Sulfur-Directed Asymmetric 1,3-Dipolar Cycloadditions of Azomethine Ylides with Enantiopure Sulfinimines†,‡

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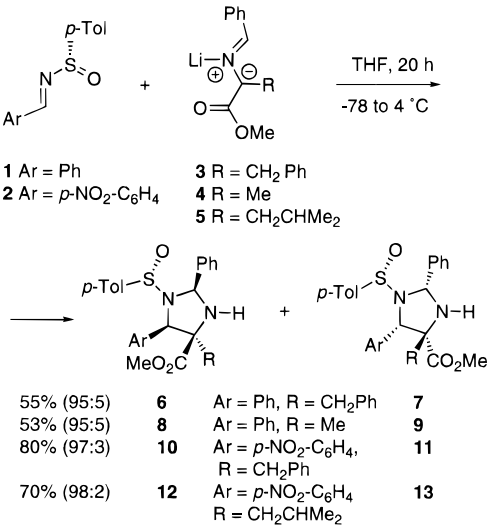
1,3-Dipolar cycloadditions are fundamental processes in organic chemistry.[1] In particular, the reaction of azomethine ylides with alkenes is a powerful method for the synthesis of pyrrolidines since up to four stereocenters are set in a single operation.[2] This has fueled intensive efforts toward the development of efficient chiral auxiliaries to render the process enantioselective.[3] In contrast, reports on cycloadditions between azomethine ylides and imines are scarce,[4] despite the well-established synthetic potential of the resulting imidazolidines.[5] Furthermore, it should be noted that the asymmetric version of this process remains elusive. In this paper, we report the first examples of a highly diastereoselective 1,3-dipolar cycloaddition of azomethine ylides with chiral sulfinimines to produce enantiopure *N*-sulfinyl imidazolidines and the straightforward transformation of one of these cycloadducts into an example of a novel class of nonsymmetrical vicinal diamines.

Enantiopure sulfinimines, readily available in both enantiomeric forms,[6] are versatile intermediates for enantioselective syntheses of a variety of targets.[7] These substrates display excellent facial selectivity upon reaction with a number of nucleophiles, and furthermore, removal or even recycling of the sulfinyl auxiliary is readily carried out under mild reaction conditions.[8] These desirable features, along with our interest in the development of sulfur-directed methodology,[9] attracted our attention to these intermediates as potential precursors to chiral imidazolidines by 1,3-dipolar cycloadditions with azomethine ylides.

Scheme 1



We selected sulfinimine **1**[6a] and *N*-benzylidene α-amino acid ester-derived ylide **3**[10] for our initial studies. Standard conditions (LiBr, Et_3N, MeCN; AgOAc, DBU, Tol) failed to promote the desired cycloaddition. Dipole generation with LDA[10] was then examined, and to our delight, the reaction between sulfinimine **1** and phenylalanine-derived dipole **3** led to a fair yield of a 95:5 mixture of cycloadducts **6** and **7**[11] (Scheme 1), along with 15−20% of unreacted starting material. From this mixture of **6** and **7**, pure **6** (45−50%) was obtained by recrystallization (hexane:ether). The reaction between **1** and dipole **4** produced imidazolidines **8** and **9** in almost identical yield and selectivity to the case above. Similarly, the more reactive substrate **2**[12] afforded excellent yields of adducts **10** and **12** as practically single isomers upon reaction with dipoles **3** and **5**, respectively.

The general structure of these adducts was readily derived from their spectral features, and the relative stereochemistry of the three ring chiral centers was deduced from differential NOE experiments. However,

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(11) All new products were fully characterized by standard techniques.

(12) Sulfinimine **2** was prepared in one step from *p*-nitrobenzaldehyde by the procedure of Davis (ref 6a).

S0022-3263(97)00005-4 CCC: $14.00

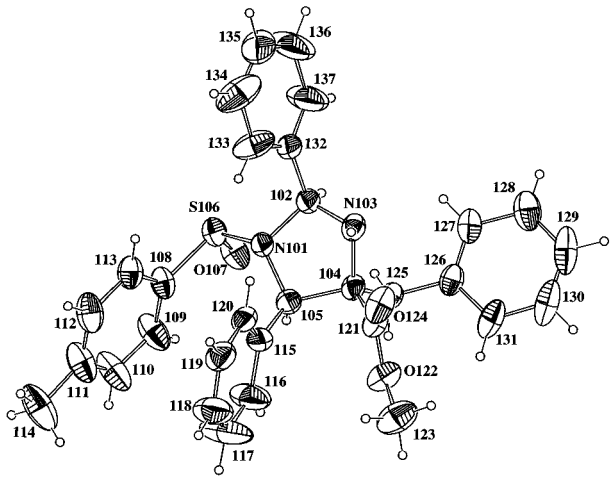
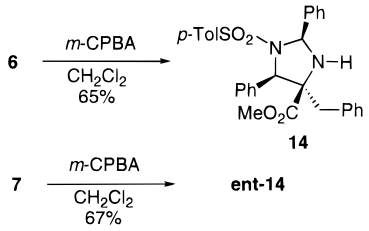


Figure 1. Final X-ray model for **6** showing its absolute chirality. Numbers only refer to C atoms.

Scheme 2



a definitive proof of the relative configuration of the ring centers and the chiral sulfur was required to establish unequivocally the predominant facial sense of the process. This was solved by an X-ray analysis of **6**, and the results obtained are shown in Figure 1.[13]

To secure that **6** and **7** were facial isomers, a sample of pure **6** was oxidized to tosyl imidazolidine **14** (Scheme 2). Under identical conditions, an enriched sample of **7** led to enantiomerically enriched *ent*-**14** of identical spectral features to those of **14** and optical rotation of opposite sign.

These cycloadducts are nicely functionalized for subsequent manipulations. Indeed, both nitrogen atoms are already differentiated, and in principle, both aryl rings could be varied readily. Furthermore, the ester group should be an additional handle for synthetic applications.

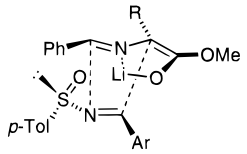
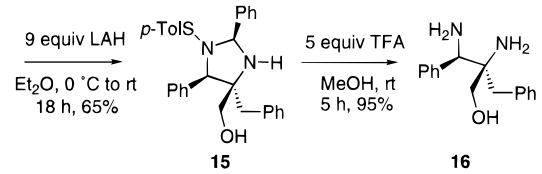


Figure 2.

Scheme 3



Scheme 3 depicts our initial studies on the reactivity of these sulfinyl imidazolidines. Treatment of **6** with TFA/MeOH[14] resulted in desulfinylation and fragmentation to produce phenylalanine methyl ester. To avoid this undesired process, reduction of the ester to the primary alcohol was attempted. Treatment of **6** with an excess of LAH resulted in concurrent deoxygenation and ester reduction, affording sulfenamide **15** in fair yield.[15] Cleavage of the sulfur−nitrogen bond and aminal methanolysis took place smoothly to produce diamine **16** in good yield.[16]

The stereochemical outcome of this cyclization may be understood in terms of predominant *endo* approach of the ylide (relative to the Ar group) to the less hindered β face of sulfinimines **1** and **2** (Figure 2) to provide adducts **6**, **8**, **10**, and **12**, respectively. Our process displays a remarkable facial selectivity of *opposite* sense to that found for most other additions to sulfinimines;[6,7] this and the high stereoselectivity found strongly support a 1,3-dipolar cycloaddition pathway.

To summarize, readily available sulfinimines react with lithiated α-imino esters with remarkable selectivity to generate enantiopure *N*-sulfinyl imidazolidines. In this cycloaddition, the chirality of sulfur is transferred to three asymmetric centers in a single synthetic operation with almost complete stereocontrol. We are currently examining the scope and limitations of this methodology as well as further applications of these cycloadducts in synthesis.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds (8 pages).

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(13) Crystal data for **6**: $C_{31}H_{30}N_2O_3S$, $M_r = 510.63$, monoclinic, $P2_1$, $Z = 4$, $a = 11.896(1)$ Å, $b = 22.893(2)$ Å, $c = 11.621(1)$ Å, $\beta = 116.57(1)°$, $F(000) = 1080$, $D_x = 1.198$ g cm^{-3}, $\mu = 1.277$ mm^{-1}, prismatic colorless crystal of 0.4 × 0.3 × 0.2 mm, graphite-monochromated Cu Kα radiation ($\lambda = 1.5418$ Å, 293 K, $\omega/2\theta$ scans, no intensity decay, absorption corrected using azimuthal scans (minimum and maximum transmision factors 0.82 and 1.00), 9402 reflections measured up to $2\theta = 130°$, $0 < h < +12$, $-26 < k < +26$, $-12 < l < +12$, 7872 observed with criterion $I > 2\sigma(I)$. Structure solved by direct methods (SIR92: Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G.; Giacovazzo, G.; Guagliardi, A.; Polidori, G. *SIR92*, Program for Crystal Stucture Solution, University of Bari, Italy, 1992), weighted full-matrix least-squares refinement against F^2 using all reflections (SHELX93: Sheldrick, G. M. *J. Appl. Crystallogr.* Manuscript in preparation), H-atoms found in difference map and refined in riding mode, 676 parameters, extinction coefficient 0.001(1), goodness of fit for all reflections 1.048, maximum shift/error 0.001, absolute structure coefficient 0.02(2) (Flack, H. D. *Acta Crystallogr. A* **1983**, *39*, 876−881), $R = 0.056$ and $R_w = 0.136$ for the observed reflections, $R = 0.069$ and $R_w = 0.151$ for all reflections, residual electron density between −0.20 and 0.16 e Å^{-3}. The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ. UK.

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(15) We found this reduction to be very sluggish presumably due to the carboxylate being very hindered. Short reaction times resulted in recovery of starting material. Intermediate reaction times (5 h) afforded mixtures of **15** and the expected sulfinamide, whose treatment with TFA/MeOH also led to diamine **16**. We are examining other procedures to carry out the selective reduction of the ester.

(16) Vicinal diamines are important chiral auxiliaries. For a review, see: Togni, A.; Venanzi, L. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 497−526. For a leading reference see: Trost, B. M.; Breit, B.; Peukert, S.; Zambrano, J.; Ziller, J. W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2386−2388. For leading references on synthesis of vicinal diamines, see: (a) Richardson, P. F.; Nelson, L. T. J.; Sharpless, K. B. *Tetrahedron Lett.* **1995**, *36*, 9241−9244. (b) Shimizu, M.; Kamei, M.; Fujisawa, T. *Tetrahedron Lett.* **1995**, *36*, 8607−8610. (c) Park, Y. S.; Boys, M. L.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 3757−3758.