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Aminals as Substrates for Sulfur Ylides: A Synthesis of Functionalized Aziridines and *N*-Heterocycles

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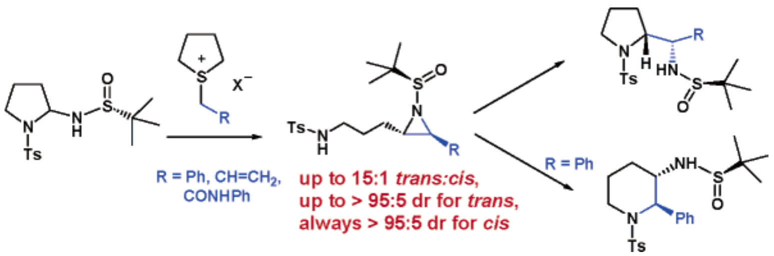
ABSTRACT

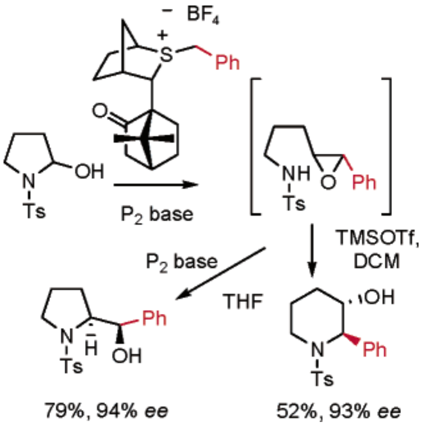


Sulfur ylides stabilized by Ar, vinyl, or amide groups react with five-membered-ring *tert*-butylsulfinyl aminals to give functionalized chiral, nonracemic aziridines in high yield and with good selectivities (up to 15:1 trans:cis, up to >95:5 trans dr, always >95:5 cis dr). The intermediate aziridines can be converted into pyrrolidines or piperidines depending on the reaction conditions.

Lactols and related hemiaminals, readily available synthetic intermediates, are masked electrophiles but nevertheless react readily with a range of nucleophiles including phosphorus ylides[1] and stabilized[2] and semistabilized[3] sulfur ylides. These reactions occur via the ring-opened aldehyde, which is only present in very low concentrations. Even so, despite the propensity for semistabilized sulfur ylides to undergo competing rearrangement reactions when the desired reaction with the electrophile is slow (because in this case it was in low concentration), we were able to achieve a highly enantioselective synthesis of functionalized pyrrolidines and piperidines (Scheme 1).[3] These reactions occur via the intermediate epoxides which can be isolated, or ring opened to give the corresponding 1,2-amino alcohols.[3]

In considering the extension of this process to the synthesis of 1,2-diamines, we required reactions of sulfur ylides with

Scheme 1. Reactions of Sulfur Ylides with *N*,*O*-Hemiacetals: Synthesis of Functionalized Pyrrolidines and Piperidines



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[1] (a) Kawada, K.; Tsushima, T. *Heterocycles* **1989**, *28*, 573. (b) Seno, K.; Hagishita, S. *Chem. Pharm. Bull.* **1989**, *37*, 948. (c) Kamata, S.; Haga, N.; Tsuri, T.; Uchida, K.; Kakushi, H.; Arita, H.; Hanasaki, K. *J. Med. Chem.* **1990**, *33*, 229. (d) Ohtani, M.; Narisada, M. *J. Med. Chem.* **1990**, *33*, 1027. (e) Holmes, A. B.; Smith, A. L.; Williams, S. F. *J. Org. Chem.* **1991**, *56*, 1393.

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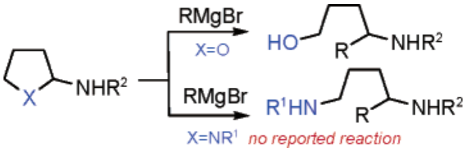
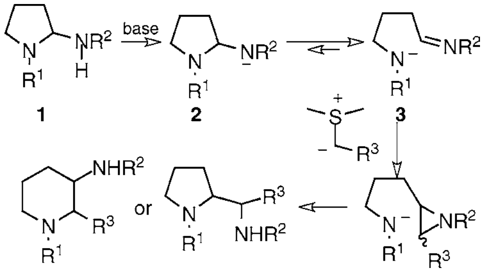
aminals. However, a search of the literature revealed that while nucleophilic additions of Grignard reagents to *N*,*O*-acetals had been described,[4] there were no reported reactions with aminals (Scheme 2). Furthermore, there were no reports of reactions of more complex nucleophiles such as ylides with either *N*,*O*-acetals or aminals. Nevertheless, we recognized a potential opportunity to effect such reactions and also to render them asymmetric. In particular, following amine deprotonation of aminal **1**, if R^2 is less anion-stabilizing than R^1 the ring-opened, active electrophile **3** will be favored over aminal **2**, thus promoting the reaction with a sulfur ylide (Scheme 3). For these reasons and to introduce asymmetry, substrate **4**[5] with R^1 = Ts and R^2 = S(O)*t*-Bu[6] was selected for a study employing the phenyl-stabilized ylide derived from **5**.

Scheme 2. Aminals as Substrates for Nucleophilic Additions

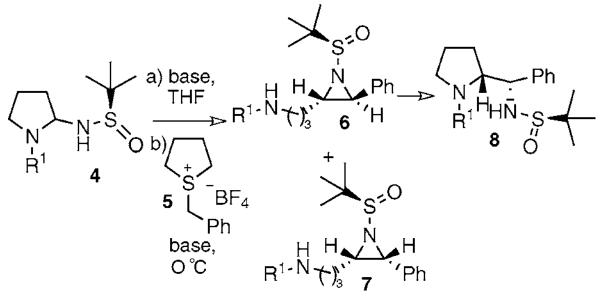


Scheme 3. Proposed Reaction of Aminals with Sulfur Ylides



Exploration of the reaction conditions revealed that the choice of base was critical to the success of the reaction (Table 1). While standard Li-, Na-, and K-hexamethyldisilazide bases gave very little product (entries 1−3), the use of the P_2-phosphazene base[7] was much more successful furnishing the desired aziridines in 77% yield (entry 4). Although high trans selectivity was observed (**6**:**7**, 13:1), diastereocontrol imparted from the *tert*-butylsulfinyl group was rather low (trans dr, 70:30). Subsequent heating of the reaction following aziridination led to ring closure to give pure pyrrolidine **8** in 46% isolated yield as a single diastereoisomer (entry 5). The less electron-withdrawing Boc group at R^1 could also be employed and although the aziridine was obtained with good diastereoselectivity in this case, the yield was rather low (entry 6). Presumably, there is a lower concentration of the active imine due to the lower pK_a of the amide (pK_a of t-BuOCONH$_2$ = 25; pK_a of TsNH$_2$ = 16)[8] and so side-reactions involving the semistabilized ylide now effectively compete with the desired reaction resulting in reduced yields.

Table 1. Reaction of Aminal **4** with Sulfur Ylide **5**



entry	conditions	overall trans:cis[a]	**6** + **7** (%)	trans dr	cis dr	**8**
1	LiHMDS, 18 h, R^1 = Ts		trace			
2	NaHMDS, 18 h, R^1 = Ts		trace			
3	KHMDS, 18 h, R^1 = Ts	6:1	11	>95:5	>95:5	
4	P_2 base, 3.5 h, R^1 = Ts	13:1	77[b]	70:30	>95:5	
5	P_2 base, 5 h, reflux 15 h, R^1 = Ts	12:1				46[c]
6	P_2 base, 3.5 h, R^1 = Boc	15:1	39	>95:5	>95:5	

[a] Overall trans/cis ratios determined by calculation from isolated yields. [b] Major *trans*-aziridine was isolated pure in 50%. [c] Pyrrolidine **8** was isolated as a single diastereomer. Piperidine **16** was also isolated in 12% yield.

Aminal **4** was subsequently reacted with a much broader range of sulfur ylides (Table 2). The electron-rich aryl sulfonium salt **9** gave broadly similar selectivity to the benzyl sulfonium salt **5** in relation to the sulfinyl auxiliary (entry 1), whereas the electron-deficient salt **10** gave improved diastereoselectivity (entry 2). Allyl- and amide-stabilized sulfonium ylides (**11** and **12**) also worked well furnishing aziridines in good yields (entries 3 and 4). In these two cases the auxiliary imparted essentially perfect stereocontrol although a mixture of *cis*- and *trans*-aziridines was obtained. In the case of the amide-stabilized ylide concomitant ring opening of the *trans*-aziridine occurred during the course of the reaction. Simply leaving the reaction mixture for longer

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(4) For selected references see: (a) Carcano, M.; Nicotra, F.; Pauza, L.; Russo, G. *J. Chem. Soc., Chem. Commun.* **1989**, 297. (b) Behr, J. B.; Erard, A.; Guillerm, G. *Eur. J. Org. Chem.* **2002**, 1256. (c) Liautard, V.; Desvergnes, V.; Martin, D. R. *Org. Lett.* **2006**, *7*, 1299.

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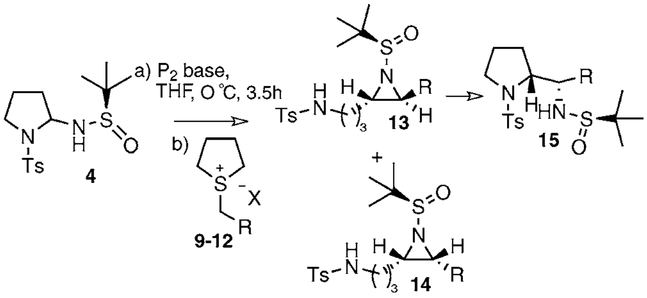
(7) P_2 base is *N*,*N*,*N*′,N′-tetraethyl-*N*′-[tris(dimethylamino)phosphoranylidene)phosphoric triamide ethylamine.

(8) pK_a values (DMSO) obtained from the following: http://www.chem.wisc.edu/areas/reich/pkatable/index.htm.

Table 2. Reaction of Aminal **4** with Various Sulfur Ylides



entry	R	overall trans:cis[a]	**13** + **14** (%)	trans dr	cis dr	**15**
1	4-MeO-Ph (**9**)	4.5:1	43	65:35	>95:5	
2	4-Cl-Ph (**10**)	11.5:1	66[b]	85:15	>95:5	
3	$CH=CH_2$ (**11**)	1.3:1	73	>95:5	>95:5	
4	CONHPh (**12**)	1.1:1	63[c]	>95:5	>95:5	29
5[d]	CONHPh (**12**)	1.1:1	45		>95:5	47

[a] Overall trans/cis ratios determined by calculation from isolated yields. [b] *trans*-Aziridine **13** was isolated in 50% as a single diastereomer. [c] Aziridines were isolated as a mixture of trans:cis 1:4. [d] Reaction time was 48 h.

reaction time resulted in complete conversion of the *trans*-aziridine into pyrrolidine **15**, leaving the *cis*-aziridine behind (entry 5).

As has been observed with aldehydes,[9] ester-stabilized ylides did not react with aminal **4**. Presumably, the higher barrier to the ring closure of the betaine (relative to aryl stabilized ylides), coupled with higher stability of the ylide promotes reversion of the betaine back to starting materials rather than ring closure.[9b]

The high cis/trans selectivity observed with aryl-stabilized ylides can be rationalized by analysis of the likely transition states involved in betaine formation (Figure 1). It has been established that betaine formation is nonreversible in the case of addition of phenyl-stabilized ylides to *N*-Ts imines,[10] and it is assumed that the same situation applies to the intermediate sulfinylimines. If this is the case, the addition transition states are responsible for the stereochemical outcome of the reaction. During betaine formation there is a preference for the sulfonium group to be gauche to the imine nitrogen to enable a positive Coulombic interaction to occur. In the case of the formation of the *trans*-aziridine, this will place the small hydrogen adjacent to the bulky sulfinyl group, but in the case of the *cis*-aziridine it places the bulky Ph group close to the sulfinyl group and so is less favored. However, steric factors may outweigh electronic factors as Robiette has suggested in related reactions of *N*-Ts imines[11] and so formation of the cis isomer may occur via TS-I instead, which again should be less favored as stabilizing Coulombic interactions are now absent. This should lead to high levels of trans selectivity. However, with allyl- or amide-stabilized ylides the cis/trans ratio was very low. In the former case this could be because the vinyl substituent is small and both anti and syn TS's are equally tolerated, and in the latter case it could be because the reaction is now reversible. Addition of amide-stabilized ylides to *N*-Ts imines has been shown to be reversible[9] and in such cases cis isomers are favored as the two carbon substituents prefer to be anti to the bulky tosyl group. The *tert*-butylsulfinyl group is likely to be of intermediate size and so may not control the stereochemistry as well, accounting for the low cis/trans selectivity observed.

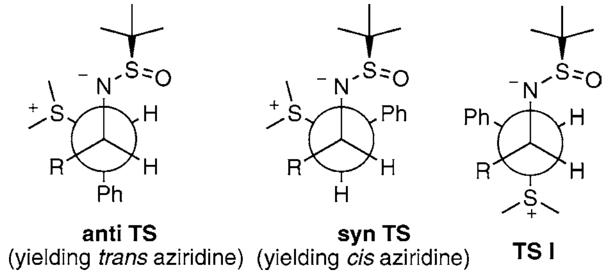


Figure 1. Proposed transition states leading to betaine intermediates.

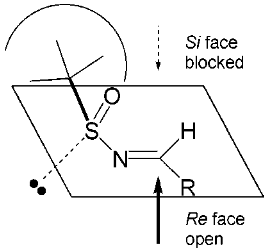


Figure 2. Proposed model for addition of ylide to the imine.

The good to excellent diastereoselectivity imparted from the auxiliary can be rationalized by the established model for the preferred conformation of the sulfinylimine (Figure 2),[12] which has been reinforced by DFT calculations.[13] The origin of this preference has been attributed to the following: (i) the repulsions between the lone pairs of electrons present on the N, S, and O atoms, (ii) the $n_N \rightarrow \sigma^*_{SO}$ negative hyperconjugation, and (iii) the intramolecular C−H···O electrostatic interaction (this H-bond is analogous to metal−oxo complexes with aldehydes as reported by Corey[14]). In the absence of metal counterions (which might otherwise chelate to the sulfinyl group or the nucleophile) this conformation is also likely to be the reactive conformation

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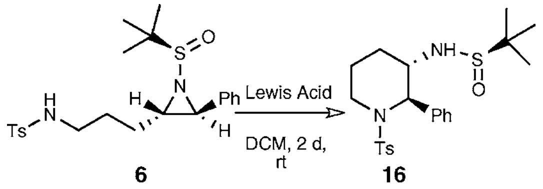
of the sulfinylimine. In this conformation the *t*-Bu group makes one face of the imine (the *Si* face) much more hindered than the other. On the basis of this established model, the stereochemistry of the major products has been assigned. Although the aziridine could be ring-opened under the reaction conditions to give pyrrolidine, we were interested in exploring if the regioselectivity could be diverted to give piperidine instead. For this reason, we explored a range of Lewis acids, and were pleased to find that Yb(OTf)$_3$ provided the piperidine cleanly and in high yield (Scheme 4). To fully realize the potential of this methodology, the *tert*-butylsulfinyl group was removed efficiently by using ethanolic HCl in dioxane from both the aziridine and piperidine (Scheme 5).[15] Piperidines with this general structure have emerged as highly potent antagonists of the NK-1 receptor, which has implications in the pathogenesis of a diverse range of diseases.[16]

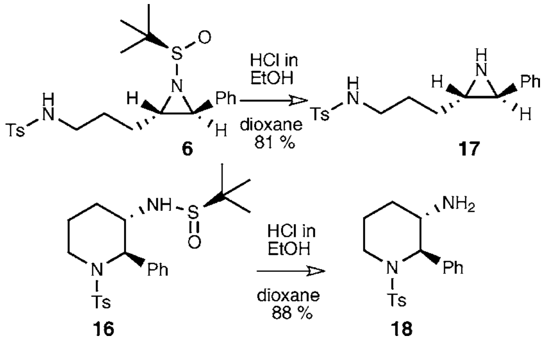
Scheme 4. Ring-Opening of Aziridine **6** to Afford Piperidine **16**



TMSOTf	49%
Yb (OTf)$_3$	93%
BF$_3$.OEt$_2$	76%

In conclusion, we have described the first reaction of aminals with sulfur ylides which lead to aziridines. By using the Ellman *tert*-butylsulfinyl group, good to perfect diastereocontrol (from the auxiliary) was achieved with aryl-, allyl-, and amide-stabilized ylides although cis/trans selectivity was more variable. The aziridines could be made to undergo ring closure under the reaction conditions to give pyrrolidines, while treatment with Yb(OTf)$_3$ led to piperidines instead.

Scheme 5. Cleavage of the *tert*-Butylsulfinyl Group



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Supporting Information Available: Procedures and full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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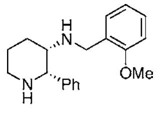

(+)-CP 99,994