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Asymmetric Synthesis of Spirocyclic Pyrrolidines and Tetrahydrofurans by Chiral Aldol Reactions and Phenylthio Migration[1]

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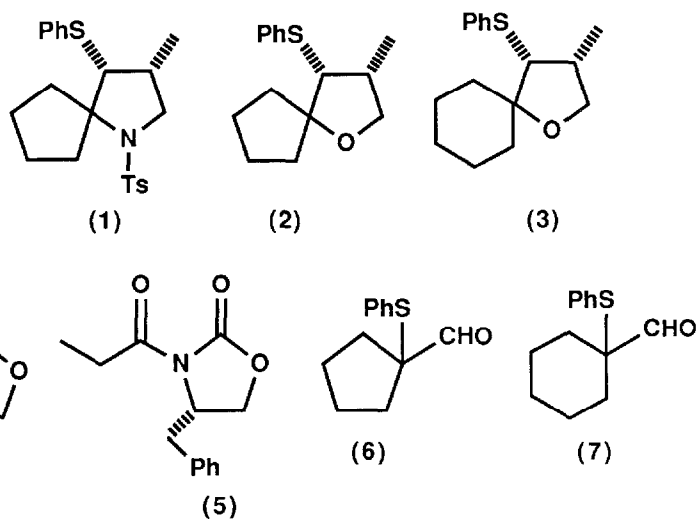
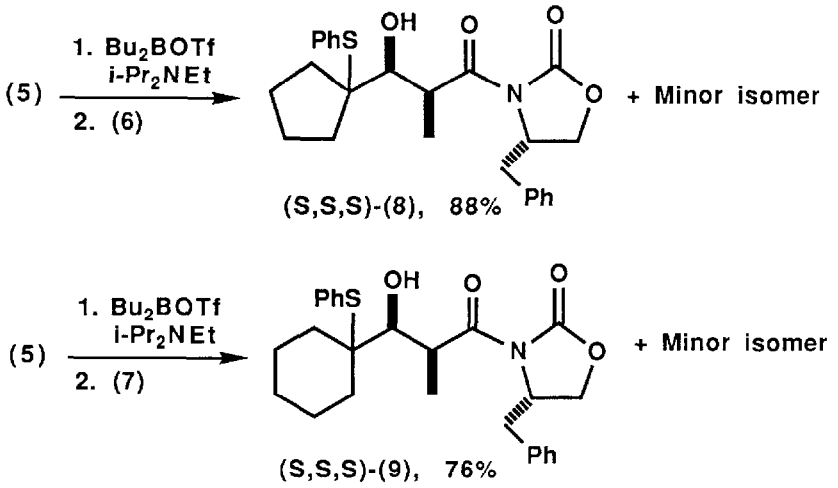
Abstract: Highly enantioselective aldol reactions of the boron enolate of (S)-N-propionyl-4-(phenylmethyl)-2-oxazolidinone with α-phenylthio cycloalkanecarbaldehydes were achieved. Cyclisation of the chiral phenylthio sulphonamide and diols gave the title compounds in excellent yields and enantiomeric excess.

As part of a developing programme[2] of coupled stereo-controlled aldol reactions and stereospecific PhS shifts in the synthesis of novel heterocyclic compounds, we report the first asymmetric synthesis of the pyrrolidine (**1**) and the tetrahydrofurans (**2**), unusual examples of 1-aza and 1-oxaspiro[4.4]nonanes, and (**3**), a 1-oxaspiro[4.5]decane. The chiral starting compounds used in this asymmetric synthesis were derived by the Evans *syn* selective chiral boron aldol methodology.[3,4] Most reports on *syn* selective asymmetric aldol reactions concern the valine-derived auxiliary[3] and few use crowded aldehydes, but we find that the boron enolate of (**5**), based on the phenylalanine-derived chiral auxiliary (**4**) combines with the crowded but reactive α-PhS aldehydes (**6**) and (**7**) in a highly diastereoselective aldol reaction, **scheme 1**.

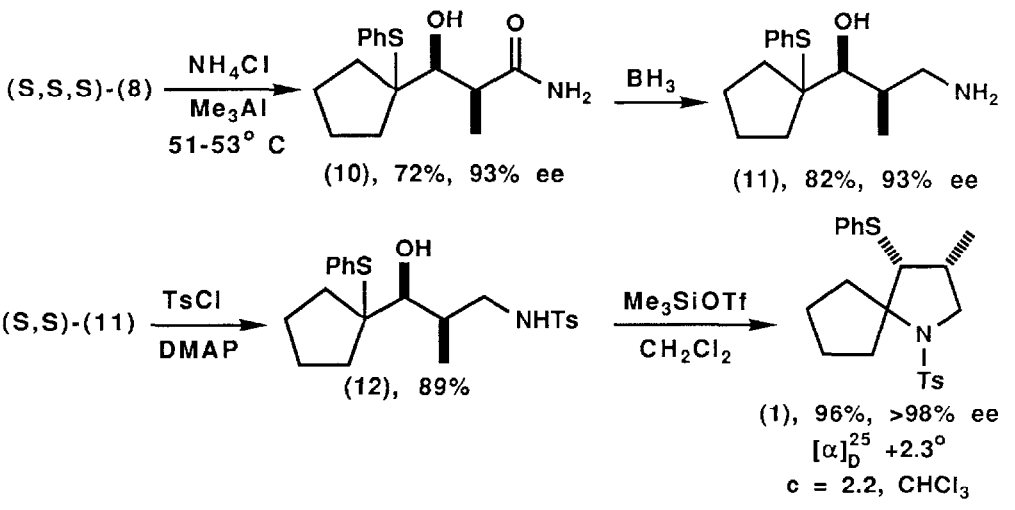


Scheme 1



The aldol reaction involving aldehyde (**6**) was more stereoselective (d.e. >90%) and was virtually complete within 5 hours of stirring at room temperature, while that involving aldehyde (**7**) was less stereoselective (d.e. 80%) and required 12-17 hours of stirring at room temperature. The diastereomeric excess in both cases was measured from the ^{1}H NMR of the crude reaction mixture[5] and the absolute sense of the chiral induction in the major products is assumed from previous work by Evans.[3] The major diastereoisomers were purified by column chromatography and used in the subsequent transformations depicted in **schemes 2** and **3**. Among other ways of removing the chiral auxiliary, transamination and reduction gave clean reactions. The enantiomeric excesses of the products resulting from this non-destructive removal of the chiral auxiliary (**4**) ranged from a minimum of 93% to a maximum of >98%.

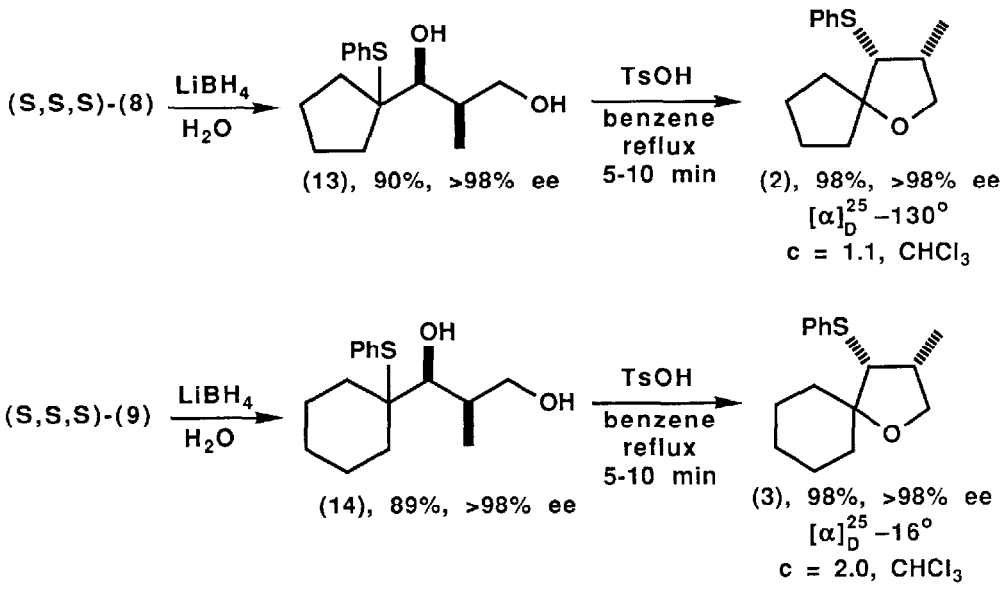
Scheme 2



The Weinreb transamination procedure[6,7] was used in the formation of (**10**) although Evans had previously described the racemisation-free removal of the chiral auxiliary via transamination[8] with the methoxy amide derivative, $Me_2AlN(OR)R$. Transamination at low temperatures (41-43 °C) was slow and yields were low (30%, with mainly recovery of starting material). At higher temperatures (51-53 °C), yields improve with long heating periods. As Coldham has already shown,[2c] tosylation of the amine (**11**) gave the sulphonamide (**12**) which cyclised stereospecifically to the pyrrolidine (**1**) with inversion at the migration terminus, **scheme 2**. A small amount of allyl sulphide was also formed.[2c] The enantiomeric excess of the amide (**10**) was determined directly by reduction to the amine (**11**) and ^1H (250 MHz) and ^{19}F NMR (235 MHz) analysis of the Mosher amides.[9]

The reductive removal of the chiral auxiliary was achieved in high chemical yield and optical purity with $LiBH_4$ in the presence of 1.0 equivalent of water, as recently reported by Penning,[10] to give the diols (**13**) and (**14**), **scheme 3**. The enantiomeric excesses of the diols (**13**) and (**14**) were determined by ^1H NMR (250 MHz) analysis of their Mosher esters.[9] Cyclisation of the diols (**13**) and (**14**) with catalytic amounts of TsOH led to the stereospecific formation of the tetrahydrofurans (**2**) and (**3**), respectively, with inversion at the migration terminus, in high yield and enantiomeric excess.

Scheme 3



The enantiomeric excess of the pyrrolidine (**1**) was determined by ^1H NMR at 250 MHz using the chiral lanthanide shift reagent, $Eu(hfc)_3$, while that of the tetrahydrofurans (**2**) and (**3**) was determined by ^1H NMR at 400 MHz using the chiral solvating alcohol, 2,2,2-trifluoromethyl-1-(9-anthryl)ethanol, (*S* or *R*), developed by Pirkle.[11] The relative (*syn*) stereochemistry of the final products (**1**), (**2**), and (**3**) was determined by NOE experiments and by comparison, in the case of tetrahydrofuran (**3**), with the racemic compound.[2]

Removal of the PhS group with Raney nickel from tetrahydrofurans[12] or pyrrolidines[2c] means that desulphurised products can be made in either enantiomeric series by changing the metal from boron to titanium[13]

(or of course from the correct enantiomer of the chiral auxiliary) in spite of the difficulty of making optically active *anti* aldols, since the relative (*syn*) stereochemistry then disappears. Removal of the toluene-*p*-sulphinate group with RedAl,[14] $Na(MeOCH_2CH_2O)_2AlH_2$, then gives optically active spirocyclic amines without either the PhS or Ts groups as both reductions have already been performed on the racemic compound.[2c]

Chiral synthesis of tetrahydrofurans,[15] exemplified by nonactic acid,[16] is well advanced, and pyrrolidines have been made by Sharpless technology[17] and from phenylglycine-derived chiral auxiliaries.[18] Both heterocyclic rings can be derived from the chiral pool – sugars and proline being the obvious sources. There are, however, almost no spirocyclic examples, though the methods used for the spirocyclic piperidine in histrionicotoxin[19] could no doubt be adapted to pyrrolidines.

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References and notes

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