Asymmetric synthesis of 2-substituted pyrrolidines by addition of Grignard reagents to γ-chlorinated *N-tert*-butanesulfinyl imine†

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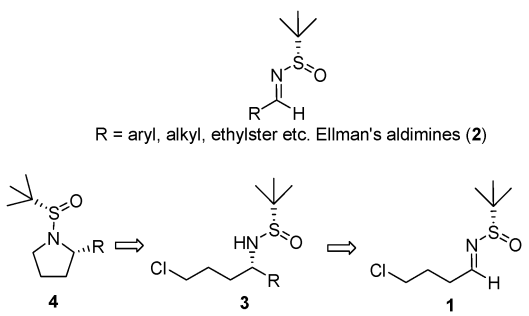
A highly diastereoselective addition of various Grignard reagents to chiral γ-chlorinated *N-tert*-butanesulfinyl imine resulting in the formation of 2-substituted pyrrolidines is reported. This method is general and also efficient for the preparation of both enantiomers of 2-aryl, 2-alkyl and 2-vinyl substituted pyrrolidines in high yields.

2-Substituted pyrrolidines constitute an important structural motif in biologically active compounds as they are found in a wide variety of natural products,[1] pharmaceuticals,[2] and effective chiral controllers in asymmetric synthesis.[3] Particularly, these compounds are pharmaceutically relevant, as over 200 compounds containing this pharmacophore are currently in advanced biological testing.[4] Known synthetic methods of these privileged structures, suffer from either long synthetic sequences, low yields, lack of generality or modest selectivity.[5] Recently, Merck scientists have reported[6] an elegant method for the asymmetric synthesis of 2-arylpyrrolidines in a highly enantioselective manner but this method also has some limitations: it is limited to the synthesis of only the (*R*)-enantiomer of aryl pyrrolidines, and it utilizes *s*-BuLi.[7] We reasoned that a direct method to access enantioenriched 2-substituted pyrrolidines would be the asymmetric addition of Grignard reagents to Ellman's type γ-chlorinated *N-tert*-butanesulfinyl imine (**1**) followed by cyclization. Whereas the diastereoselective addition of Grignard reagents to Ellman's aldimines (**2**)[8] is well established, the asymmetric addition of Grignard reagents to Ellman's type γ-chlorinated



Scheme 1 Ellman's aldimines and retrosynthetic analysis

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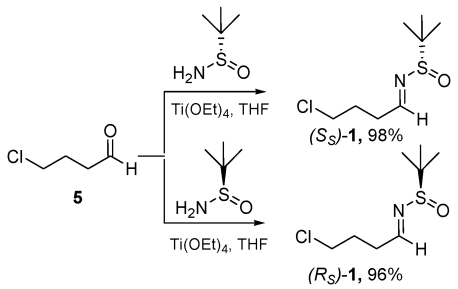
† Electronic supplementary information (ESI) available: Complete experimental procedures, characterization data, copies of NMR spectra and single X-ray crystallographic data for compound **4b**. CCDC 747534. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b917435d



Scheme 2 Synthesis of γ-chloro *N*-sulfinyl aldimine (S_S)-**1** and γ-chloro *N*-sulfinyl aldimine (R_S)-**1**.

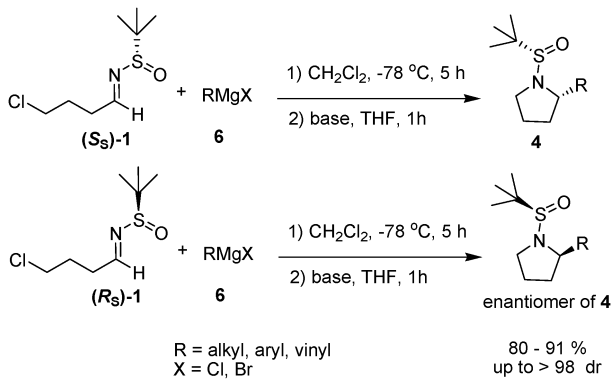
N-tert-butanesulfinyl imine (**1**) followed by cyclization has not been described (Scheme 1) to our knowledge.[9] Herein, we report a general and a practical method for the diastereoselective addition of Grignard reagents to Ellman's type γ-chlorinated *N-tert*-butanesulfinyl imine (**1**), followed by cyclization in a one-pot procedure to give 2-substituted pyrrolidines.

γ-Chloro *N*-sulfinyl aldimine (S_S)-**1**[10] was synthesized in high yield *via* condensation of 4-chlorobutanal (**5**) (1.0 equiv.)[11] with (S_S)-*tert*-butanesulfinamide (1.0 equiv.)[12] in the presence

Table 1 Ring closing of chiral δ-chloro sulfinamide **3a** by treatment with base

Entry	Sulfinamide	Base	Temp. °C	Time/ h	Solvent	Yield [a]%
1	3a	BuLi	−78 (0)	1	THF	65
2	3a	NaH	−78 (0)	1	THF	79
3	3a	LiHMDS	23	1	THF	98
4	3a	NEt_3	Δ	12	MeCN	76
5	3a	KOH	Δ	12	THF–H_2O	85

[a] Isolated yield of analytically pure products.



Scheme 3 Reaction of various Grignard reagents with γ-chlorinated *N-tert*-butanesulfinyl imines.

of 1.1 equiv. of $Ti(OEt)_4$ in THF at room temperature for 12 h. In the same way, the γ-chloro *N*-sulfinyl aldimine (R_S)-**1**, was synthesized *via* condensation of **5** with (R_S)-*tert*-butanesulfinamide (Scheme 2).

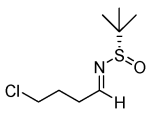
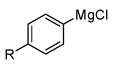
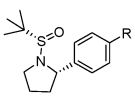
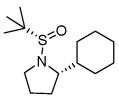
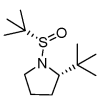
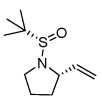
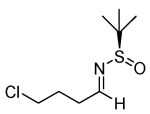
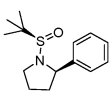
Treatment of γ-chloro *N*-sulfinyl aldimine (S_S)-**1** (1.0 equiv.) with phenylmagnesium chloride (**6a**, 1.5 equiv.) in CH_2Cl_2 at −78 °C for 5 h followed by NH_4Cl work-up afforded the crude δ-chloro sulfinamide **3a** in high diastereomeric ratio (d*r* 97 : 3).[13] The diastereoselectivity of the reaction was determined to be 97 : 3 by ^1H NMR analysis of the crude product. A series of bases (BuLi, NaH, LiHMDS, Et_3N, and KOH) were investigated in different solvents to facilitate the cyclization reaction of pure δ-chloro sulfinamide (S_S,*S*)-**3a** towards 2-phenylpyrrolidine (S_S,*S*)-**4a**. Addition of 1.1 equiv. of BuLi in THF at −78 °C and subsequently warming to 0 °C for 1 h provided (S_S,*S*)-**4a** in 65% yield (Table 1, entry 1). Better results were obtained if NaH was used as a base under the latter conditions (Table 1, entry 2). Heating **3a** for 12 h in boiling CH_3CN, in the presence of 4 equiv. of Et_3N, afforded 76% of corresponding (S_S,*S*)-**4a** (Table 1, entry 4). In the same way, heating of **3a** for 12 h in boiling H_2O–THF (1 : 1), in the presence of 3 equiv. of KOH, afforded 85% of corresponding (S_S,*S*)-**4a** (Table 1, entry 5). Best results were obtained if (S_S,*S*)-**3a** was stirred at room temperature for 1 h with 1.5 equiv. of LiHMDS in THF (Table 1, entry 3).

Experimentally, it was shown that the crude δ-chloro sulfinamide **3a** could also be converted to the corresponding 2-phenylpyrrolidine **4a** in high yield (91% in two steps) and with a high diastereomeric ratio (d*r* 97 : 3) by stirring at room temperature for 1 h in the presence of 1.5 equiv. of LiHMDS. More importantly, no epimerization reaction occurred during the cyclization (Scheme 3).

Encouraged by these results, we turned our attention to other substituted aromatic Grignard reagents. Interestingly, a large number of substituted aromatic Grignard reagents, such as *p*-methoxy-, *p*-methyl-, *p*-bromo-,[14] *p*-*tert*-butyl-reagents, reacted cleanly with γ-chlorinated *N*-(*tert*-butanesulfinyl) imine (**1**) followed by base-catalyzed cyclization leading to corresponding 2-arylpyrrolidines **4b–4e** (Table 2, entries 2–5) in good yields (83–89%) and high diastereomeric ratios (up to 96 : 4). 2-(*p*-Bromophenyl)-pyrrolidine (S_S,*S*)-**4b** was obtained as a colorless crystalline solid (mp 110–112 °C). The structure and absolute stereochemistry of (S_S,*S*)-**4b** was confirmed by single crystal X-ray diffraction analysis (Fig. 1).‡

Similarly, reaction of aliphatic Grignard reagents such as cyclohexylmagnesium chloride (**6f**) and *tert*-butylmagnesium

Table 2 Asymmetric addition of various Grignard reagents to γ-chlorinated *N*-*tert*-butanesulfinyl imine

Entry	Substrate (**1**)	Reagent (**6**)	Product (**4**)[c]	Yield (%)[a]	d*r*[b]
					
1	**1a**	**6a**: R = H	**4a**	91	97 : 3
2	**1a**	**6b**: R = Br	**4b**	83	95 : 5
3	**1a**	**6c**: R = Me	**4c**	86	95 : 5
4	**1a**	**6d**: R = OMe	**4d**	88	96 : 4
5	**1a**	**6e**: R = *t*-Bu	**4e**	85	94 : 6
					
6	**1a**	**6f**	**3f**	90	97 : 3
					
7	**1a**	**6g**	**4g**	84	95 : 5
					
8	**1a**	**6h**	**4h**	82	92 : 8
					
9	Enantiomer of **1a**	**6a**	Enantiomer of **4a**	90	97 : 3
10	Enantiomer of **1a**	**6b**	Enantiomer of **4b**	85	95 : 5
11	Enantiomer of **1a**	**6d**	Enantiomer of **4d**	83	96 : 4

[a] Isolated yield of analytically pure products. [b] The diastereoselectivity was determined by ^1H NMR. d*r* relative to sulfur. [c] All reactions were performed using 1.2 equiv. of Grignard agent at −78 °C for 5 h. Followed by isolation of crude product and cyclization using LiHMDS, rt, 1 h in THF unless otherwise stated.

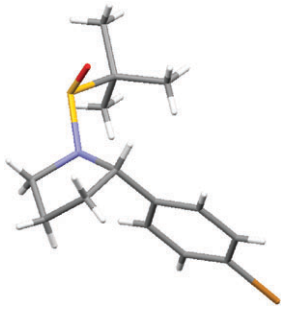


Fig. 1 X-ray crystal structure of **4b**.

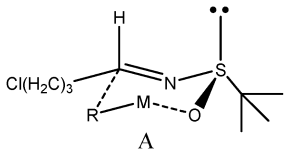
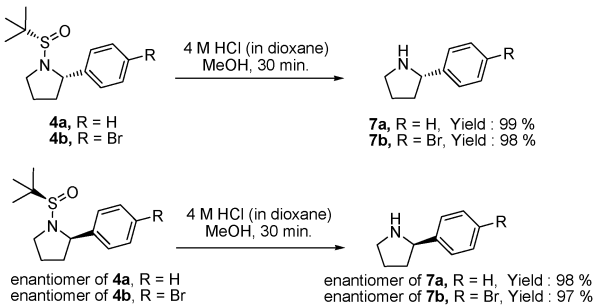


Fig. 2 Possible transition state A.



Scheme 4 Deprotection of sulfinyl group.

chloride (**6g**) smoothly reacted with (S_S)-**1**, followed by the cyclization affording the corresponding 2-cyclohexylpyrrolidine **4f** and 2-*tert*-butylpyrrolidine **4g** in 90% and 84% yield (d*r* 97 : 3 and 95 : 5), respectively (Table 2, entries 6, 7). Likewise, reaction of (S_S)-**1** with vinylmagnesium chloride (**6h**) and followed by the cyclization also proceeded to 2-vinylpyrrolidine (**4h**) in 82% yield with d*r* 92 : 8 (Table 2, entry 8).

Noticeably, the reaction of (R_S)-**1** with phenylmagnesium chloride (**6a**), followed by cyclization, smoothly proceeded to the enantiomer of 2-phenylpyrrolidine (*ent*-**4a**) in 90% yield with d*r* 97 : 3 (Table 2, entry 9). Similarly the reaction of (R_S)-**1** with **6b** and **6d** followed by cyclization afforded the enantiomer of 2-(4-bromophenyl)pyrrolidine (*ent*-**4b**) and enantiomer of 2-(4-methoxyphenyl)pyrrolidine (*ent*-**4d**) in 85% and 88% yield (d*r* 95 : 5 and 96 : 4), respectively. (Table 2, entry 10, 11). A possible mechanistic model to explain the observed stereoselectivity is depicted in Fig. 2, which involves a chair-like transition state (A).[8b]

Finally, the sulfinyl group can be cleaved readily under mild acidic conditions to provide free amine **7** in quantitative yield (Scheme 4).

In summary, we have described an efficient, highly diastereoselective addition of various Grignard reagents to chiral γ-chlorinated *N*-(*tert*-butanesulfinyl) imine affording enantiomerically pure 2-substituted pyrrolidines. This method is useful for the preparation of both enantiomers of 2-substituted pyrrolidines. Extension of this work is currently under way in our laboratory.

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Notes and references

‡ Single crystals of $C_{14}H_{20}BrNOS$ **4b** were recrystallised from ethyl acetate, mounted in inert oil and transferred to the cold gas stream of the diffractometer. Crystal structure determination of **4b**: **Crystal data**. $C_{14}H_{20}BrNOS$, M = 330.29, orthorhombic, a = 6.1888(4), b = 10.0920(6), c = 24.6826(17) Å, U = 1541.61(17) Å^3, T = 298(2) K, space group $P2_12_12_1$, Z = 4, 3679 reflections measured, 3654 unique (R_{int} = 0.034) which were used in all calculations. The final $wR(F_2)$ was 0.077 (all data) and $R/(F_0)$ was 0.071 (all data).

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