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Use of α-Chlorinated *N*-(*tert*-Butanesulfinyl)-imines in the Synthesis of Chiral Aziridines

Bram Denolf,[†] Sven Mangelinckx,[†] Karl W. Törnroos,[‡] and Norbert De Kimpe*,[†]

Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium, and Department of Chemistry, University of Bergen, Allegaten 41, N-5007 Bergen, Norway

norbert.dekimpe@UGent.be

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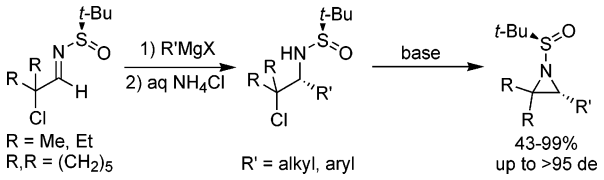
ABSTRACT



Reaction of chiral α-chloro *tert*-butanesulfinyl aldimines with Grignard reagents efficiently afforded *β*-chloro *N*-sulfinamides in high diastereomeric excess. The latter compounds were cyclized toward the corresponding chiral aziridines in a high-yielding one-pot reaction or after separate treatment with base. The diastereoselectivity obtained in the newly synthesized *β*-chloro sulfinamides is explained via the coordinating ability of the α-chloro atom with magnesium resulting in the opposite stereochemical outcome as generally observed for nonfunctionalized *N*-sulfinyl imines.

α-Halogenated imines have received considerable attention as versatile intermediates for the synthesis of biologically active compounds.[1] The simple synthesis of α-halo imines from the corresponding readily available α-chloro aldehydes or α-chloro ketones and the subsequent cyclization, after a nucleophilic addition reaction, toward azaheterocycles make the α-halogenated imidoyl function an interesting building block.[2] Even though these α-halogenated imines have found wide application, their use is not without problems (e.g., hydrolytically unstable, poor electrophiles).[1d] The use of a chiral N-protective group to activate the imino function for nucleophilic addition in a diastereofacial way and for easy removal after reaction under mild conditions is of interest to synthesize a variety of compounds. The diastereoselective addition of organometallics to *N*-sulfinyl imines, pioneered by Davis[3] and Ellman,[4] has proven to be a straightforward method to synthesize chiral amines, amino alcohols, and amino acids, among other interesting compounds. The use of halogenated *N*-sulfinyl imines has been limited to some fluorinated examples,[5] despite the advantageous reactivity of known alkylated and arylated halogenated imines mentioned. A few examples of chloro or bromo *N*-sulfinyl imines are described,[6] but their reactivity has not been investigated up to now. Incorporation of a chlorine atom in *N*-sulfinyl imine **2**, as compared to *N*-sulfinyl imine **1**, could lead to chiral aziridines, which are of considerable interest in organic chemistry,[7−10] in a very straightforward way. The stereoselective synthesis of aziridines **4** via α-halo *N*-sulfinyl imines

[†] Ghent University.
[‡] University of Bergen.

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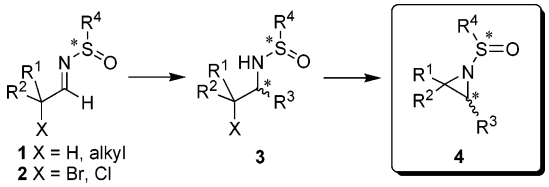
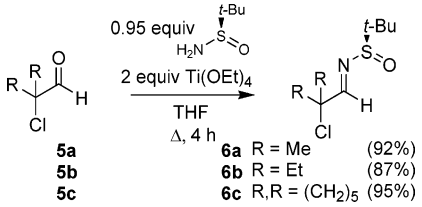
Scheme 1



2 has not been described (Scheme 1). In this report, the above methodology with α-halo *N*-sulfinyl imines **2**, carrying a chiral (*R*$_S$)-*tert*-butanesulfinyl group at nitrogen, will be worked out toward the chiral synthesis of aziridines.

α-Chloro *N*-sulfinyl aldimines (*R*$_S$)-**6**, a new class of functionalized *N*-sulfinyl imines, were synthesized via condensation of α-chloro aldehydes **5** (1.1 equiv)[1d] with (*R*$_S$)-*tert*-butanesulfinamide in the presence of 2 equiv of Ti(OEt)$_4$ in THF under reflux (Scheme 2).

Scheme 2. Synthesis of α-Chloro *N*-Sulfinyl Aldimines (*R*$_S$)-**6**



α-Chloro *N*-sulfinyl aldimines (*R*$_S$)-**6** were isolated in high yields (87−95%) after distillation to separate the small excess of aldehydes **5** used.

Upon treatment of α-chloro *N*-sulfinyl imine (*R*$_S$)-**6a** with 2 equiv of EtMgBr in dichloromethane at −78 °C for 4 h and subsequent stirring for 12 h at ambient temperature, 3-ethylaziridine **8a** was formed in modest yield (46%) and diastereoselectivity (dr = 70:30) (Table 1, entry a).

Table 1. Addition of Grignard Reagents Across α-Chloro *N*-Sulfinyl Aldimine (*R*$_S$)-**6a**

	R′ (equiv)	solvent	*t* (h) [°C]	product	yield %[a] (dr)[b]
a	Et (2.0)	CH_2Cl_2	4 [−78][c]	**8a**	46 (70:30)
b	Ph (2.0)	CH_2Cl_2	1 [−78][d]	**9b**	43 (98:2)
c	Et (2.0)	CH_2Cl_2	4 [−78]	**9a**	73 (88:12)
d	Ph (1.1)	CH_2Cl_2	5 [−78][c,d]	**9b**	82 (99:1)
e	Et (1.1)	CH_2Cl_2	4 [−78][c]	**8a**	95[e] (96:4)
f	Et (1.1)	toluene	4 [−78]	**9a**	94[e] (95:5)
g	Et (1.1)	THF	4 [−78]	**9a**	92[e] (72:28)
h	Et (1.1)	Et_2O	4 [−78]	**9a**	96[e] (78:22)
i	Et (1.1)	CH_2Cl_2	4 [−78]	**9a**	95[e] (96:4)

[a] Determined by a mass balance after chromatography. [b] Determined by NMR analysis of the reaction mixture. [c] Followed by stirring at room temperature for 12 h. [d] Addition of the Grignard reagent at −97 °C. [e] Determined by a mass balance of the reaction mixture.

The temperature effect was of great importance for both the yield and the stereoselectivity of the addition reaction. Reaction of aldimine (*R*$_S$)-**6a** with 2 equiv of PhMgCl for 4 h at −78 °C and subsequent stirring at room temperature for 12 h yielded a complex reaction mixture from which only traces of the desired 2-phenylaziridine **8b** were obtained next to some of the corresponding arylated β-chloro *N*-sulfinamide **9b**. At higher temperatures (−20 °C), side reactions became even more important and it was a major drawback if PhMgCl was used as the reagent of choice. In contrast, if the Grignard reagent was added at −97 °C and the reaction mixture was allowed to react further at −78 °C for 5 h, a very clean addition reaction yielded β-chloro *N*-sulfinamide (*R*$_S$,*R*)-**9b**. No traces of the corresponding aziridine (*R*$_S$,*R*)-**8b** were detected under these conditions.

By lowering the excess of Grignard reagent, the yields of β-chloro sulfinamide (*R*$_S$,*R*)-**9b** improved. Even more, the diastereoselectivity was also slightly improved (Table 1, entries a−e). A lower diastereoselectivity was obtained in ethereal solvents, such as THF or diethyl ether. The use of noncoordinating solvents such as dichloromethane or toluene resulted in better diastereoselectivities (Table 1, entries f−i).

The best results were obtained if 1.1 equiv of Grignard reagent was allowed to react with aldimine (*R*$_S$)-**6a** in dichloromethane at −78 °C for 4−5 h. Though the addition of PhMgCl was preferred at −97 °C, these low-temperature conditions were not required for the addition reaction of EtMgBr, vinylMgBr, and allylMgCl. Upon treatment of (*R*$_S$)-**6a** with Grignard reagent, under the former conditions, β-chloro *N*-sulfinamides (*R*$_S$,*R*)-**9** were isolated in high yield (82−99%) and diastereoselectivity (62:38−99:1) (Scheme 3). Reaction of allylMgCl with (*R*$_S$)-**6a** afforded β-chloro *N*-sulfinamide (*R*$_S$,*R*)-**9d** in 99% yield but as a (62:38) mixture of diastereomers (Scheme 3). Both diastereomers were separated by flash chromatography after further ring closure (vide infra) toward the aziridines (*R*$_S$,*R*)-**8d** and (*R*$_S$,*S*)-**8d** in 57% and 10% yield, respectively. Notably, addition of *i*-PrMgCl to (*R*$_S$)-**6a** at −97 °C and reaction at

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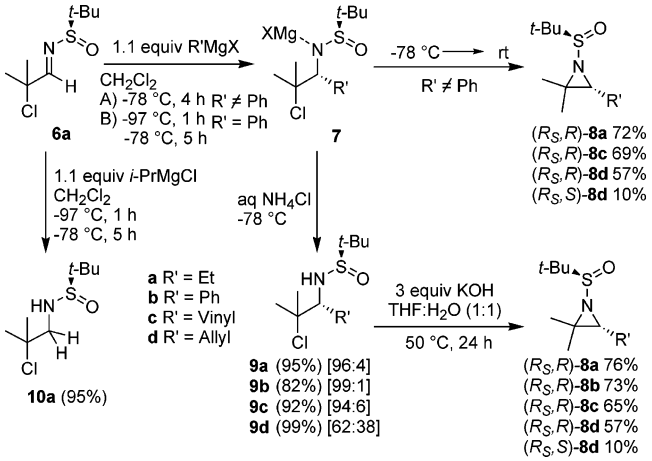
Scheme 3. Stereoselective Aziridination of Imine (R_S)-**6a**



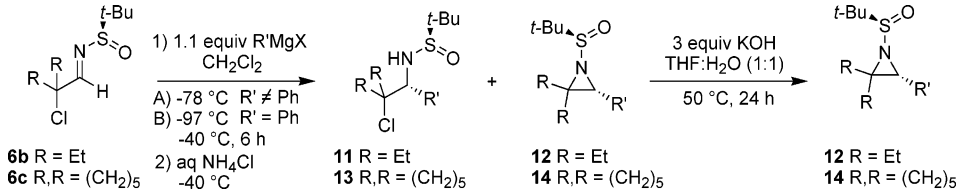
−78 °C resulted in the reduction of the imidoyl function affording the reduced β-chloro sulfinamide **10a** in high yield (95%) (Scheme 3).[11]

Quenching of the reaction mixture of (R_S)-**6a** upon treatment with Grignard reagent (R′ ≠ Ph) with aq NH_4Cl at −78 °C after 4 h afforded the alkylated β-chloro *N*-sulfinamide (R_S,*R*)-**9** in high yield (92−99%). Moreover, if the reaction mixture was allowed to stir at room temperature after completion of the addition at −78 °C, the desired aziridines **8** were isolated in excellent yield (Scheme 3). However, if R′ = Ph, it was noticed that the β-chloro *N*-sulfinamides (R_S,*R*)-**9b** were not ring closed toward the corresponding aziridines (R_S,*R*)-**8b** if the reaction mixture was stirred at ambient temperature for 12 h (Table 1, entry d). Longer reaction times or higher temperatures did not afford the desired aziridines (R_S,*R*)-**8b** in acceptable yield. Therefore, a series of bases (BuLi, LDA, NaH, and K_2CO_3) were applied in different solvents to facilitate the cyclization reaction of β-chloro *N*-sulfinamide (R_S,*R*)-**9b** toward aziridine (R_S,*R*)-**8b** (Supporting Information).

Experimentally, it was shown that KOH in H_2O/THF (1:1 ratio) at 50 °C gave the best results to ring close the β-chloro *N*-sulfinamide (R_S,*R*)-**9b** toward the corresponding aziridine (R_S,*R*)-**8b** in high yields. Even more, these conditions were applied to all β-chloro *N*-sulfinamides (R_S,*R*)-**9** affording the corresponding aziridines (R_S,*R*)-**8** in excellent yield without detectable loss of chirality. Thus, these aziridines **8** were synthesized in a high-yielding one- or two-pot reaction (Scheme 3) and were obtained as a single diastereomer after flash chromatography.

Upon treatment of the more sterically hindered α-chloro *N*-sulfinyl imine (R_S)-**6b** (R = Et) with EtMgBr at −78 °C for 4 h in THF, most of the aldimine (R_S)-**6b** was recovered. Almost no addition reaction was observed under the latter conditions (Table 2, entry a). Upon raising the temperature from −78 °C to −40 °C, after the addition of the Grignard reagent at −78 °C or −97 °C (vide supra), depending on the reagent used, mixtures of the β-chloro *N*-sulfinamide (R_S,*R*)-**11** and the corresponding aziridine (R_S,*R*)-**12** were obtained in reasonable yield. The β-chloro *N*-sulfinamides (R_S,*R*)-**11** could only be isolated in low yields after flash chromatography of the reaction mixture. Various attempts failed to synthesize the β-chloro *N*-sulfinamide (R_S,*R*)-**11a** as such, without any of the aziridine **12a** present. However, if the reaction mixture was stirred for 12 more hours at ambient temperature, the β-chloro *N*-sulfinamides (R_S,*R*)-

Table 2. Optimization of the Addition of Grignard Reagents Across α-Chloro *N*-Sulfinyl Aldimine (R_S)-**6b**,**c**



entry	substrate	reagent	equiv	solvent	*t* (h) [°C] (rt)	product	yield %[d] (%)[e]	(dr)[f]
a	**6b**	EtMgBr	2	THF	4 [−78]	**11a**	8	(−)
b	**6b**	EtMgBr	1.1	CH_2Cl_2	3 [−40][a] 12 (rt)	**12a**	83	(86:14)
c	**6b**	EtMgBr	1.1	CH_2Cl_2	1 [−40][a] 12 (rt)	**12a**	29	(−)
d	**6b**	EtMgBr	1.1	CH_2Cl_2	6 [−40][a] 12 (rt)	**12a**	82	(92:8)
e	**6b**	EtMgBr	1.1	Et_2O	6 [−40][a] 12 (rt)	**12a**	84	(78:22)
f	**6b**	EtMgBr	1.1	toluene	6 [−40][a] 12 (rt)	**12a**	81	(91:9)
g	**6b**	PhMgCl	1.1	CH_2Cl_2	6 [−40][b] 12 (rt)	**11b**	77	(96:4)
h	**6b**	EtMgBr	1.1	CH_2Cl_2	6 [−40][a,c]	**12a**	82 (66)	(92:8)
i	**6b**	PhMgCl	1.1	CH_2Cl_2	6 [−40][b,c]	**12b**	77 (57)	(96:4)
j	**6b**	vinylMgBr	1.1	CH_2Cl_2	6 [−40][a,c]	**12c**	83 (62)	(93:7)
k	**6b**	allylMgCl	1.1	CH_2Cl_2	6 [−40][a,c]	**12d**	90 (45)[21]	(62:38)
l	**6c**	EtMgBr	1.1	CH_2Cl_2	6 [−40][a]	**13a**	(25)	(−)
m	**6c**	EtMgBr	1.1	CH_2Cl_2	6 [−40][a,c]	**14a**	82 (63)	(92:8)
n	**6c**	PhMgCl	1.1	CH_2Cl_2	6 [−40][b,c]	**14b**	43 (20)	(70:30)
o	**6c**	vinylMgBr	1.1	CH_2Cl_2	6 [−40][a,c]	**14c**	85 (56)	(86:14)
p	**6c**	allylMgCl	1.1	CH_2Cl_2	6 [−40][a,c]	**14d**	84 (41)	(70:30)

[a] Addition of the Grignard reagent at −78 °C. [b] Addition of the Grignard reagent at −97 °C. [c] Subsequent ring closure with 3 equiv of KOH in THF/H_2O (1:1) for 24 h at 50 °C. [d] Determined by a mass balance of the reaction mixture. [e] Isolated yield of the (major) [minor] diastereomer after flash chromatography. [f] Determined by NMR analysis of the reaction mixture.

11 were ring closed toward the corresponding aziridines **12** if R′ ≠ Ph.

If the reaction was performed for less than 6 h at −40 °C before raising the temperature to 20 °C for 12 h, lower diastereoselectivities were obtained, which was an indication that the reaction was not completed at −40 °C (Table 2; entries b−d).

Altering the solvent from CH_2Cl_2 to Et_2O or toluene did not improve the yield or the stereoselectivity of the reaction (entries d−f).

Thus, addition of 1.1 equiv of Grignard reagent to imine (R_S)-**6b** in dichloromethane at −78 °C and subsequent stirring for 6 h at −40 °C afforded a mixture of β-chloro *N*-sulfinamide (R_S,*R*)-**11** and aziridine (R_S,*R*)-**12**, after aqueous workup. The latter mixture was treated with base (3 equiv of KOH) at 50 °C for 24 h to obtain the ring-closed *N*-sulfinyl aziridine **12** (Table 2). No racemization was observed under these conditions. These conditions were applied with good result (77−90% yield and dr of 62:38−96:4) for the synthesis of a variety of new chiral sterically hindered aziridines (R_S,*R*)-**12a**−**d** starting from α-chloro *N*-sulfinyl imine (R_S)-**6b** (Table 2). It was found that chiral 1-azaspiro[2.5]octanes (R_S,*R*)-**14a**−**d** could be synthesized in moderate to good yield (43−85%) and diastereoselectivity (70:30−92:8), starting from α-chloro *N*-sulfinyl imine (R_S)-**6c** under these optimized conditions (Table 2). All chiral aziridines **12**,**14** were obtained as a single enantiomer [(R_S,*R*)-**12**,**14**] after flash chromatography. β-Chloro *N*-sulfinamide (R_S,*R*)-**13a** could be isolated as a pure product in 25% yield, starting from α-chloro *N*-sulfinyl imine (R_S)-**6c**, after the addition of 1.1 equiv of EtMgBr at −78 °C, subsequent stirring for 6 h at −40 °C, aqueous workup with NH_4Cl at this temperature, and subsequent flash chromatography of the crude reaction mixture (Table 2, entry l).

In the literature, no precedents of the synthesized amides (R_S,*R*)-**9**,**13** or aziridines (R_S,*R*)-**8**,**12**,**14** have been reported. The *N*-sulfinamides (R_S,*R*)-**9**,**13** and *N*-sulfinyl aziridines (R_S,*R*)-**8**,**12**,**14** could be deprotected by simple treatment with a saturated solution of dry HCl in dioxane. Stirring for 5 min at room temperature afforded the HCl salts of the β-chloro amines (*R*)-**18**,**19** or aziridines (*R*)-**15**−**17** in high yield (>90%) and purity (>80%) (Scheme 4). Deprotection of *N*-sulfinyl aziridine (R_S,*R*)-**8b** resulted mainly in aziridine (*R*)-**15b**, though up to 15% of β-chloro amine (*R*)-**18b** (R = Me; R′ = Ph) was also formed.

Without any of the β-chloro amines (*R*)-**18**,**19** or aziridines (*R*)-**15**−**17** reported in the literature, the absolute configuration had to be determined by X-ray diffraction analysis. From the X-ray diffraction analysis of *N*-(*tert*-butanesulfinyl)-2,2-dimethyl-3-phenylaziridine (R_S)-**8b** the absolute configuration of the structure was undoubtedly characterized as being the (R_S,*R*)-aziridine **8b**. This configuration is opposite to the one that is predicted via the chelation-controlled transition state **A** (Figure 1), which is the general intermediate

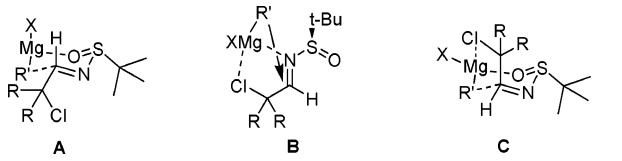
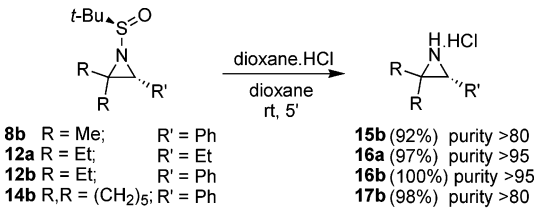


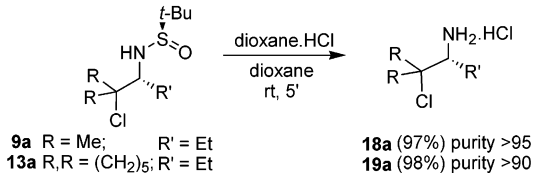
Figure 1. Proposed transition states.

proposed for nonfunctionalized *N*-sulfinyl imines.[4,12] The reversal of the stereochemical outcome of the reaction is attributed to the α-coordinating ability of the chlorine atom as depicted in Figure 1 (transition states **B** and **C**). The reversal of selectivity is analogous to the results obtained with other *N*-sulfinyl imines containing an α-coordinating group, such as a nitrogen or oxygen atom.[12a,13]

In conclusion, a novel stereoselective synthesis of chiral 2-arylated and 2-alkylated aziridines (*R*)-**15**−**17** has been developed. Reaction of α-chloro *N*-sulfinyl imines (R_S)-**6** with Grignard reagents afforded β-chloro *N*-sulfinamides (R_S,*R*)-**9** in good yields or **11** and **13** as nonisolated intermediates. The latter compounds were ring closed toward the corresponding *N*-sulfinyl aziridines (R_S,*R*)-**8**,**12**,**14** in a high-yielding one-pot reaction or after separate treatment with base. Chiral aziridines (*R*)-**15**−**17** were synthesized by subsequent deprotection of the N-protecting group. The absolute configuration of the aziridines formed was proven by X-ray analysis.

Scheme 4. *N*-Sulfinyl Deprotection in 1,4-Dioxane·HCl





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Supporting Information Available: Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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