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Synthesis of enantiopure pyrrolidine and piperidine derivatives via ring closing metathesis†

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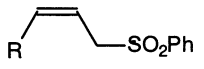
Abstract

The additions of lithiated allylsulfone carbanion to chiral *N*-sulfinylimines were found to proceed with good to excellent selectivity. The resulting intermediates **4a–d** after transformation to dienylamides **7a–d** and **16a–d**, were converted to functionalized enantiopure piperidines and pyrrolines, respectively, via ring closing metathesis (RCM). © 2000 Elsevier Science Ltd. All rights reserved.

Synthetic approaches to enantiopure 5- and 6-membered azaheterocycles have elicited a great deal of interest recently, because of their potential use as valuable intermediates for the synthesis of complex organic molecules. Several of these functionalized pyrrolidines and piperidines have been shown recently to exhibit diverse biological activities, especially as excellent glycosidase inhibitors.[1] Furthermore, chiral 2-substituted pyrrolidines and piperidines occur as natural products and are useful as chiral bases, chiral auxiliaries, and chiral ligands.[2] Therefore, considerable attention has been focussed in recent years on the synthesis of enantiopure pyrrolidine[3] and piperidine[4] derivatives.

In connection with our studies leading to chiral pyrrolidine and piperidine derivatives, we recently disclosed the synthesis of chiral non-racemic 2-arylpyrrolines via a [3+2] MIRC reaction [5a] and of 2-arylpiperidines via stereoselective addition[5b] of lithiated allylsulfone carbanions to optically pure (+)-(*S*)-(*E*)-*N*-*p*-toluenesulfinylimines. However, the addition of allylsulfone **1** was found to proceed only with moderate diastereoselectivity (45–57%, major isomer), presumably due to the coordinating hydroxyl appendage. In this communication we report a general enantioselective synthesis of functionalized 2-arylpiperidines, as well as of 2-aryl-3-pyrroline derivatives, utilizing the highly diastereoselective addition of simple allylsulfone **2** to arylsulfinylimines **3a–d**.



1 R = CH_2OH

2 R = H

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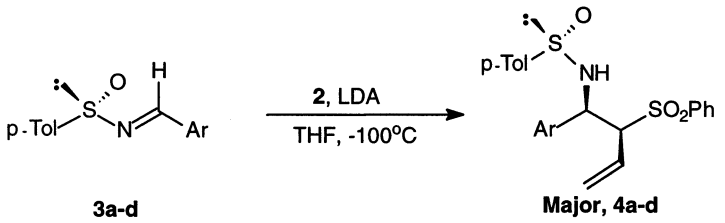
The required sulfinylimines were prepared by following the procedure of Davis et al.[6] The allylsulfone **2** was deprotonated by lithium diisopropylamide (LDA) in THF at −100°C followed by the addition of representative sulfinylimines **3a–d** in THF to afford the adducts **4a–d** in 85–100% yields (Eq. (1)).



(1)

The ^{1}H NMR spectra of these adducts **4a–d** indicated the presence of only two of the four possible diastereomers suggesting that control of stereoselectivity of the addition was total at one of the two prochiral centers. The observed diastereoselectivity can be rationalized by invoking a six membered cyclic transition state (Fig. 1), wherein Li^+ chelation between one of the sulfonyl oxygens and the sulfinylimine nitrogen forms a six membered chair, which directs the aryl group to the equatorial position due to 1,3-diaxial Ar/Ph (SO_2) repulsion[7] thus allowing the sulfonyl carbanion to attack exclusively from the *si* face on the C=N bond.

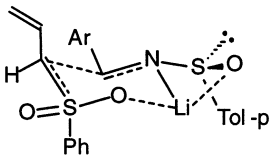
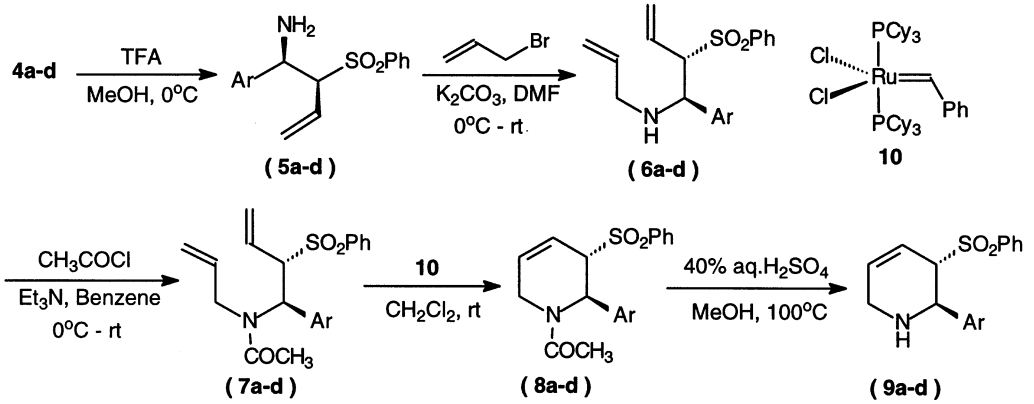


Figure 1.

Desulfinylation of compounds **4a–d** by treatment with trifluoroacetic acid (TFA) in methanol at 0°C afforded chromatographically separable (SiO_2), diastereomeric free amines, the *syn* **5a–d** being major (62–88%). Monoallylation followed by protection of the secondary amines **6a–d** by means of an acyl group set the stage for a metathesis ring closure. While amine **6a** did not undergo metathesis, treatment of a 0.1 M CH_2Cl_2 solution of the amides **7a–d** with 5 mol% of Grubbs RCM catalyst[8] **10** at room temperature for 2–3 h afforded functionalized piperidine derivatives **8a–d** in high yields (Scheme 1). Hydrolysis of the amide function of **8a–d** furnished the target functionalized piperidines **9a–d**. The results of our studies are summarized in Table 1.



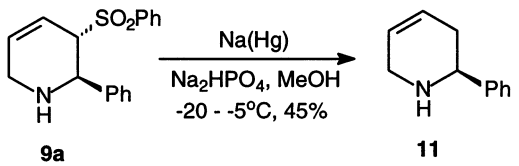
Scheme 1.

Table 1
Synthesis of **4a–d** and elaboration to functionalized piperidines **9a–d**

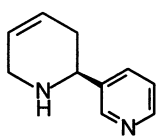
Entry	Ar	Yield (%)[a]						**9**[c]
		4[b]		**5**	**6**	**7**	**8**	**9**	$[\alpha]_D^{25}$
A	Ph	84	(90:10)	74	76	79	86	69	+128° (*c* 1.05)
B	*p*-MePh	100	(95:5)	88	72	74	82	74	+112° (*c* 1.9)
C	*p*-MeOPh	88	(89:11)	71	76	73	80	70	+118° (*c* 1.2)
D	2-Furyl	96	(67:33)	62	79	83	89	60	+148° (*c* 0.7)

[a] All yields refer to isolated yields.
[b] Numbers in paranthesis for **4** refer to diastereomeric ratio.
[c] Solvent methanol.

In order to determine the absolute configurations of (+)-2-arylpiperidines **9a–d**, it was first necessary to establish the relative stereochemistry of the aryl and phenylsulfonyl groups. ^{1}H NMR and NOESY experiments indicated a *trans* relationship with the Ar and $PhSO_2$ groups occupying pseudo diaxial positions[9] since the H_5 and H_6 protons are in a *gauche* relationship ($J_{5,6}=2.7$ Hz) in accordance with our previously reported (+)-2-arylpiperidines, whose absolute configurations were established as 5(*S*)-phenylsulfonyl-6(*R*)-aryl-1,2,5,6-tetrahydropyridine based on a conversion to (*S*)-anatabine.[5b] Furthermore, to ascertain that there was no difference in the stereochemical course of our previous reactions leading to (*S*)-anatabine and that of 5(*S*)-phenylsulfonoyl-6(*R*)-aryl-1,2,5,6-tetrahydropyridines reported here, we effected reductive desulfonation on **9a** to get **11** using sodium amalgam (Eq. (2)). The observed negative specific rotation $[\alpha]_D^{20}$ −80° (*c* 0.6, $CHCl_3$) for **11**[10] again suggested that the absolute configuration is the same as that of optically pure (*S*)-anatabine[11] whose $[\alpha]_D$ is −176°.

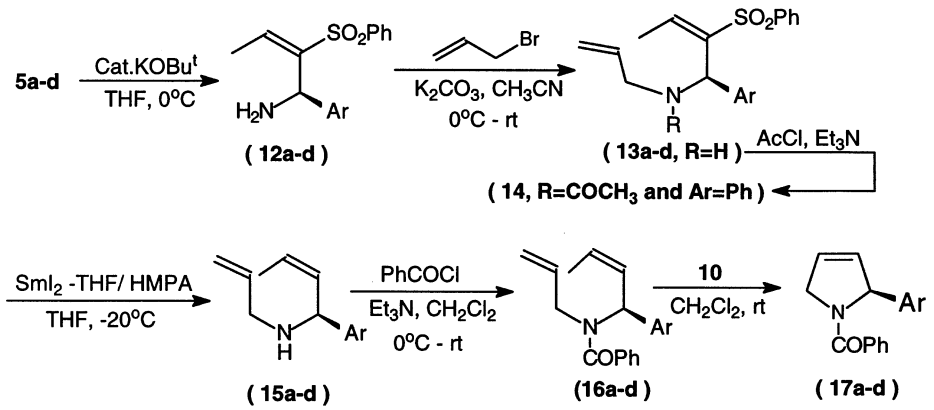


9a **11** (2)



(*S*) - Anatabine

After having established a general route for the enantioselective synthesis of functionalized piperidines, our attention was turned toward the possibility of employing one of the above intermediates also for the construction of enantiopure pyrrolidine derivatives. In order to demonstrate this strategy, we started with optically pure amine diastereomer **5a**, which was isomerised to **12a** using a catalytic amount of KO^{t}Bu in THF at 0°C. Monoallylation of amine **12a** to procure **13a** followed by protection of the secondary amine function by means of an acyl group to afford **14** (cf. Scheme 2), set the stage for a critical ring closure. Application of Grubbs RCM catalyst **10** and Schrock's Mo catalyst for the RCM process under standard reaction conditions led only to a total recovery of the starting material.



Scheme 2.

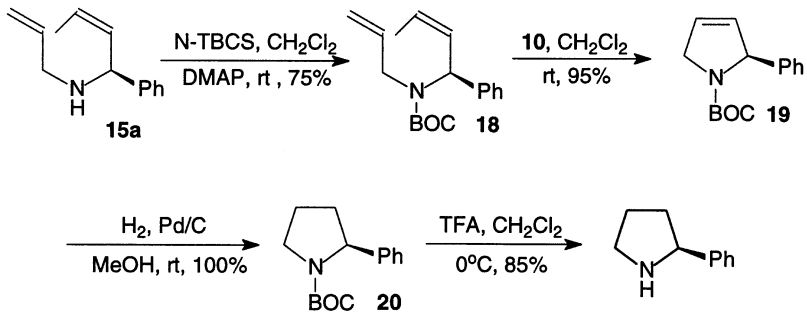
Since we suspected that failure of a metathesis was due to the presence of the electron withdrawing sulfone moiety on the double bond, we attempted to remove the phenylsulfonyl group in compound **13a**. While this was not successful with other reagents (Na–Hg,[12] Al–Hg,[13] $Na_2S_2O_7$,[14] K on graphite,[15] and *n*-Bu_3SnH[16]), SmI_2–THF/HMPA,[17] (4 equiv., −20°C) did effect a smooth desulfonation to yield amine **15a** in 62% yield and similar reduction of compounds **13b–d** followed by benzoyl protection of the derived amines **15a–d** furnished amides **16a–d** in good yield. Indeed, treatment of a 0.1 M CH_2Cl_2 solution of these amides with 5 mol% of catalyst **10** yielded pyrrolidine derivatives **17a–d** in excellent yield (cf. Table 2). The synthetic sequence is as shown in Scheme 2.

Table 2
Synthesis of 2-aryl-3-pyrroline derivatives

		Yield (%)[a]					**17**[b]
Entry	Ar	**12**	**13**	**15**	**16**	**17**	$[\alpha]_D^{25}$
A	Ph	78	72	62	100	94	−144° (*c* 0.95)
B	*p*-MePh	73	83	65	96	89	−301° (*c* 1.7)
C	*p*-MeOPh	85	78	59	82	90	−277° (*c* 0.86)
D	2-Furyl	74	78	59	75	85	−119° (*c* 2)

[a] All yields refer to isolated yields.
[b] Solvent methanol.

In order to assess the enantiopurity of 2-aryl-3-pyrroline derivatives **17a–d** obtained as shown in Scheme 2, we targeted the known *N*-Boc-2-phenylpyrrolidine,[3d] thereby showing the absolute stereochemistry as well by extrapolating this sequence to (*S*)-2-phenylpyrrolidine. To implement our plan, we protected amine **15a** by means of the Boc group, and subsequent olefin metathesis produced pyrroline **19**. Hydrogenation of **19** in the presence of 10% Pd/C afforded the known pyrrolidine **20**, whose analysis by chiral stationary phase HPLC on the Whelk-0 column indicated that it to be single isomer (>99.9%). Further, removal of the Boc group as shown in Scheme 3 afforded the known (*S*)-2-phenylpyrrolidine which showed $[\alpha]_D^{25}$ −23° (*c* 1.9, MeOH), lit.[3a] $[\alpha]_D$ −22° (*c* 0.3, MeOH).



Scheme 3. N-TBCS = *N-tert*-butyloxycarbonyloxysuccinimide

In conclusion, we have developed efficient protocols for the syntheses of both 5- and 6-membered enantiopure azaheterocycles, which do not rely on amino acids as a chiral source. This methodology which utilizes a simple allylsulfone and (*S*)-arylsulfinylimines via ring closing metathesis should also be applicable to procure the enantiomers of **9a–d** and **17a–d** by employing (*R*)-sulfinylimines. Further elaboration of these molecules into biologically important azasugars is underway in our laboratory.

Acknowledgements

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