$, $LiBHEt_3$, $LiAlH_4$, and DIBAL-H, across *N*-*tert*-butanesulfinyl α-chloro aldimines **5a,b** was monitored with stirring in THF for 12 h at room temperature (Table 1). Reduction of *N*-*tert*-butanesulfinyl α-chloro imines (R_S)-**5a,b** with 2 equiv of $NaBH_4$ or 9-BBN yielded β-chloro sulfinamides (R_S)-**10a,b** quantitatively with little or no formation of the ring-closed product, i.e., aziridines **11a,b** (<2%), while the reduction of *N*-*tert*-butanesulfinyl α-chloro imines (R_S)-**5a,b** with $LiBH_4$, $LiBHEt_3$, DIBAL-H, and $LiAlH_4$ afforded mixtures of β-chloro sulfinamides (R_S)-**10a,b** and *N*-(*tert*-butylsulfinyl)-aziridines **11a,b** in a complex reaction mixture. Deprotection of the *N*-sulfinyl group by the HCl liberated during the ring closing step was a common observed side reaction complicating the spectrum of the reaction mixture. Full conversion of *N*-*tert*-butanesulfinyl α-chloro imines (R_S)-**5** toward β-chloro sulfinamides (R_S)-**10a,b** was observed if an excess of reducing agent was used in all cases except one. If $NaCNBH_3$ (2 equiv) was used, *N*-*tert*-butanesulfinyl α-chloro imines (R_S)-**5a,b** were recovered in 51% and 66% yield, respectively, on the basis of ^{1}H NMR (Table 1, entries 3 and 4). Consequently, the reduction of *N*-*tert*-butanesulfinyl α-halo imines (R_S)-**12** was tested for all reducing agents, apart from $NaCNBH_3$.

N-*tert*-Butanesulfinyl α-chloro aldimines (R_S)-**5** were reduced in excellent yield to afford the corresponding β-chloro *tert*-butanesulfinamides (R_S)-**10**. In contrast, if *N*-*tert*-butanesulfinyl α-halo ketimines **12** were reduced toward β-halo *tert*-butanesulfinamides **13** or *N*-(*tert*-butylsulfinyl)aziridines **14**, a stereogenic center was formed, so two diastereomers could be formed.

In a first attempt, reduction of *N*-*tert*-butanesulfinyl α-chloro ketimine (R_S)-**12a** was tried with $NaBH_4$ (2 equiv) in dry THF at room temperature for 12 h, affording β-chloro sulfinamide (R_S,*S*)-**13a** in 99% yield but in disappointing stereoselectivity (58:42 dr). The major diastereomer of the β-chloro sulfinamide **15a** formed after reduction of α-halo ketimine **12a** with $NaBH_4$ was assigned as (R_S,*S*)-**13a** by evaluation with known enantiopure aziridines in the literature (vide infra). As reported in Table S2 in the Supporting Information, changing the time, the solvent, and the amount of $NaBH_4$ added did result in a substantial improvement of the β-chloro sulfinamide (R_S,*S*)-**13a** formed. Shortening of the reaction from 12 to 1 h changed neither the yield nor the stereoselectivity of the reaction. Enhanced diastereoselectivities were observed at reduced temperature, but with substantial prolongation of the reaction time. Surprisingly, the reaction rate was improved without loss of diastereoselectivity by addition of small amounts of MeOH. The reaction at −78 °C was finished within 1 h, yielding 98% sulfinamide (R_S,*S*)-**13a** in 98:2 diastereoselectivity. It turned out that MeOH increased the reaction rate to a high extent without affecting the diastereoselectivity of the reaction performed. Notably, if the solvent was changed to MeOH, the solvent interaction on the reactive intermediate was borne out in the low diastereoselectivity obtained.

TABLE 2. Ring Closure of Chiral β-Chloro Sulfinamides 10a and 13a by Treatment with Base



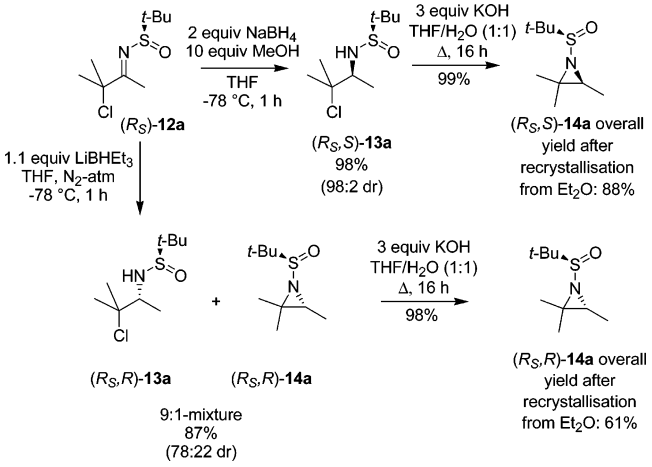
entry	sulfinamide	base	amt, equiv	temp, °C	time, h	solvent	yield,[a] %
1	**13a**	BuLi	1.1	−78 (rt)	1 (1)	THF	60
2	**13a**	NaH	1.1	−78 (rt)	1 (1)	THF	73
3	**10a**	Et_3N	3	Δ	16	MeCN	70
4	**13a**	KOH	3	Δ	8	THF/H_2O (1:1)	87
5	**13a**	KOH	3	Δ	16	THF/H_2O (1:1)	99[b]

[a] Conversion determined by NMR analysis of the reaction mixture. [b] Determined by a mass balance of the reaction mixture.

Notably, enantiopure β-halo sulfinamide (R_S,*S*)-**13a** formed was not ring closed toward the corresponding aziridine (R_S,*S*)-**14a** under the conditions used (2 equiv of $NaBH_4$ in the presence of 2 equiv of MeOH at −78 °C for 1 h in THF). Moreover, if the reaction temperature of the reduction of ketimine (R_S)-**12a** was allowed to increase to room temperature, after 1 h of reaction at −78 °C, no aziridine was formed. Further stirring at reflux temperature was insufficient to ring close the β-halo sulfinamide (R_S,*S*)-**13a** quantitatively toward the corresponding *N*-(*tert*-butylsulfinyl)aziridine (R_S,*S*)-**14a**. Strong bases, such as BuLi or NaH, afforded aziridine **14a** in a rather costly procedure (cooling and drying conditions were needed). Addition of 1.1 equiv of BuLi at −78 °C and subsequent stirring for 1 h at room temperature provided *N*-(*tert*-butylsulfinyl)aziridine **14a** in 60% conversion on the basis of the ^{1}H NMR spectrum (Table 2, entry 1). Better results were obtained if NaH was used as a base under the latter conditions (Table 2, entry 2). Heating β-chloro sulfinamide **10a** for 16 h in boiling MeCN, in the presence of 3 equiv of Et_3N, afforded 70% of the corresponding aziridine **11a** (Table 2, entry 3). Beneficial results were obtained if β-chloro sulfinamide **13a** was stirred for 8 h with 3 equiv of KOH in H_2O/THF (1:1 ratio).

Experimentally, it was shown that *N*-(2-chloro-1,2-dimethylpropyl)sulfinamide **13a** could also be quantitatively converted toward the corresponding *N*-(*tert*-butylsulfinyl)aziridine **14a** by being stirred overnight (16 h) in boiling THF/H_2O (1:1 ratio) in the presence of 3 equiv of KOH (Table 2). Importantly, only one diastereomer of *N*-(*tert*-butylsulfinyl)-2,2,3-trimethylaziri-

SCHEME 3. Reversal of Stereofacial Attack in the Reduction of *N*-Sulfinyl α-Chloro Imine (R_S)-12a with $NaBH_4$ vs $LiBHEt_3$



dine (**14a**) could be observed in ^{1}H NMR and/or HPLC. Thus, no epimerization reaction occurred.

The reducing agent was also altered from $NaBH_4$ to $LiBH_4$, 9-BBN, $LiBHEt_3$, $LiAlH_4$, and DIBAL-H to examine the generality of the reduction reaction. Reduction of *N*-*tert*-butanesulfinyl α-chloro ketimine (R_S)-**12a** with 1.1 equiv of $LiAlH_4$ or DIBAL-H in dry THF at −78 °C afforded the resulting sulfinamide (R_S,*S*)-**13a** in combination with the *N*-(*tert*-butylsulfinyl)aziridine (R_S,*S*)-**14a** in less than 1 h in good yield (90−95%) but with disappointing selectivity (56:44 to 63:37 dr). Better results were obtained if ketimine (R_S)-**12a** was reduced with 2 equiv of 9-BBN or $LiBH_4$ in THF at −78 °C for 1 h (88−93%, 70:30 to 81:19 dr). Reaction of ketimine (R_S)-**12a** with 2 equiv of $LiBH_4$ in THF with additional MeOH did improve the outcome slightly but still was not competitive in comparison with the $NaBH_4$ reduction. Better results were obtained if $LiBHEt_3$ was used as a reducing agent. It was gratifying to observe that reduction of ketimine (R_S)-**12a** with 1.1 equiv of $LiBHEt_3$ in dry THF at −78 °C afforded β-chloro sulfinamide (R_S,*R*)-**13a** together with aziridine (R_S,*R*)-**14a** (∼9:1 mixture) after 1 h in 87% yield with 78:22 dr (Scheme 3). Most important, the stereoselectivity of the reaction was altered as compared to that of the reduction with $NaBH_4$ (Scheme 3). However, it has to be reported that the intermediate β-halo sulfinamide (R_S,*R*)-**13a** could not be synthesized without partial ring closure toward *N*-(*tert*-butylsulfinyl)aziridine (R_S,*R*)-**14a**. Aziridine (R_S,*R*)-**14a** was formed almost quantitatively (98% yield) after separate treatment of β-halo sulfinamide (R_S,*R*)-**13a** with 3 equiv of KOH in boiling THF/H_2O (1:1) for 16 h. Recrystallization from Et_2O afforded *N*-(*tert*-butylsulfinyl)-aziridine (R_S,*R*)-**14a** as a single diastereomer in 61% overall yield. Thus, *N*-(*tert*-butylsulfinyl)aziridines (R_S,*R*)-**14a** and (R_S,*S*)-**14a** were synthesized separately in high yield and with excellent stereoselectivity, depending on the reducing reagent used (Scheme 3).

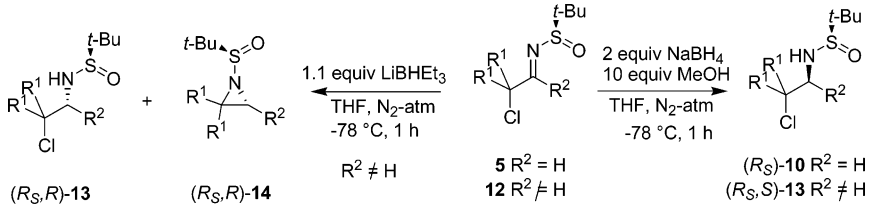
The hydride reduction was tested for its generality. Therefore, *N*-*tert*-butanesulfinyl α-chloro imines (R_S)-**5** and -**12** were treated with $NaBH_4$ and $LiBHEt_3$ under the conditions as optimized before (vide supra). These results are listed in Table 3.

Aldimines (R_S)-**5a,b** were reduced with $NaBH_4$ in excellent yields (>95%) to afford the corresponding β-chloro sulfinamide (R_S)-**10**, but crucially, all ketimines (R_S)-**12** were reduced toward chiral β-halo sulfinamides (R_S,*S*)-**13** in greater than 90% yield with excellent stereoselectivity (>95:5 dr) within 1 h at −78 °C in THF after addition of 2 equiv of $NaBH_4$ and 10 equiv of MeOH. Therefore, an attempt was made to purify the β-halo sulfinamides (R_S,*S*)-**13c**−**e** by flash chromatography and afterward, upon treatment with base, to further ring close sulfinamides (R_S,*S*)-**13c**−**e** to the corresponding aziridines (R_S,*S*)-**14c**−**e**. However, it turned out that β-halo sulfinamides (R_S,*S*)-**13c**−**e** could only be purified by flash chromatography with major loss of product on the column (solvent mixture petroleum ether−ethyl acetate, 85:15). Partial ring closure and/or *N*-sulfinyl deprotection were the two major side reactions on the column. Since both diastereomers were partially overlapping in the ^{1}H NMR spectra, and different rotamers were further complicating the spectrum, the diastereomeric ratio could not be accurately established for β-halo sulfinamides (R_S,*S*)-**13c**−**e**. Therefore, the latter sulfinamides (R_S,*S*)-**13c**−**e** were further ring closed to *N*-(*tert*-butylsulfinyl)-2-arylaziridines (R_S,*S*)-**14c-e** to obtain the diastereomeric ratio by ^{1}H NMR analysis. The diastereomeric ratio of the *N*-(*tert*-butylsulfinyl)aziridines (R_S,*S*)-**14c**−**e** obtained after separate treatment with base turned out to be greater than 90:10. Thus, both aliphatic and aromatic β-halo sulfinamides (R_S,*S*)-**13** were synthesized in high yield (>90%) and stereoselectivity (>90:10 dr) by treatment of *N*-*tert*-butanesulfinyl α-halo imines (R_S)-**12** with 2 equiv of $NaBH_4$ for 1 h at −78 °C in THF, with little MeOH as cosolvent. Noteworthy, if *N*-(*tert*-butylsulfinyl)-2-phenylaziridine (R_S,*S*)-**14c** was stirred for 4 more days in refluxing H_2O/THF (1:1 ratio), in the presence of 3 equiv of KOH, no epimerization was observed after workup as judged by ^{1}H NMR spectroscopy. All *N*-(*tert*-butylsulfinyl)aziridines **14** were synthesized quantitatively from β-halo sulfinamides **13** by reflux overnight (16 h) in THF/H_2O (1:1 ratio) in the presence of 3 equiv of KOH.

Aziridines (R_S,*R*)-**14** were synthesized via a two-step procedure starting from the corresponding ketimines (R_S)-**12**. Reduction of the latter *N*-*tert*-butanesulfinyl α-halo ketimines (R_S)-**12** with $LiBHEt_3$ in THF for 1 h at −78 °C, followed by treatment with 3 equiv of KOH in boiling THF/H_2O (1:1 ratio) for 16 h, afforded aziridines (R_S,*R*)-**14** in good yield (76−85%) with high diastereoselectivity (78:22 to 92:8 dr). Recrystallization from Et_2O of the *N*-(*tert*-butylsulfinyl)aziridines (R_S,*R*)-**14** formed resulted in the isolation of the enantiopure *N*-(*tert*-butylsulfinyl)aziridines (R_S,*R*)-**14** in 86−96% yield (Table 3).

Apparently, simultaneously with our research Coyler et al. have been investigating the reduction of nonfunctionalized *N*-sulfinyl imines.[15] The reduction of *N*-*tert*-butanesulfinyl ketimines with 3 equiv of $NaBH_4$ proceeded in high yield with good diastereomeric excess in wet THF (with 2% water). It has been described that the temperature was allowed to increase from −50 °C to room temperature over 3 h.[15] These results are in accordance with our findings, but it seems that the vicinal halogen atom activates the imino bond. If *N*-*tert*-butanesulfinyl α-chloro imine (R_S)-**12a** was reduced by means of 2 equiv of $NaBH_4$ in THF with 10 equiv of MeOH at −50 °C, a reduced diastereomeric excess, compared to that of the reduction at −78 °C, was observed. Also, the reduction of *N*-*tert*-butanesulfinyl α-chloro imine (R_S)-**12a** was terminated within 40 min at −78 °C, whereas the reduction of *N*-(1,2,2-trimethylethylidene)-*tert*-butanesulfinamide has been reported to be completed only after 3 h at higher temperature. Noteworthy, whereas aziridine (R_S,*S*)-**14a**, obtained after the reduction of *N*-*tert*-butanesulfinyl

TABLE 3. Reduction of *N*-Sulfinyl α-Chloro Imines (R_S)-5 and -12 Using $NaBH_4$ vs $LiBHEt_3$

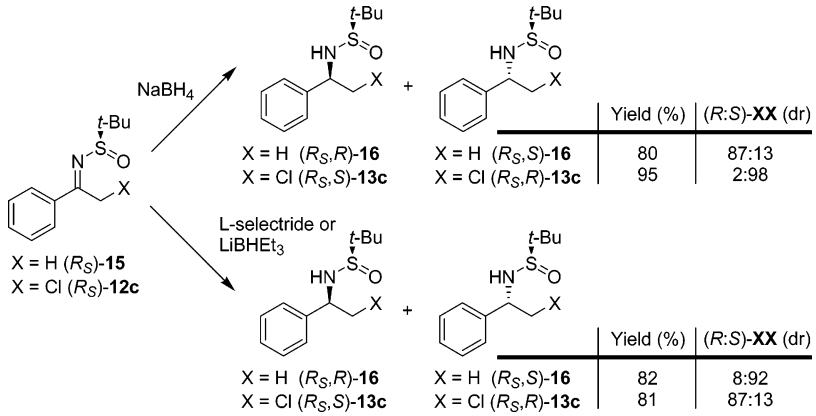


12a R^2 = Me; R^1 = Me
12b R^2 = Me; R^1 = Et
12c R^2 = Ph; R^1 = H
12d R^2 = 4-ClC_6H_4; R^1 = H
12e R^2 = 4-BrC_6H_4; R^1 = H
5a R^2 = H; R^1 = Me
5b R^2 = H; R^1 = Et

entry	substrate	reagent	product	ratio **13**:**14**[a]	yield,[b,c] %	dr[d]
1	(R_S)-**5a**	$NaBH_4$	(R_S)-**10a**		99 (95)	
2	(R_S)-**5b**	$NaBH_4$	(R_S)-**10b**		97 (95)	
3	(R_S)-**12a**	$NaBH_4$	(R_S,*S*)-**13a**	1:0	98 (88)	98:2
d	(R_S)-**12a**	$LiBHEt_3$	(R_S,*R*)-**13a**/**14a**	9:1	87 (61)	78:22
4	(R_S)-**12b**	$NaBH_4$	(R_S,*S*)-**13b**	1:0	92 (92)	99:1
5	(R_S)-**12b**	$LiBHEt_3$	(R_S,*R*)-**13b**/**14b**	18:1	80 (57)	80:20
6	(R_S)-**12c**	$NaBH_4$	(R_S,*S*)-**13c**	1:0	95 (90)	>98:2[e]
7	(R_S)-**12c**	$LiBHEt_3$	(R_S,*R*)-**13c**/**14c**	5.5:1	81 (62)	87:13[e]
8	(R_S)-**12d**	$NaBH_4$	(R_S,*S*)-**13d**	1:0	94 (89)	>98:2[e]
9	(R_S)-**12d**	$LiBHEt_3$	(R_S,*R*)-**13d**/**14d**	4:1	85 (66)	89:11[e]
10	(R_S)-**12e**	$NaBH_4$	(R_S,*S*)-**13e**	1:0	98 (91)	>98:2[e]
11	(R_S)-**12e**	$LiBHEt_3$	(R_S,*R*)-**13e**/**14e**	2.5:1	83 (71)	92:8[e]

[a] Determined by NMR analysis of the isolated product. [b] Determined by a mass balance of the isolated product. [c] In parentheses is given the yield (%) determined by a mass balance of the isolated *N*-sulfinylaziridine (R_S,*R*)-**14** after ring closure and subsequent recrystallization from Et_2O. [d] Determined by NMR analysis of the isolated product. [e] Determined by NMR analysis of the corresponding aziridine after ring closure.

SCHEME 4. Reversal of Stereofacial Attack in the Reduction of *N*-Sulfinyl Imines (R_S)-12c and -15a with Hydrides



α-chloro ketimine (R_S)-**12a** with $NaBH_4$ in THF with 10 equiv of MeOH as cosolvent, is synthesized in better yield and stereoselectivity as compared to the aziridine (R_S,*R*)-**14a**, synthesized by reaction of ketimines (R_S)-**12a** with $LiBHEt_3$, an inverse reactivity trend is reported by Coyler et al. for nonfunctionalized *N*-*tert*-butanesulfinyl imines (Scheme 4).[15] It has been reported that the reduction of the latter imines, such as (R_S)-*N*-(1-phenylethylidene)-*tert*-butanesulfinamide [(R_S)-**15a**] in wet THF (2% H_2O) afforded (R_S,*R*)-*N*-(1-phenylethyl)-*tert*-butanesulfinamide [(R_S,*R*)-**16a**] in 80% yield with 74% diastereoselectivity. The opposite *C*-epimer (R_S,*S*)-**16a** was obtained in 82% yield with 84% diastereoselectivity after reduction of imine (R_S)-**15a** with L-Selectride in dry THF. (R_S)-*N*-(2-Chloro-1-phenylethylidene)-*tert*-butanesulfinamide [(R_S)-**12c**], the α-chloro analogue of the latter imine (R_S)-**15a**, was reduced with $NaBH_4$ under the optimized conditions as mentioned before, yielding 95% (R_S,*S*)-*N*-(2-chloro-1-phenylethyl)-*tert*-butanesulfinamide [(R_S,*S*)-**13c**] with an excellent diastereomeric ratio (>98:2). However, reduction of *N*-*tert*-butanesulfinyl α-chloro imine **12c** with superhydride never yielded aziridine (R_S,*R*)-**15c** after ring closure, in greater than 87:13 diastereomeric ratio. It appears that the vicinal chloro atom has a contribution in both the reactivity and stereoselectivity of the reaction.

The chiral *N*-(*tert*-butylsulfinyl)aziridines (R_S,*S*)-**14** and (R_S,*R*)-**14** could be deprotected by simple treatment with a saturated solution of dry HCl in dioxane. Stirring of 5 mmol of aziridine **14** with 5 mL of saturated 1,4-dioxane·HCl for 15 min at room temperature in dry diethyl ether afforded the aziridinium chloride salts **17** in high yield (90−95%) and purity (90−95%) (Scheme 5).

The stereochemistry of aziridines **14** was checked by comparison of the optical rotation of *N*-(*tert*-butylsulfinyl)aziridine **14c** ($[\alpha]_D^{20}$ +310 vs +298 reported) and its spectroscopical data with literature values.[16] Hence, it was found that *N*-sulfinylaziridines (R_S,*S*)-**14** were synthesized via reduction of *N*-*tert*-butanesulfinyl α-halo ketimine **12** with $NaBH_4$, while *N*-

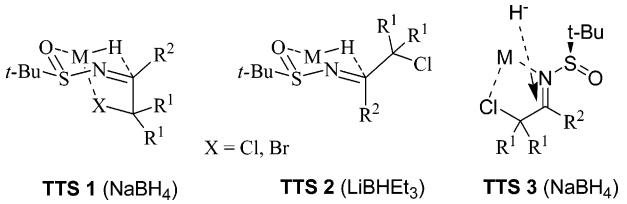
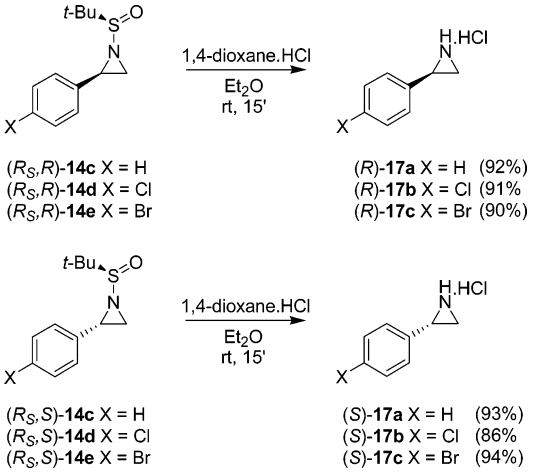


FIGURE 1. Proposed transition states for the reduction of ketimine (R_S)-**12**.

SCHEME 5. *N*-Sulfinyl Deprotection of Aziridines 14 in 1,4-Dioxane Hydrochloride/Diethyl Ether



sulfinylaziridines (R_S,*R*)-**14** were formed via the reduction with superhydride ($LiBHEt_3$).

The origin of the reversal of diastereofacial attack upon changing the reducing agent from $NaBH_4$ to a lithiated hydride species was explained very recently by Coyler et al. via a cyclic transition state (TTS) in the former case ($NaBH_4$) and an open transition state for the latter reduction ($LiBHEt_3$).[15] Due to the incorporation of one extra functional group, slightly more complex transition states are proposed in the present paper for the reduction of *N*-sulfinyl α-halo ketimines. Hence, if the sulfinyl oxygen atom participates in the delivery of the hydride ($NaBH_4$ reduction, Figure 1, TTS 1), the chloro atom is considered to complex also with the reducing agent, inducing a flip of the haloalkyl substituent in the Zimmerman−Traxler TTS from the equatorial toward the axial position. An identical switchover of stereoselectivity has already been observed for α-functionalized substituents, next to the imino function.[10a,17] More reactive reagents, such as $LiBHEt_3$, react too fast with *N*-*tert*-butanesulfinyl ketimines (R_S)-**12** to allow the haloalkyl substituent to flip toward an axial position (Figure 1, TTS 2). An open transition state, with the halogen atom in an α-position of the imino function, is not considered. Starting from the Cram−Chelate model na *Re*-face attack is favored. Thus, this would be a secondary possible intermediate in the reaction of $NaBH_4$ with ketimine (R_S)-**12** (Figure 1, TTS 3).

In conclusion, it has been demonstrated that enantiopure aziridines are formed in high yields with excellent, predictable diastereofacial control via reduction of *N*-sulfinyl α-halo imines. Depending on the reagent used both *C*-epimers of *N*-(*tert*-butylsulfinyl)aziridines were formed. For one epimer the intermediate β-halo *N*-sulfinamide could be isolated. Further treatment with base afforded chiral *N*-(*tert*-butylsulfinyl)-aziridines in quantitative yields. The latter compounds could be further deprotected toward the corresponding aziridinium salts.

Experimental Section

(R_S)-(−)-*N*-(2-Chloro-2-methylpropyl)-*tert*-butanesulfinamide [(R_S)-10a]. Imine (R_S)-**5a** (2.10 g, 10 mmol) was dissolved in THF (20 mL). To the stirred solution was then added $NaBH_4$ (0.76 g, 20 mmol) at room temperature, after which stirring was continued for 12 h before quenching with NH_4Cl (5 mL), aqueous $KHCO_3$ (20 mL), and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to furnish (R_S)-**10a** as a colorless oil (2.10 g, 99%). Pure β-chloro *N*-sulfinamide **10a** was obtained after recrystallization from Et_2O. Mp 88.6 ± 0.2 °C. $[\alpha]_D$ −11 (*c* 0.05, MeOH). IR (NaCl, cm^{-1}): ν_{max} 1057, 1369, 1457, 2973, 3210. MS: *m*/*z* (M + H) 212.2/214.2 (100). ^1H NMR (300 MHz, $CDCl_3$): δ 1.27 (9H, s), 1.58 (3H, s), 1.61 (3H, s), 3.17 (1H, dd, J = 13.5 Hz, 8.9 Hz), 3.45 (1H, dd, J = 13.5 Hz, 5.2 Hz), 3.73 (1H, dd (br), J = 8.9 Hz, 5.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.7, 29.6, 30.4, 56.4, 57.9, 70.0. Anal. Calcd for $C_8H_{18}ClNOS$: C, 45.38; H, 8.57; N, 6.61. Found: C, 45.58; H, 8.50; N, 6.72.

(R_S,*S*)-*N*-(2-Chloro-1,2-dimethylpropyl)-*tert*-butanesulfinamide [(R_S,*S*)-13a]. Imine (R_S)-**12a** (2.24 g, 10 mmol) was dissolved in THF (45 mL) and cooled to −78 °C. To the stirred solution were then added MeOH (4.6 mL, 100 mmol) and $NaBH_4$ (0.76 g, 20 mmol). Then the reaction was stirred for 1 h at −78 °C before quenching with NH_4Cl (5 mL), saturated aqueous $KHCO_3$ (20 mL), and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to furnish pure β-chloro *N*-sulfinamide **13a** (2.20 g, 89%) as white crystals after recrystallization from Et_2O. Mp: 54.4 ± 0.2 °C. $[\alpha]_D$ −44 (*c* 0.7, MeOH). IR (KBr, cm^{-1}): ν_{max} 1054, 1364, 1459, 2980, 3247. MS: *m*/*z* (M^+ + H) 226.2/228.2 (100). ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (9H, s), 1.27 (3H, d, J = 6.6 Hz), 1.55 and 1.68 (2 × 3H, 2 × s), 3.48 (1H, dq, J = 4.4 Hz, 6.6 Hz), 3.96 (1H, d (br), J = 5.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.7, 22.7, 27.8, 30.6, 55.9, 59.9, 74.6. Anal. Calcd for $C_9H_{20}ClNOS$: C, 47.88; H, 8.93; N, 6.20. Found: C, 47.71; H, 8.86; N, 6.35.

(R_S,*S*)-*N*-(*tert*-Butylsulfinyl)-2,2,3-trimethylaziridine [(R_S,*S*)-14a]. β-Chloro sulfinamide **13a** (2.26 g, 10 mmol) was dissolved in a 1:1 mixture of H_2O/THF (45 mL), and KOH (1.68 g, 30 mmol) was added. The stirred mixture was warmed to reflux temperature. When the reaction was complete (16 h), the reaction mixture was cooled to 0 °C. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Aziridine **14a** (1.55 g, 88%) was obtained as pure colorless crystals after recrystallization from Et_2O. Mp: 54.0 ± 0.2 °C. $[\alpha]_D$ −88 (*c* 0.7, MeOH). IR (KBr, cm^{-1}): ν_{max} 1081, 1361, 1457, 2928, 2961. MS: *m*/*z* (M^+ + H) 190.1 (100). ^1H NMR (300 MHz, $CDCl_3$): δ 1.21 (3H, d, J = 5.8 Hz), 1.24 (9H, s), 1.26 (3H, s), 1.58 (3H, s), 2.32 (1H, q, J = 5.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.5, 21.5, 21.6, 22.3, 44.8, 46.2, 55.7. Anal. Calcd for $C_9H_{19}NOS$: C, 57.10; H, 10.12; N, 7.40. Found: C, 57.26; H, 10.27; N, 7.53.

(R_S,*R*)-*N*-(*tert*-Butylsulfinyl)-2,2,3-trimethylaziridine [(R_S,*R*)-14a]. Imine (R_S)-**12a** (1.12 g, 5 mmol) was dissolved in THF (22 mL) and the solution cooled to −78 °C. To the stirred solution was then added $LiBHEt_3$ dropwise (1 M in THF, 5.5 mL). Then the reaction was stirred for 1 h at −78 °C before quenching with

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NH_4Cl (5 mL), saturated aqueous $KHCO_3$ (20 mL), and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to furnish a colorless oil which was dissolved in a 1:1 mixture of H_2O/THF (22 mL) to which KOH (0.84 g, 15 mmol) was added. The stirred mixture was warmed to reflux temperature. When the reaction was complete (16 h), the reaction mixture was cooled to 0 °C. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Aziridine (R_S,*R*)-**14a** (0.53 g, 61%) was obtained as pure colorless crystals after recrystallization from Et_2O. Mp: 60.6 ± 0.3 °C. $[\alpha]_D$ −115 (*c* 1.3, MeOH). IR (KBr, cm^{-1}): ν_{max} 1080, 1363, 1457, 2929, 2960. MS: *m*/*z* (M^+ + H) 190.1 (100), 134.1 (65). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (3H, s), 1.20 (9H, s), 1.21 (3H, d, J = 5.8 Hz), 1.40 (3H, s), 2.54 (1H, q, J = 5.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.5, 20.6, 20.9, 22.6, 36.4, 42.9, 55.9. Anal. Calcd for $C_9H_{19}NOS$: C, 57.10; H, 10.12; N, 7.40. Found: C, 57.31; H, 10.19; N, 7.52.

(*S*)-2-(4-Chlorophenyl)aziridinium Chloride [(*S*)-17b]. *N*-(*tert*-Butylsulfinyl)aziridine (R_S,*S*)-**14d** (1.29 g, 5 mmol) was dissolved in dry diethyl ether (20 mL) before the flask was placed in a water bath. To the stirred solution was then added dropwise 5 mL of freshly prepared saturated dioxane hydrochloride. The mixture was allowed to stir for 15 min at room temperature before the solution was concentrated in vacuo (10 mL). The crystals were filtered and washed with Et_2O (5 mL) before drying in vacuo. Recrystallization from Et_2O afforded analytically pure white crystals (91%). Mp: 203.0 ± 0.1 °C. $[\alpha]_D$ −46 (*c* 0.8, MeOH). IR (KBr, cm^{-1}): ν_{max} 1491, 1510, 1605, 1998, 2957. MS: *m*/*z* (M^+ + H) 190.2/192.3/194.2 (100). ^{1}H NMR (300 MHz, CD_3OD): δ 3.52 (1H, d, J = 5.8 Hz), 3.52 (1H, d, J = 8.5 Hz), 5.27 (1H, dd, J = 8.5, 5.8 Hz), 7.45 and 7.51 (2 × 2H, 2 × d, J = 8.8 Hz). ^{13}C NMR (75 MHz, CD_3OD): δ 47.2, 59.6, 130.1, 130.3, 136.5, 137.4.

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Supporting Information Available: Reaction optimization of the reduction of (R_S)-**12a** with $NaBH_4$ and the experimental details and characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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