Hemiaminals as substrates for sulfur ylides: Direct asymmetric syntheses of functionalised pyrrolidines and piperidines†

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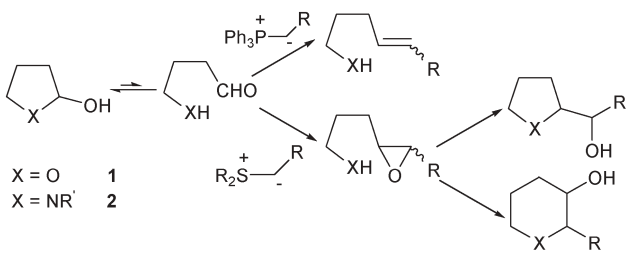
Phenyl stabilised chiral sulfur ylides react with five-membered-ring hemiaminals to give functionalised pyrrolidines directly with high enantioselectivity. The reaction can be diverted to give piperidines instead by isolation of the intermediate epoxide and treatment with TMSOTf.

Lactols **1** [1] and related hemiaminals **2** [2] are well known to react with phosphorus ylides to give ω-unsaturated alcohols or amines. Such reactions occur *via* the ring opened aldehyde, which is only present at very low concentrations. We wished to investigate whether such readily available substrates[3] could also react with sulfur ylides, especially because the ω-epoxy alcohol/amine product had the potential to ring close directly to form heterocycles with control of stereochemistry (Scheme 1). However, the low concentration of the active electrophile posed significant problems with sulfur ylides, especially semi-stabilised ones. With such substrates, if reaction with the electrophile is slow (*e.g.* as is the case with Michael acceptors[4]) competing ylide equilibration followed by Sommelet–Hauser rearrangement can dominate instead.[5]

Aware of these potential problems, we began our studies with cyclic hemiaminals of different ring size bearing different groups on nitrogen (Table 1). These studies showed that strong electron withdrawing groups on nitrogen (Ts group), contained in a 5-membered rather than the more stable 6-membered ring were required to provide sufficient concentration of the open chain aldehyde to allow ylide reaction to proceed (entry 2, Table 1). In the absence of such features, ylide equilibration followed by Sommelet Hauser rearrangement leading to sulfide **5** was the dominant pathway. We had selected the phosphazene base (P_2 base)[6] for this study because in parallel studies of different bases



Scheme 1 Reaction of lactols **1** and hemiaminals **2** with ylides.

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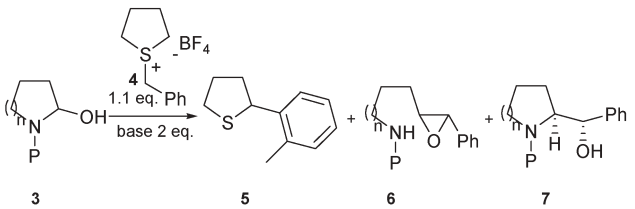
Table 1 Reaction of different hemiaminals **3** with sulfonium salt **4**

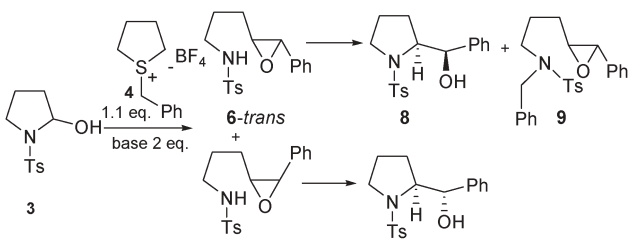


Entry	P	*n*	Conditions	Yield[a] (%) 5[b]	6 (*trans* : *cis*)[c]	7
1	Boc	1	P_2 base, THF, 0 °C, 18 h	80	14 (5 : 1)	0
2	**Ts**	**1**	**P_2 base, DCM, 0 °C, 3 h**	**0**	**54 (1:0)**	**18**
3	Ts	2	P_2 base, DCM, 0 °C, 18 h	70	33 (1.5 : 1)	0
4	Cbz	2	P_2 base, DCM, −78 °C, 4 h	100	0	0

[a] Yield based on **3**. [b] Yield based on sulfonium salt **4**. [c] Diastereoselectivity determined by ^{1}H NMR of the crude reaction mixture.

(Table 2), this base proved to be the most effective. Other bases were either less efficient or generated the by-product **9** (entries 1, 2, Table 2). The by-product **9** is formed from alkylation of the aminoepoxide **6** by the sulfonium salt **4** acting as the electrophile.

Table 2 Optimisation of conditions for the reaction of hemiaminal **3** with sulfonium salt **4**



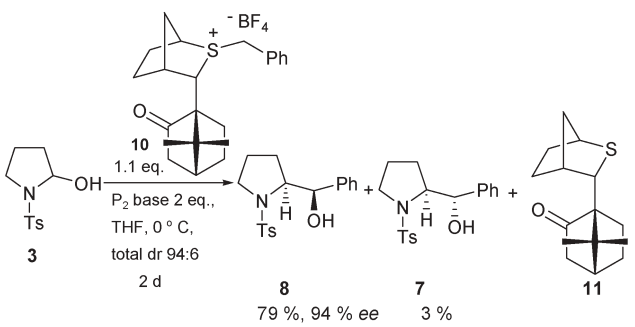
Entry	Conditions	Yield (%) 6(*trans* : *cis*)	7	8	9(*trans* : *cis*)
1	DBU, DCM, 5 h, 0 °C	21 (2:1)	traces	0	20 (2:1)
2	DBU, DCM, 7 h, 0 °C	24 (6:1)	7	0	23 (2:1)
3	LiHMDS, THF, 7 h, 0 °C	5 (1:0)	1	0	0
4	NaH, THF, 7 h, 0 °C	31 (1:1)	2	0	0
5	KHMDS, THF, 7 h, 0 °C	26 (2:1)	4	0	0
6	P_2 base, THF, 7 h, 0 °C	27 (1:0)	0	61	0
7	**P_2 base, THF, 18 h, 0 °C**	**0**	**0**	**89**	**0**
8	**P_2 base, DCM, 3 h, 0 °C**	**54 (1:0)**	**18**	**0**	**0**
9	P_2 base, DCM, 18 h, 0 °C	24 (1:0)	22	44	0

Using the more basic P_2 base, more of the sulfonium salt was deprotonated, rendering it unavailable to act as an electrophile for alkylation of the sulfonamide. Using the P_2 base a mixture of epoxide **6** together with pyrrolidines **7** and **8** were obtained depending on the reaction conditions.

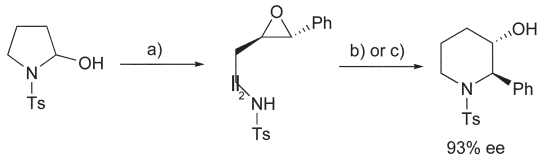
In dichloromethane at short reaction time, a mixture of *trans* epoxide **6** and pyrrolidine **7** was obtained (entry 8, Table 2). This indicated that the ratio of *trans* : *cis* epoxides initially obtained was 54 : 18 (3 : 1). At longer reaction time, more of the *trans* epoxide was converted into pyrrolidine **8** (entry 9,Table 2). However in THF, epoxide **6** was formed with *trans* selectivity (>95 : 5) (entry 6,Table 2) and at extended reaction time, pyrrolidine **8** was formed exclusively (entry 7,Table 2). Through isolating *trans* epoxide **6** and subjecting it to the reaction conditions, we established that pyrrolidine **8** was derived from the *trans* isomer and therefore that pyrrolidine **7** was derived from the *cis*-isomer. This also allowed us to predict the stereochemistry of **8** (assuming inversion), which was subsequently proved by X-ray analysis.

Having discovered a highly diastereoselective synthesis of pyrrolidines, we sought to make it asymmetric. Using the chiral sulfonium salt **10**,[7] pyrrolidine **8** was obtained in good yield (79%) with high enantiomeric excess (94% ee) and the sulfide was efficiently reisolated (82% yield). The diastereoselectivity was slightly lower this time (96 : 4) and a small amount of pyrrolidine **7** (3%) was also isolated (Scheme 2). This represents a very efficient asymmetric route to functionalised pyrrolidines.

Under the reaction conditions, epoxide **6** underwent clean regioselective ring opening at the C^1 position to give the five-membered ring pyrrolidine, in accordance with Baldwin's rules.[8,9] However, we wished to investigate whether ring opening could be diverted to the C^2 position to furnish piperidines instead. A survey of the literature revealed that in the related ring opening reaction involving oxygen nucleophiles, the normally favoured tetrahydrofuran formation could be diverted to pyran formation in substrates possessing cation stabilising groups under acidic/Lewis acidic conditions.[10,11] However, such reactions had not been extended to the corresponding nitrogen analogues. We therefore isolated epoxide **6** and subjected it to a variety of Lewis acids. Of the Lewis acids tested,[12] TMSOTf and $Sc(OTf)_3$ were found to be effective at promoting ring opening of the epoxide at the C_1 position cleanly, affording piperidine **12** as a single diastereomer in very high yield (Scheme 3). The *trans* diastereomer **12** was expected but the low coupling constant (broad singlet) observed for the C1 proton was a concern. An X-ray structure proved that the relative stereochemistry was indeed *trans* and that the low coupling



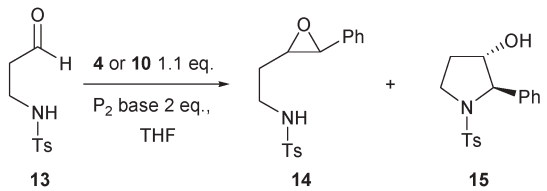
Scheme 2 Direct asymmetric synthesis of pyrrollidines.



Reaction conditions and reagents: a) **10**, P_2 base, DCM, r.t., 3 h, 54 %; b) TMSOTf, DCM, 2 d, r.t., 98 %; c) $Sc(OTf)_3$, DCM, 3 d, r.t., 92 %

Scheme 3 Ring opening of epoxide **6** at C_1 position.

Table 3 Expansion of the methodology utilising aldehyde **13**



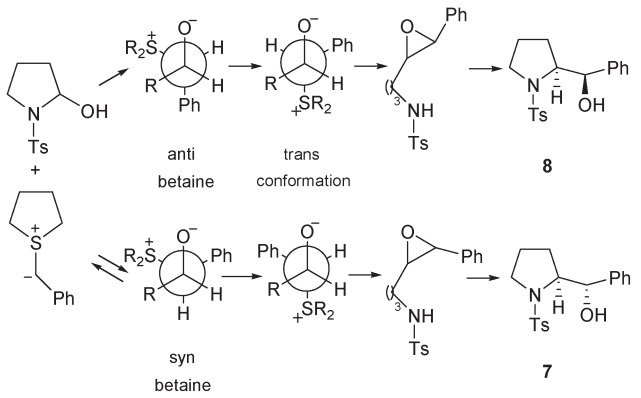
Entry	Conditions Time (Temp.)	Sulfonium salt	Products (%) **14** (*trans* : *cis*)	**15** (% ee)
1	7 h (0 °C)	**4**	21 (1:0)	39 (—)
2	7 h (0 °C) 48 h (r.t.)	**4**	10 (1:0)	62 (—)
3	7 h (0 °C) 11 h (65 °C)	**4**	0	71 (—)
4	7 h (0 °C) 11 h (r. t.)	**10**	11 (1:0)	55
5	**7 h (0 °C) 11 h (65 °C)**	**10**	**0**	**76 (91)**

constant observed was due to the substituents adopting diaxial positions leaving the protons H_1 and H_2 diequatorial. Once more, the process was rendered asymmetric using the chiral sulfonium salt **10** *furnishing the piperidine* ***12*** *with high enantioselectivity (93% ee)*.

The epoxidation–cyclisation sequence was further extended to β-amino aldehyde **13** (Table 3). This substrate behaved similarly to the aminal **3**, but cyclisation reaction was slower. Simply heating the reaction mixture, after the epoxidation reaction was complete enhanced the rate of cyclisation giving pyrrolidine **15** in high yield and as a single diastereomer (entry 3, Table 3). The stereochemistry of **15** was proved by X-ray analysis again. Once again, use of the chiral sulfonium salt **10** rendered the reaction asymmetric (91% *ee*, entry 5, Table 3).

The high diastereoselectivity observed in the reaction was unexpected since reaction of phenyl-stabilised sulfur ylides with unbranched aliphatic aldehydes normally gives subtantial quantities of the *cis* epoxide.[13] The mechanism of the reaction involves four distinct steps: formation of the betaine with charges adjacent to each other, followed by bond rotation to the *trans* conformation, ring closure to the epoxide, and the final step is ring opening/cyclisation (Scheme 4). From DFT calculations and cross-over experiments we have established that the second step, bond rotation, is the rate and selectivity determining step. The high *trans* selectivity observed with the current electrophiles indicates that the barrier to bond rotation is substantially higher for the *syn* betaine resulting in reversibility back to the starting materials. The reaction then partitions down the productive *antibetaine* pathway leading to the *trans* epoxide.

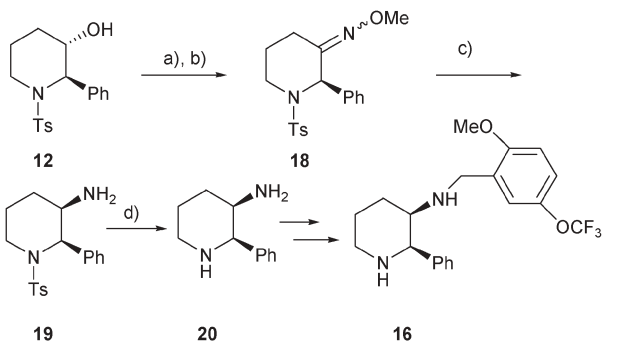
The synthetic utility of this novel methodology was demonstrated by its application in the synthesis of the potent



Scheme 4 Mechanism of the ylide epoxidation reaction.

neurokinin-1 (NK-1) receptor antagonist CP-122,721 **16**.[14] *Trans*-disubstituted piperidine **12** was transformed to *cis*-piperidine **19** (89% ee) by oxidation, followed by selective reduction of methoxyimine **18** (Scheme 5), Finally, deprotection of **19** led to the known intermediate **20**[14,15] which has been converted to **16**.[14]

In conclusion, we have described a new method for directly forming pyrrolidines and piperidines with control of relative and absolute stereochemistry from readily available hemiaminals. The methodology uses chiral sulfur ylides and the process occurs *via* γ-amino epoxides that undergo ring closure under the reaction conditions (base) to give pyrrolidines or under Lewis acidic conditions to give piperidines.



Scheme 5 Application of the methodology in the synthesis of CP-122,721 **16**.

CCDC 298299–298301. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b602226j

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