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Synthesis of Chiral Non-racemic 2-Arylpyrrolines by a [3+2] Cycloaddition Route[1]

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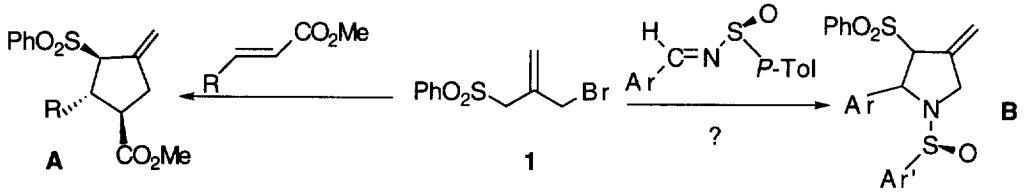
Abstract : A new and efficient diastereoselective (upto 76% de) synthesis of 2-aryl-3-pyrroline derivatives **3a-f** has been achieved by [3+2] cycloaddition of allylsulfone **1** and non-racemic sulfinimines **2**. Separation of the diastereomers led to optically pure 2(R)-pyrrolines (62-72% yield). The N-sulfinyl auxiliary can be removed with TFA. Copyright © 1996 Elsevier Science Ltd

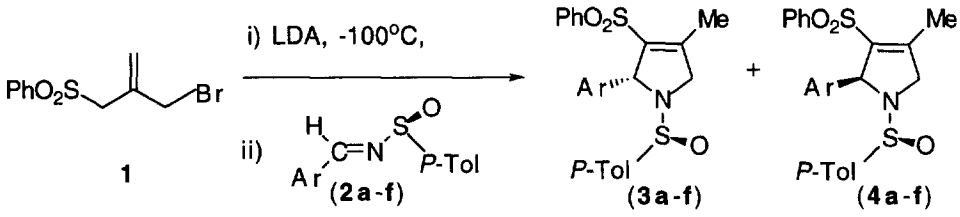
Many naturally occuring alkaloids and biologically active compounds posses the pyrrolidine moiety as a basic skeleton.[2] Numerous reports have described the application of pyrrolidine or pyrroline derivatives as chiral ligands,[3] chiral auxiliaries,[4] chiral bases,[5] and chiral building blocks for supramolecular chemistry.[6] A wide variety of synthetic approaches to the pyrroline or pyrrolidine skeleton are available. Most of the syntheses of chiral pyrrolidines emerge from natural amino acids as chiral auxiliaries[7] or are based on diastereoselective alkylation[8] or asymmetric hydrogenation[9] of an existing pyrroline moiety.

Herein, we describe a general approach to chiral non-racemic 2-arylpyrrolidine derivatives employing a [3+2] cycloaddition strategy[10] that involves the anion of allyl sulfone **1** and non-racemic sulfinimines[11] **2** as the chiral source. Based on our studies of **1** with unsaturated esters to afford **A**[12] we visualised that reaction of 3-(benzenesulfonyl)-2-bromomethyl-1-propene **1** , a 1,3-dipole equivalent of trimethylenemethane (TMM), with electrophilic imines **2** could lead, hopefully in a diastereoselective manner, to functionalized 4-methylenepyrrolidines **B**.



The required chiral sulfinimines (**2a-f**) were prepared employing the method of Davis *etal.*[13]Though, initially reaction of the anion of **1** with sulfinimine (S)-**2a** led to a mixture of ill-defined products, optimization (LDA at -100° C and utilization of HMPA) led to isolation of a cycloadduct in 70% yield. The adduct was shown by NMR to be a pyrroline formed as a 7.3:1 mixture of two diastereomers, **3a** and **4a**, separable by chromatography on silica gel. The ^{1}H NMR spectrum of **3a** showed a broad singlet at δ 2.26(3H), two *ddd* at δ 4.28 and 4.56(each 1H) and *dq* at δ 5.74(1H). The corresponding signals in ^{13}C NMR at δ 13.0(*q*), 60.3(*t*),

67.7(*d*) further confirmed the assigned structure. All our attempts to isolate an 4-exomethylene derivative(see **B**) were unsuccessful; apparently under the basic conditions isomerisation of the *exo* to the *endo* double bond occurs readily[14] due to the presence of the neighbouring sulfone function. The reaction was found to be general with other aryl sulfinimines (**2b-f**) giving rise to the corresponding 3-pyrroline derivatives (**3b-f** and **4b-f**)[15] in good yield and with a diastereomeric ratio of 3:1 to 7:1(Table I). The observed diastereoselection is presumably attributable to Li^+ chelation in the transition state between the sulfone and sulfinimine oxygens.



Scheme 1

Table I: Formation of chiral pyrrolines **3a-f** and **4a-f** and yields of **3** by reaction of **1** with **2a-f** at -100°C

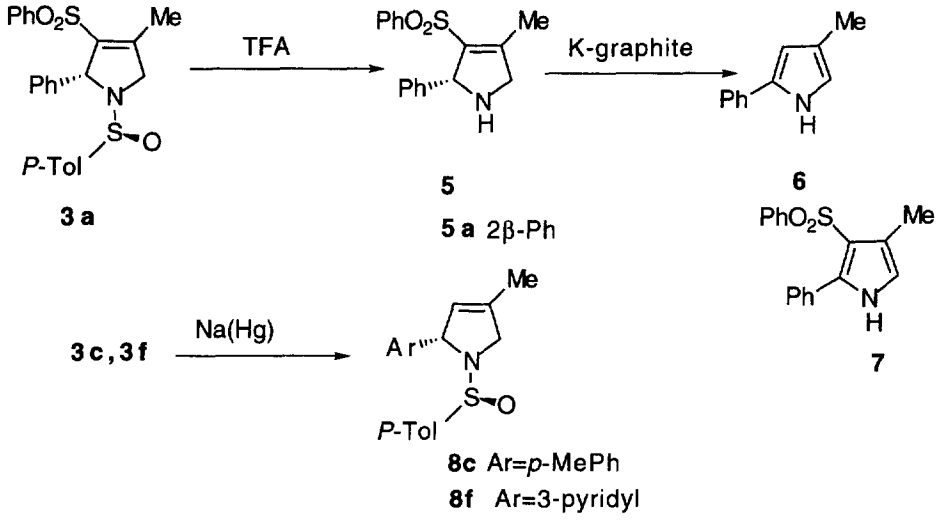
Entry	Ar	Ratio[a] **3:4**	Yield[b] (%)	$[\alpha]_D^{25}$ of **3**
a	Ph	88:12	70	-81.8(c 1.1,$CHCl_3$)
b	*p*-MeOPh	75:25	62	-92.8(c 1.2, $CHCl_3$)
c	*p*-MePh	86:14	72	-83.8(c0.84, $CHCl_3$)
d	*p*-ClPh	83:17	68	-130(c 1,$CHCl_3$)
e	2-Furyl	88:12	70	-38(c 1.05, MeOH)
f	3-Pyridyl	86:14	66	-70(c 1, $CHCl_3$)

(a) based on ^{1}H NMR of crude product (b) Isolated yield of the major diastereomer **3**. The minor diastereomer **4** was isolated in 10-20% yield.

In a typical experiment, 1 mmol of **1** in 1mL of THF was added to a solution of LDA (1.2 equiv.) in THF at -100°C. After 10 min, sulfinimine (S)-**2a** (1.1 equiv.) was added slowly and the solution was stirred at -100°C for 30 min. HMPA was added and the mixture was stirred at -90°C for further 2h (Scheme 1). Quenching of the reaction mixture with saturated aq. NH_4Cl solution and work up afforded the crude 1-*p*-toluenesulfinyl-4-methyl-2-phenyl-3-benzenesulfonyl-3-pyrroline as a 7.3:1 mixture of two diastereomers **3a** and **4a**. The two diastereomers were easily separated by silica gel flash chromatography using 4:6 ethyl acetate:pet.ether. X-ray crystallographic analysis of **3a** establishes the absolute configuration as 2(R), S(S).[16]

The N-sulfinyl group in **3a** was removed by treating with 2-equiv. of TFA in methanol at 0°C for 3-4 h and pyrroline **5** was isolated in 90% yield $[[\alpha]_D^{25}=-42°$ (c 0.95, MeOH)]. Removal of the sulfinyl group from **4a**, gave pyrroline **5a**, the enantiomer of **5** $[[\alpha]_D^{25}=+50°$ (c 1.0, MeOH)] indicating the diastereomeric

relationship between (R,S) **3a** and (S,S) **4a**. Attempts to desulfonate **3a** cleanly using Na(Hg) were unsuccessful and refluxing of **3a** with sodium dithionite and sodium hydrogencarbonate in aqueous methanol[17] afforded compounds **6** and **7** in 80% yield in a 3:1 ratio. We succeeded in obtaining pyrrolines **8c** and **8f** by reaction of **3c** and **3f** respectively with Na(Hg). Treatment of **5** with potassium on graphite[18] in THF at 20°C yielded 2-phenyl-4-methylpyrrole **6** as the only isolable product in 60% yield (Scheme 2). Hence, this methodology can serve as a short route to 2-arylpyrrole derivatives[19] starting from **1** and racemic sulfinimines.



Scheme 2

In summary, this methodology based on Michael addition of **1** to (S)-sulfinimines **2** serves as a novel and efficient stereoselective route to optically active 2(R)-arylpyrroline derivatives. Starting from (R)(-) sulfinimines **2** and **1**, the antipode of **3** can be prepared. Further elaboration of these chiral pyrrolines is in progress.

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14. Similar results were also obtained in the absence of HMPA but the reaction has to be slowly warmed to 0°C for an overall period of 6h.
15. All compounds were characterized by ^{1}H and ^{13}C NMR, mass spectroscopy. Data for compound **3a**: mp. 186-188°C, ^{1}H NMR ($CDCl_3$) (300 MHz) δ 2.26(*bs*, 3H), 2.3(*s*, 3H), 4.28(ddd, J-16,2,1 Hz, 1H), 4.56(ddd, J=16,5.5,1.5 Hz, 1H), 5.74(dq, J=5,1.5 Hz, 1H), 6.64-6.68(m, 2H), 6.84-7.08(m, 4H), 7.14-7.44(m, 8H) ^{13}C NMR ($CDCl_3$) δ 149.3(s), 141.0(s), 140.9(s), 138.8(s), 136.3(s), 132.6(d), 128.9(d), 128.3(d), 128.2(d), 127.5(d), 127.3(d), 126.9(d), 125.7(d), 67.7(d), 60.3(t), 21.0(q), 13.0(q). ms 438(MH^+), 332, 298(100), 222, 143. Observed mass= 438.1095 (for MH^+, calculated value= 438.1197).
16. We thank Professor A.I.Meyers, Colorado State University, for providing the X-ray analysis of **3a**. Details will be published in a full paper.
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