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Synthesis of chiral vicinal C_2 symmetric and unsymmetric bis(sulfonamide) ligands based on *trans*-1,2-cyclohexanediamine by aminolysis of *N*-tosylaziridines

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Abstract—The ring opening of *N*-tosylaziridines with aliphatic amines can be efficiently catalyzed by lithium perchlorate to provide derivatives of the *trans*-1,2-diamine in high yields. The reaction was used in desymmetrization of several cyclic *N*-tosylaziridines using chiral amines. Using this strategy, an efficient synthesis of chiral vicinal C_2 symmetric bis(sulfonamide) and unsymmetrical bis(sulfonamide) ligands based on *trans*-1,2-cyclohexanediamine was developed.

One of the most important factors in the advancement of catalytic asymmetric synthesis is the design and development of new chiral ligands. In catalytic asymmetric systems, small changes in the donating ability of a ligand or the size of its substituents can have a dramatic effect on the catalyst efficiency and enantioselectivity.[1–3] C_2 symmetric bis(sulfonamide) ligands of the type **1** (Fig. 1) are electronically different from and bind well to early transition metals[4] and main group elements.[5] This type of ligand has been used in the asymmetric Diels–Alder reaction,[5,6] the alkylation of aldehydes,[7] the cyclopropanation of allylic alcohols[8] and the amination of *N*-acyloxazolidones.[9] The chemistry of these ligands has been very well studied in the field of asymmetric synthesis. However, no work has been done using unsymmetrical bis(sulfonamide) ligands of type **2**.[10,11] This is mainly due to their non-availability and difficulty in mono-sulfonylation of a 1,2-diamine such as **3**. Palladium catalyzed monoarylation of 1,2-diamine **3** has been developed, but yields were not high.[12] Walsh and co-workers have developed a very good method for the synthesis of unsymmetrical bis(sulfonamides) via an amino-sulfonamide **4** from the commercially available corresponding diamine.[13] In this letter, we report a new approach to this type of chiral ligand based on aminolysis of aziridines.

It was envisaged that if *N*-tosylcyclohexyl aziridine were opened with a benzylamine in a diastereoselective manner, the product could be converted into an amino-sulfonamide after debenzylation. With this idea in mind, several *N*-tosyl aziridines were synthesized using known procedures.[14] Although ring opening of such *N*-activated aziridines with aromatic amines has been studied extensively using Lewis acids,[15] little has been published on their opening with aliphatic amines.[16] At the outset,

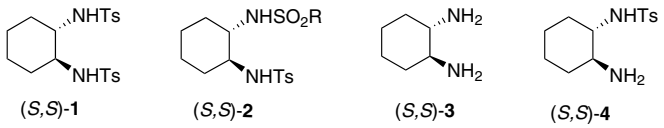

Figure 1. Cyclohexane-based symmetrical and unsymmetrical chiral ligands.

Keywords: Chiral C_2 symmetric and unsymmetric ligands; Sulfonamide ligands; Aminolysis; Aziridines.
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several Lewis acids such as $Cu(OTf)_2$ (70%), $Zn(OTf)_2$ (81%), $Sn(OTf)_2$ (78%), $YbCl_3$ (70%), $ErCl_3$ (68%) and $LiClO_4$ (88%), were screened for opening of *N*-tosylcyclohexyl aziridine with benzylamine in MeCN at room temperature for more than 24 h. From this study, it appeared that $LiClO_4$ was more effective as indicated by isolated yields. Long reaction times at room temperature prompted us to try the same reaction at reflux using $LiClO_4$ as the catalyst. To our delight, the reaction was complete in 4 h and the ring-opened product was obtained in 94% yield (Table 1, entry 1). The *trans* stereochemistry of the product was deduced from the coupling constants ($J = 10.48$ and 3.92 Hz) of the signal at 2.29 ppm (–C*H*–NH–) in the ^1H NMR spectrum. The ring-opening reaction was also tried with other amines such as phenethylamine, piperidine, morpholine and *N*-ethoxycarbonyl piperazine. In all cases, high yields of product were obtained (Table 1, entries 2–5). The reaction was extended to a few other *N*-tosyl aziridines and the results are summarized in Table 1.[18] Aziridines derived from cyclopentene and cyclohexa-1,4-diene gave the ring-opened products in good to excellent yields (Table 1, entries 6–9). An acyclic terminal aziridine gave products resulting from terminal attack only (Table 1, entries 10 and 11).

Once the methodology for cleavage of *N*-tosylaziridines with aliphatic amines,[18] especially benzylamine was established, it was extended to chiral amines. Initially, (*R*)-α-methylbenzylamine was used for desymmetrization of *N*-tosylcyclohexyl aziridine in the presence of $LiClO_4$ in MeCN. The reaction was complete in 6 h at reflux temperature and the product was obtained in 94% yield as a separable mixture of diastereomers in a 1:1 ratio (Table 2, entry 1). The reaction was scaled up to 25 g scale without any problem. The (*S*,*S*,*R*)-**9** diastereomer is more polar (R_f 0.28) than (*R*,*R*,*R*)-**9** (R_f 0.42). The absolute stereochemistry was established by X-ray analysis (vide infra). The ring-opening reaction proceeded well with (*R*)-3,3-dimethyl-2-butylamine also and a separable mixture of diastereomers (1:1 ratio) was obtained in 82% yield (Table 2, entry 2). The above reaction was also extended to the tosylaziridine from cyclopentene. Although good to excellent yields of the ring-opened products were obtained, the diastereomers could not be separated by column chromatography. Another chiral amine, (*R*)-1-(3-methoxy phenyl)ethylamine was also tried, but also proved inseparable by column chromotography (Table 2, entry 4). The mono-tosylaziridine of cyclohexa-1,4-diene gave a similar result to that of cyclohexene, where diastereomers could be separated (Table 2, entry 6).

In order to prove the absolute stereochemistry of product **9**, the less polar diastereomer was methylated with MeI to afford **15a** whose crystal analysis (Fig. 2) proved it to be (*R*,*R*,*R*)-**9**. In order to show the versatility, several alkylated amines were synthesized (Scheme 1). Surprisingly, alkylation of (*R*,*R*,*R*)-**9** with 2-methoxybenzyl bromide under identical conditions did not give the desired product. Instead, the reaction took place on the nitrogen to which tosyl group was attached, thus giving **16** in 72% yield (Scheme 1). The structure of **16** was confirmed by X-ray crystal structure (Fig. 2). This is strange, especially having the fact that the same reaction with benzyl bromide provided **15f** where alkylation took place on the other nitrogen. The reason for this anomaly could be due to steric interaction between the methyl group on the chiral centre and *ortho*-methoxy group on the benzyl bromide.

After successful synthesis of enantiopure ring-opened product **9**, we planned to synthesize several chiral ligands. Thus, the (*S*,*S*,*R*)-**9** diastereomer was subjected

Table 1. Reaction of *N*-tosyl aziridines with chiral aliphatic amines catalyzed by $LiClO_4$ in MeCN at reflux temperature

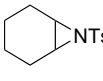
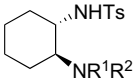
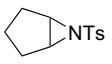
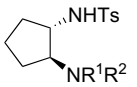
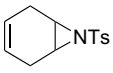
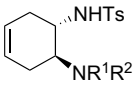
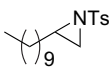
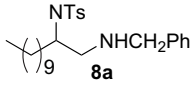
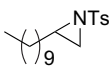
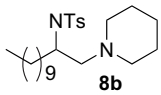
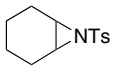
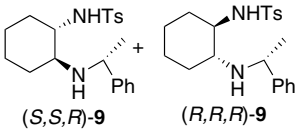
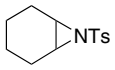
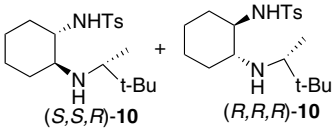
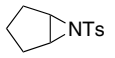
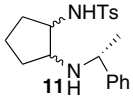
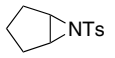
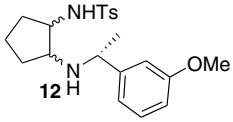
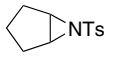
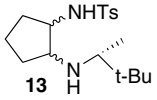
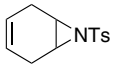
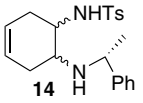
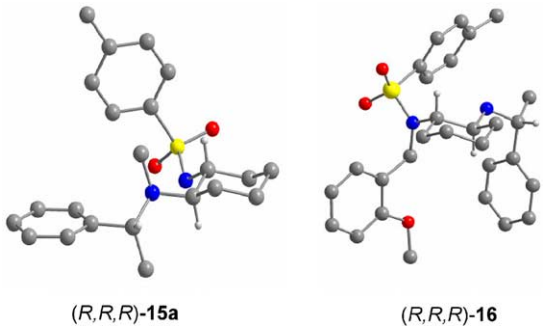
Entry	Aziridines		Products	% Yield (time, h)
1			**5a**;[15a] $R^1 = 4H$, $R^2 = CH_2Ph$	94 (4)
2			**5b**;[16b] $R^1 = H$, $R^2 = CH_2CH_2Ph$	87 (5)
3			**5c**; NR^1R^2 = piperidino	88 (2)
4			**5d**; NR^1R^2 = morpholino	95 (5)
5			**5e**; NR^1R^2 = *N*-ethoxycarbonyl piperazine	96 (2)
6			**6a**;[17] $R^1 = H$, $R^2 = CH_2Ph$	88 (6)
7			**6b**; NR^1R^2 = morpholino	93 (5)
8			**7a**; $R^1 = H$, $R^2 = CH_2Ph$	92 (6)
9			**7b**; NR^1R^2 = morpholino	92 (6)
10			 **8a**	89 (4)
11			 **8b**	90 (4)

Table 2. Reaction of *N*-tosyl aziridines with chiral aliphatic amines catalyzed by $LiClO_4$ in MeCN at reflux

Entry	Azirdines	Products[a]	% Yield (time, h)
1		 (*S,S,R*)-**9** (*R,R,R*)-**9**	94 (6)
2		 (*S,S,R*)-**10** (*R,R,R*)-**10**	82 (6)
3		 **11**	79 (6)
4		 **12**	93 (6)
5		 **13**	80 (6)
6		 **14**	83 (8)

The diastereomers separated on TLC only for entries 1, 2 and 6.
[a] In all cases, the products were obtained in a 1:1 diastereomeric ratio.

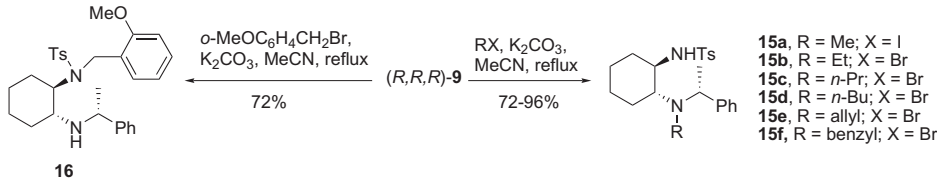


(*R,R,R*)-**15a** (*R,R,R*)-**16**

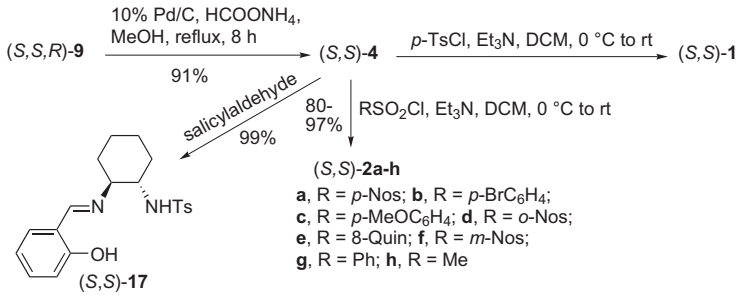
Figure 2. X-ray crystal structures of the sulfonamides.[19]

to debenzylation (Pd/C and $HCOONH_4$) to provide the amino-sulfonamide (*S,S*)-**4** in 91% yield. This is an important precursor for several chiral ligands. For example, (*S,S*)-**4** was tosylated to provide the C_2 symmetric bis(sulfonamide) ligand (*S,S*)-**1**. Its treatment with various sulfonyl chlorides provided a series of enantiopure unsymmetrical vicinal bis(sulfonamide) ligands (*S,S*)-**2a**–**h** in good to excellent yields. The amino-sulfonamide (*S,S*)-**4** compound was also converted into an important chiral ligand **17**[10a] in quantitative yield (Scheme 2).[13a]

In conclusion, we have developed an efficient method for the desymmetrization of *N*-tosyl aziridines in the presence of $LiClO_4$. We have used the method to synthesize a variety of chiral ligands. To the best of our knowledge, this is the first straightforward method for the synthesis of chiral unsymmetrical bis(sulfonamide) ligands based on *trans*-1,2-diaminocyclohexane.



Scheme 1.



Scheme 2.

Acknowledgements

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18. General procedure for ring cleavage of *N*-tosylaziridine with amine in the presence of $LiClO_4$: The amine (1.25 mmol) was added to a solution of *N*-tosyl aziridine (1 mmol) and $LiClO_4$ (0.1 mmol) in *anhydrous* acetonitrile (6 mL) under an argon atmosphere at rt. The reaction mixture was refluxed until completion of the reaction (usually 4–8 h, monitoring by TLC). Most of the acetonitrile was removed in vacuo and the crude reaction mixture was partitioned between EtOAc and water. The organic layer was washed with water, brine and dried over anhydrous sodium sulfate. It was concentrated in vacuo to give a crude product, which was

purified by silica gel column chromatography using EtOAc and hexane to give the pure vicinal amino-sulfonamide.

19. Crystallographic data for (*R*,*R*,*R*)-**15a** and (*R*,*R*,*R*)-**16** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC-280469 and 280470, respectively. This data can be obtained free of charge via the internet www.ccdc.cam.ac.uk/conts/retrieving.html or by sending an email to deposit@ccdc.cam.ac.uk.