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# STEREOCONTROLLED AMIDOCYCLISATIONS WITH PHENYLTHIO MIGRATION

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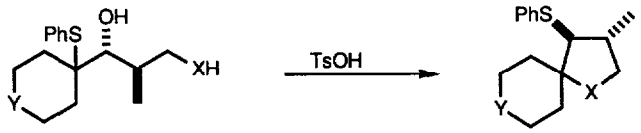
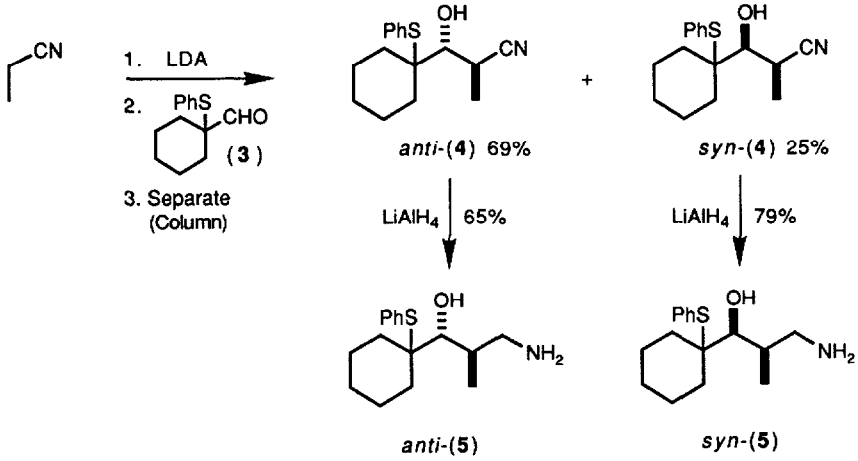
*Rearrangement of β-hydroxysulphides proceeds through an episulphonium ion which can be captured intramolecularly by the nitrogen atom of carbamates, ureas, or sulphonamides to give single diastereoisomers of pyrrolidines. With a free amine no capture takes place, instead allylic sulphides are formed.*

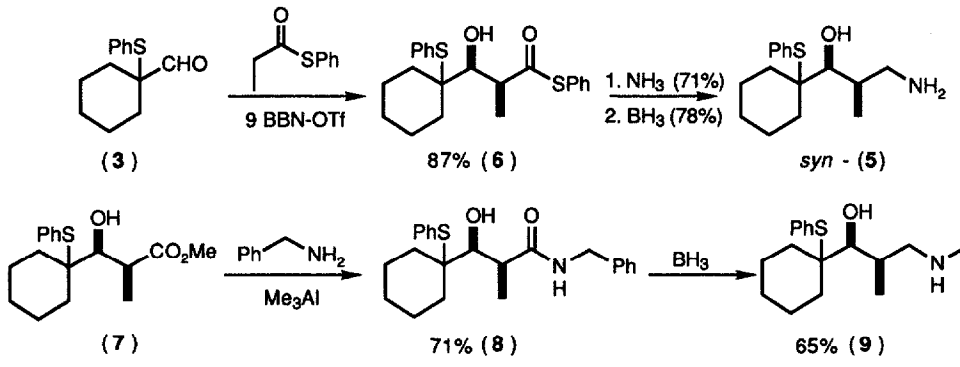
We have recently reported[1,2] that an oxygen atom can capture an episulphonium ion with complete stereochemical control to form cyclic ethers [(**2**), X=O, Y=$CH_2$] and lactones. We wished to extend this useful procedure to the formation of cyclic amines, also with stereochemical control. One approach is to substitute Y=$CH_2$ for Y=MeN, as described previously.[3] We now report the stereospecific formation of pyrrolidines [eg. (**2**), X=NR, Y=$CH_2$] in high yield.



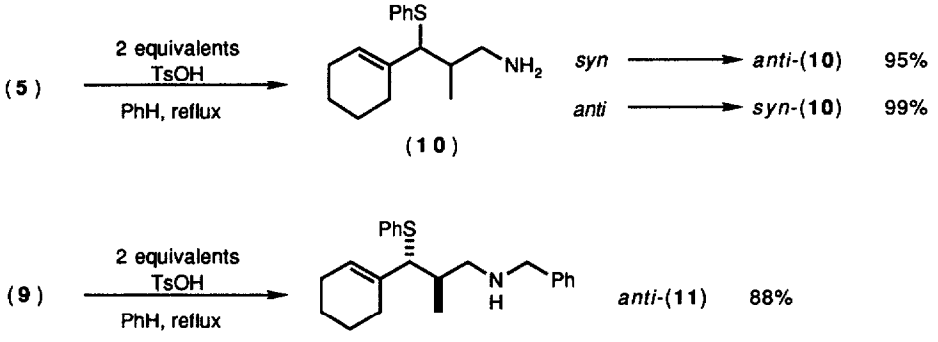

*anti*-(**1**) *anti*-(**2**)

The amines (**5**) were prepared by reduction of the nitriles (**4**) with $LiAlH_4$. The α-PhS aldehyde[4] (**3**) and the anion of propionitrile gave the nitriles (**4**), which were separable by column chromatography. A *syn*-selective aldol[5] with Masamune's thioester and this aldehyde (**3**) provided a *syn*-selective route to compound (**5**) after aminolysis ($NH_3$) and reduction ($BH_3$) of the aldol product (**6**). Secondary amines [eg. (**9**)] could be prepared by reduction of amides (**8**), made from the corresponding methyl esters (**7**) with $RNH_2$ and trimethylaluminium.[6]






Rearrangement of the amines (**5**) and (**9**) with toluene-*p*-sulphonic acid (TsOH) gave exclusively the allylic sulphides (**10**) and (**11**) respectively, with no formation of any cyclic amine. The allylic sulphides are formed stereospecifically, and in high yield. Under a variety of other conditions in which the episulphonium ion is formed [eg. MsCl, $SOCl_2$, TMSOTf ($Me_3SiOSO_2CF_3$), $TiCl_4$], no cyclic amine was produced.

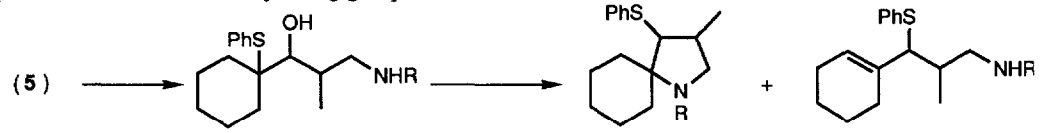



The amines (**5**) were converted into the corresponding amides, ureas, carbamates and sulphonamides as shown in table 1. The products (**12**) were treated under conditions for rearrangement (TsOH or TMSOTf) to give a mixture of the pyrrolidines (**13**) and the allylic sulphides (**14**), table 2. For example, entry 6 with *syn*-(**12d**) and TMSOTf gave almost exclusively the cyclised product *syn*-(**13d**). The formation of both (**13**) and

**Table 1**

| Starting Material | Reagents | Product | R | Yield |
|---|---|---|---|---|
| *syn*-(**5**) | MeCOCl | *syn*-(**12a**) | COMe | 73% |
| *syn*-(**5**) | PhNCO | *syn*-(**12b**) | CONHPh | 89% |
| *anti*-(**5**) | PhNCO | *anti*-(**12b**) | CONHPh | 97% |
| *syn*-(**5**) | EtOCOCl | *syn*-(**12c**) | $CO_2Et$ | 99% |
| *anti*-(**5**) | EtOCOCl | *anti*-(**12c**) | $CO_2Et$ | 98% |
| *syn*-(**5**) | $TolSO_2Cl$ | *syn*-(**12d**) | $SO_2Tol$ | 94% |
| *anti*-(**5**) | $TolSO_2Cl$ | *anti*-(**12d**) | $SO_2Tol$ | 96% |

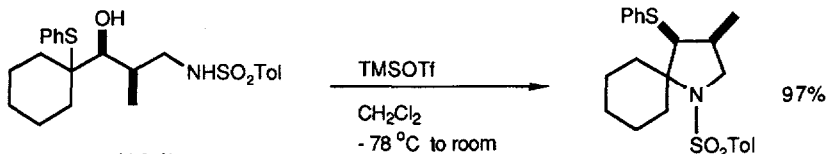
(**14**) is stereospecific, with inversion at the migration terminus [*syn*-(**12**) gives only *syn*-(**13**) and *anti*-(**14**), *anti*-(**12**) only *anti*-(**13**) and *syn*-(**14**)], as shown by n.O.e. experiments on *syn*- and *anti*-(**13d**) and *syn*-(**13b**). Under our usual conditions for PhS migration (TsOH), the yield of the pyrrolidine (**13**) was higher in more polar solvents (entry 2). The yield of (**13**) increased further and gave more consistent results with TMSOTf (entries 3,4,6,7). The yield of the pyrrolidine (**13**) increases along the series amide<urea≈carbamate< sulphonamide. Excellent yields of the spirocyclic amine (**13d**) are produced with TMSOTf (entries 6,7). These conditions give comparable or even higher yields than the reported amido-halogenation,[7]-selenenylation,[8] and -sulphuration[9] of alkenes, and also have the advantage of full stereochemical control. The amidohalogenation of alkenes with NBS with different amido groups has been shown to follow a similar trend in which sulphonamides were the best cyclising groups.[7d]




(**12**) (**13**) (**14**)

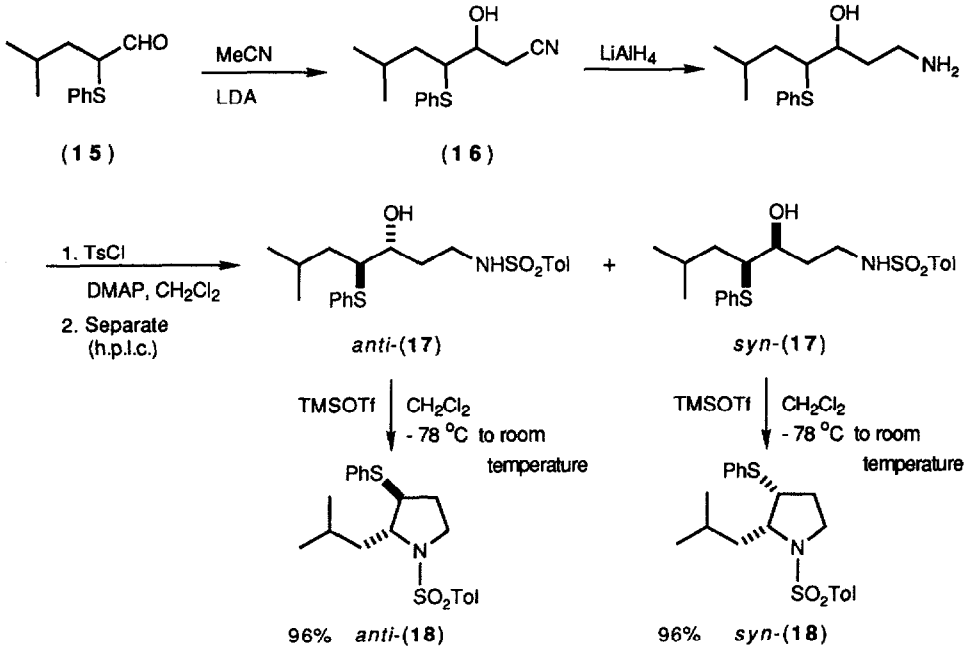
**Table 2**

| Entry | Starting Material | R | Conditions[10] | Yield (13) | Yield (14) |
|---|---|---|---|---|---|
| 1 | *syn*-(**12a**) | COMe | TsOH | -- | 91% |
| 2 | *syn*-(**12b**) | CONHPh | TsOH, $CH_2Cl_2$ | 65% | 22% |
| | | | TsOH, PhH | 21% | 70% |
| | | | TMSOTf | 66% | 18% |
| 3 | *anti*-(**12b**) | CONHPh | TsOH, $CH_2Cl_2$ | 15% | 59% |
| | | | TMSOTf | 61% | 17% |
| 4 | *syn*-(**12c**) | $CO_2Et$ | TsOH, $CH_2Cl_2$ | 34% | 62% |
| | | | TMSOTf | 74% | 20% |
| 5 | *anti*-(**12c**) | $CO_2Et$ | TsOH, $CH_2Cl_2$ | 88% | 9% |
| | | | TMSOTf | 63% | 35% |
| 6 | *syn*-(**12d**) | $SO_2Tol$ | TsOH, $CH_2Cl_2$ | 84% | 16% |
| | | | TMSOTf | 97% | 2% |
| 7 | *anti*-(**12d**) | $SO_2Tol$ | TsOH, $CH_2Cl_2$ | 81% | 18% |
| | | | TMSOTf | 90% | 9% |




*syn*-(**12d**) *syn*-(**13d**)

We have further investigated the synthetic usefulness of the cyclisation reaction by changing the tertiary to a secondary migration origin. The previous examples in table 2 all involve phenylthio migration from a tertiary migration origin to a secondary terminus. We have found[2] that secondary to secondary phenylthio migration is slower and more prone to steric effects when oxygen is the intramolecular nucleophile. Reduction and tosylation of the nitriles (**16**), formed in a 3:1 ratio from the α-PhS aldehyde (**15**), gave the sulphonamides (**17**), which were separated by h.p.l.c. On treatment with TMSOTf, each isomer cyclised stereospecifically in essentially quantitative yield to give a single and different isomer of (**18**).

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## References and Notes

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10. Reactions in TsOH (0.8 equivalents) were refluxed until no starting material remained (5 min to 9 h). With TMSOTf in THF or $CH_2Cl_2$ at -78 °C reactions were allowed to warm to room temperature. Yields after chromatography.

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