



# Diastereoselective addition of chiral azomethine ylides to cinnamoyl moieties, attached to chiral auxiliaries

Staffan Karlsson\* and Hans-Erik Högberg\*

Chemistry, Department of Natural and Environmental Sciences, Mid Sweden University, SE-851 70 Sundsvall, Sweden

Received 14 August 2001; accepted 20 August 2001

**Abstract**—Doubly diastereoselective 1,3-dipolar cycloadditions of chiral azomethine ylides to cinnamoyl moieties, attached to chiral auxiliaries, were investigated. The resulting *trans*-3,4-disubstituted pyrrolidines were obtained in diastereomeric ratios of up to 78:22. The influence on this ratio by the constitution of the chiral ylide was found to be rather small. © 2001 Elsevier Science Ltd. All rights reserved.

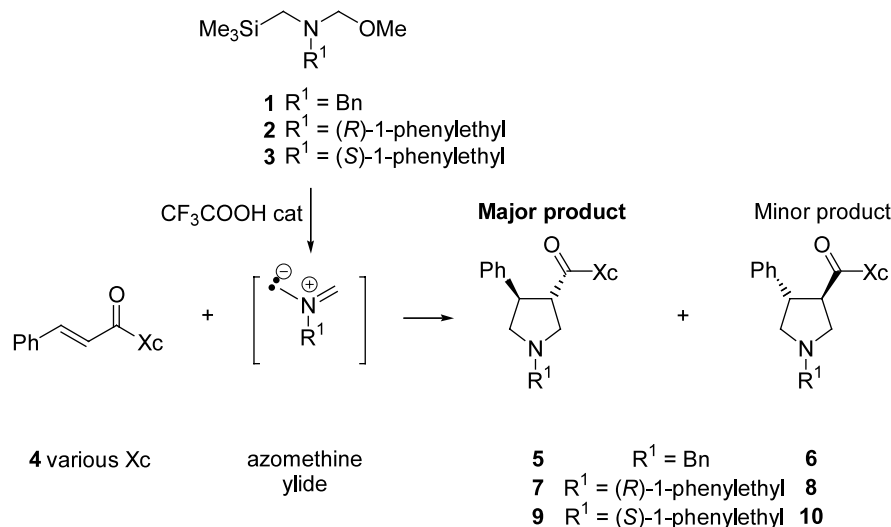
## 1. Introduction

Various techniques are in use for the preparation of enantiomerically pure polysubstituted pyrrolidine derivatives. The 1,3-dipolar cycloaddition of an azomethine ylide to a dipolarophile, has become one of the most efficient approaches, as it allows the introduction of several stereogenic centres in a diastereo- as well as enantioselective manner in a single step.<sup>1–3</sup>

The asymmetric 1,3-dipolar cycloaddition of the azomethine ylide precursor **1** to  $\alpha,\beta$ -unsaturated dipo-

larophiles attached to chiral auxiliaries (Xc), such as oxazolidinones and camphorsultam (e.g. **4**), have recently been studied by others<sup>4</sup> as well as by us.<sup>5</sup> We obtained the major diastereoisomeric pyrrolidine **5** and the minor one **6** as two separable compounds in ratios of up to 74:26, when camphorsultam<sup>6</sup> was used as the auxiliary (Scheme 1).










The diastereoselectivity obtained in the reaction of **1** with **4** is modest, but the use of chirality in the dipole precursor (e.g. compound **2** or **3**) would result in a doubly diastereoselective reaction. Chiral non-racemic



Scheme 1.

\* Corresponding authors. E-mail: staffan.karlsson@mh.se; hans-erik.hogberg@mh.se

**Table 1.** Diastereoselectivity in the reaction of cinnamoyl compounds **4** with the achiral or chiral azomethine ylides obtained from its precursors **1**, **2** or **3**

Entry <sup>a</sup>	Substrate <b>4</b> Xc =	Solvent	Dipole precursor	Products Major (Minor)	diastereomeric ratio <sup>b</sup>
1 <sup>c</sup>		toluene	<b>1</b>	<b>5 (6)</b>	70:30
2 <sup>d</sup>		toluene	<b>2</b>	<b>7 (8)</b>	75:25
3 <sup>d</sup>		toluene	<b>3</b>	<b>9 (10)</b>	66:34
4 <sup>c</sup>		CH <sub>2</sub> Cl <sub>2</sub>	<b>1</b>	<b>5 (6)</b>	64:36
5 <sup>d</sup>		CH <sub>2</sub> Cl <sub>2</sub>	<b>2</b>	<b>7 (8)</b>	75:25
6 <sup>d</sup>		CH <sub>2</sub> Cl <sub>2</sub>	<b>3</b>	<b>9 (10)</b>	57:43
7 <sup>c</sup>		CH <sub>2</sub> Cl <sub>2</sub>	<b>1</b>	<b>5 (6)</b>	74:26
8 <sup>d</sup>		CH <sub>2</sub> Cl <sub>2</sub>	<b>2</b>	<b>7 (8)</b>	78:22
9 <sup>d</sup>		CH <sub>2</sub> Cl <sub>2</sub>	<b>3</b>	<b>9 (10)</b>	71:29

<sup>a</sup> The experiments were performed following the procedure reported by us previously.<sup>5</sup>

<sup>b</sup> Determined on the crude products by <sup>1</sup>H NMR measurements.

<sup>c</sup> Ref. 5.

<sup>d</sup> The cycloadducts were isolated as diastereomeric mixtures.

1-phenylethylamine is a cheap and common precursor for the preparation of chiral dipolar compounds and is often used for this purpose.<sup>7</sup> Thus, when the appropriate enantiomer of the azomethine ylide precursor is reacted with **4**, improved diastereoselectivity can be expected.

Herein, we present some doubly diastereoselective 1,3-dipolar cycloadditions of chiral azomethine ylides from precursors **2** (or **3**) to chiral cinnamoyl derivatives **4**, resulting in the *trans*-3,4-disubstituted pyrrolidines **7** and **8** (or **9** and **10**), see Scheme 1.

## 2. Results and discussion

The diastereoselectivity obtained in the reactions of the chiral azomethine ylide precursors **2** and **3**, respectively, with the cinnamoyl compounds **4** containing various chiral auxiliaries (Scheme 1), is summarised in Table 1. For comparison, the corresponding reactions with the achiral azomethine ylide precursor **1** with compounds of the type **4** under the same conditions<sup>5</sup> are included.

When the reactions of the achiral azomethine ylide precursor **1** were compared with those of the chiral precursor **2**, we noticed a small increase in diastereoselectivity in all cases examined. It was obvious that the diastereoselectivity was mainly controlled by the chiral auxiliary attached to the dipolarophilic cinnamoyl moiety. However, the chiral dipolar precursors used here were easily obtained from inexpensive starting materials.

Thus, although moderate, this double asymmetric induction is a useful step toward optimising the diastereoselectivity of such reactions.

## Acknowledgements

This work was supported by the Swedish Natural Science Research Council (NFR) and the Mid Sweden University.

## References

- Lown, J. W. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1.
- Karlsson, S.; Högberg, H.-E. *Org. Prep. Proced. Int.* **2001**, *33*, 103–172.
- Gothelf, K. V.; Jörgensen, K. A. *Chem. Rev.* **1998**, *98*, 863–909.
- Ma, Z.; Wang, S.; Cooper, C. S.; Fung, A. K. L.; Lynch, J. K.; Plagge, F.; Chu, D. T. W. *Tetrahedron: Asymmetry* **1997**, *8*, 883–887.
- Karlsson, S.; Han, F.; Högberg, H.-E.; Caldirola, P. *Tetrahedron: Asymmetry* **1999**, *10*, 2605–2616.
- Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1241–1250.
- See for example: (a) Fray, A. H.; Meyers, A. I. *Tetrahedron Lett.* **1992**, *33*, 3575–3578; (b) Fray, A. H.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 3362–3374; (c) Wittland, C.; Flörke, U.; Risch, N. *Synthesis* **1997**, 1291–1295.