Auxiliary Controlled 1,3-Dipolar Cycloadditions of Chiral Stabilized Azomethine Ylides

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Summary: It is demonstrated that Oppolzer's camphor sultam serves as an effective chiral auxiliary for 1,3-dipolar cycloadditions of carbonyl-stabilized azomethine ylides.

Stereocontrolled azomethine ylide cycloadditions hold considerable potential for the asymmetric synthesis of complex pyrrolidine-containing molecules.[1] While good stereocontrol has been achieved in the intermolecular version of this reaction by attaching chiral auxiliaries to the dipolarophile component,[2] the development of a general chiral auxiliary for azomethine ylides is ongoing.[3] There are five issues which need to be considered when evaluating the utility of such systems for asymmetric synthesis: (1) availability of the auxiliary, (2) diastereofacial selectivity, (3) endo/exo selectivity, (4) geometry of 1,3-disubstituted ylides, and (5) auxiliary removal/recovery. Suffice it to say that none of the chiral systems reported so far appears to satisfy all of these requirements. Particularly noteworthy is the fact that all of the known systems require destructive removal of a chiral auxiliary attached to nitrogen. We now report that Oppolzer's sultam can serve as a recoverable chiral auxiliary for carbonyl stabilized azomethine ylides.

Analysis of the transition state models put forth[4] for thermal (cyclo)additions to C(sp^2)COX* systems (where X* = Oppolzer's camphor sultam) suggested to us that azomethine ylides which incorporate this substructure might also fall under the same diastereofacial control elements. Such carbonyl-stabilized azomethine ylides[5] may be conveniently generated by thermolytic ring opening of aziridine-2-carboxylic acid derivatives[6] or condensation of a glycine derivative with an aldehyde followed by tautomerization.[7] The starting chiral aziridine-2-carboximides **1a/b** were prepared in high yields from the known (+)-*N*-propenoylbornane-2,10-sultam[8] via a two-step sequence involving (1) alkene bromination and (2) double displacement by either benzylamine or *p*-anisidine.[9] A variation of Oppolzer's published route to α-amino acids was used to synthesize the chiral glycyl sultam **11**.[10]

Table 1. Auxiliary-Controlled 1,3-Dipolar Cycloadditions of Azomethine Ylides

entry	azomethine ylide[a]	dipolarophile	major cycloadduct(s)	facial selectivity[b]	combined yield[c] (%)
1	**2a**	3	**4a**	9:1	60
2	**2b**	3	**4b**	11:1	82
3	**2a**	5	**6**/7 (1.8:1)	10:1	73[d]
4	**2a**	8	**9**/10 (2:1)	e	92
5	12	3	13	6:1	57[d]
6	12	5	14	7:1	84
7	12	8	15	5:1	53[d]

[a] Procedure A (ylides **2a/b**): the indicated aziridine (0.2 M) and dipolarophile (3 equiv) were combined in toluene and heated in a sealed Pyrex tube (T = 160–205 °C, t = 6–20 h). Procedure B (ylide **12**): a mixture of amine **11** (0.034 M), benzaldehyde (1.5 equiv), dipolarophile (5–10 equiv), and 4-Å molecular sieves (ca. 0.3 g/mL) in toluene was heated (T = 75–85 °C, t = 2–3 h) until the reaction was judged complete by TLC. [b] Kinetic diastereomer ratios were determined from the crude ^{1}H NMR spectra. [c] The combined (total) yield of cycloadducts after flash chromatography on silica gel. [d] Between 5 and 7% of other minor cycloadducts were also formed. [e] The minor facial diastereomers could not be detected.

Thermolysis of aziridines **1a/b** produced the corresponding N-substituted azomethine ylides **2a/b** which underwent 1,3-dipolar cycloadditions to electron-deficient alkenes (see Table 1).[11] With dimethyl maleate (**3**) as the dipolarophile, cycloadducts **4a** and **4b** were obtained as the major products (entries 1 and 2) which conforms to exclusive endo cycloaddition to the *Z*-ylide **2a/b**. The trans orientation of H-2 and H-3 in these adducts was readily deduced in the "b-series" where H-2 appeared as a singlet (dihedral angle = 90°) in the ^{1}H NMR spectra of both **4b** and the minor facial diastereomer **4b'** (not shown). While cycloadditions to *N*-phenylmaleimide (**5**) occurred in good chemical yield, the endo selectivity was considerably eroded (**6**:7 = 1.8:1) with this dipolarophile (entry 3). Cycloaddition to the unsymmetrical dipolarophile, methyl acrylate (**8**), led to the formation of regioisomers **9** and **10** in a ratio of 2:1 (entry 4). It should be noted that the poor endo/exo and regioselectivity associated with dipolarophiles **5** and **8** mirror Tsuge's observations with related (achiral) N-substituted azomethine ylides. More importantly, however, the observed diastereofacial selectivity (ds = 6:1 up to 11:1) was on the

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(4) A review of the use of Oppolzer's sultam in this context has recently appeared; see: Kim, B. H.; Curran, D. P. *Tetrahedron* **1993**, *49*, 293.

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(7) (a) Grigg, R.; Kemp, J.; Sheldrick, G.; Trotter, J. *J. Chem. Soc., Chem. Commun.* **1978**, 109. (b) Joucla, M.; Hamelin, J.; *Tetrahedron Lett.* **1978**, 2885. (c) Tsuge, O.; K. Ueno, K.; Oe K. *Chem. Lett.* **1979**, 1407. (d) Tsuge, O.; Kanemasa, S.; Ohe, M.; Yorozu, K.; Takenaka, S.; Ueno, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4067.

(8) Vandewalle, M.; Van der Eycken, J.; Oppolzer, W.; Vullioud, C. *Tetrahedron* **1986**, *42*, 4035. An improved preparation of this substance was recently reported: Thom, C.; Kocienski, P. *Synthesis* **1992**, 582.

(9) Cf. Nakamura, I.; Harada, K. *Heterocycles* **1978**, *9*, 473 and references cited therein. Although not relevent here, this auxiliary-mediated aziridination is itself diastereoselective and can be used to prepare enantiomerically pure aziridine-2-carboxylic acid derivatives in high yields. Dogan, O.; Pillai, S. Unpublished results.

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(11) All of the compounds depicted in this paper exhibited satisfactory spectral and/or analytical data.

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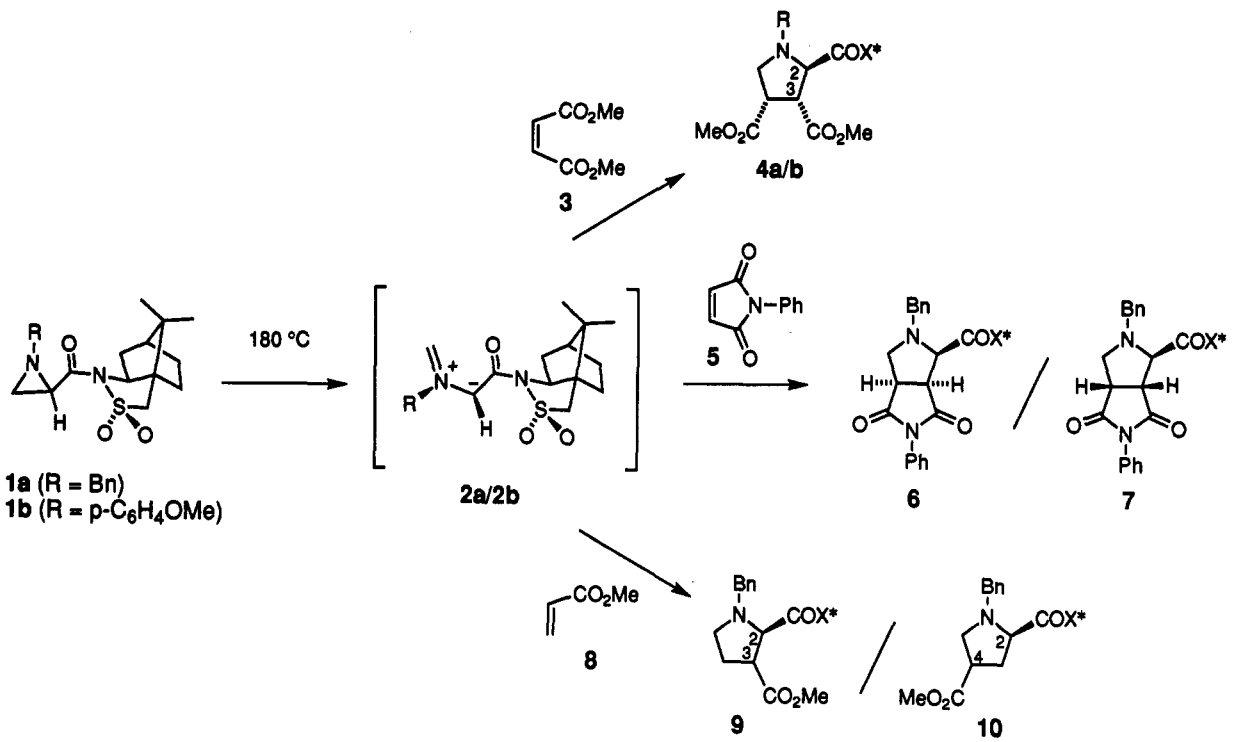
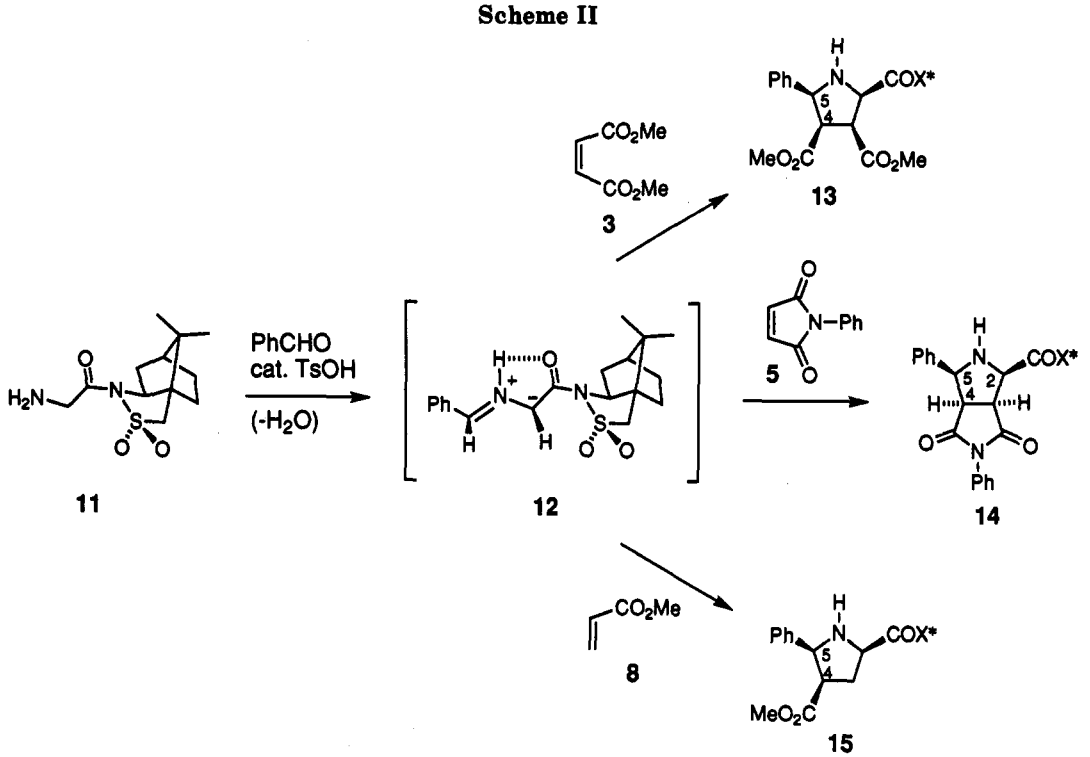
Scheme I



Scheme II



order of that usually associated with Oppolzer's sultam auxiliary.

Dipolar cycloadditions of the NH azomethine ylide **12**, generated via the "imine tautomerization route", were also investigated. Thus, the glycyl sultam **11** was condensed with benzaldehyde to give an intermediate imine (not shown) that underwent acid-catalyzed tautomerization to the 3-phenyl substituted azomethine ylide **12** which could be trapped with the same dipolarophiles **3**, **5**, and **8** (entries 5–7). In each case, the major product was that configuration in which all pyrrolidine substituents were cis to one another, resulting from an endo approach of the dipolarophile to the *E*,*E*-ylide **12**. This stereochemical assignment was readily deduced for adducts **13** and **15** by the characteristic upfield shift of the 4-CO_2Me ^1H NMR signal due to the shielding effect of the 5-phenyl group (see ref 7d). With adduct **14**, on the other hand, the cis relationships between H-2, H-4, and H-5 were established by a series of NOE difference experiments. As with **2a/b**, the diastereofacial selectivity associated with ylide **12** is uniformly good (ds = 6–7:1). Even though, at this point, we can only assume that the absolute sense of asymmetric induction follows the Oppolzer–Curran model, our results do demonstrate that a reusable chiral auxiliary can be

successfully incorporated into an azomethine ylide for purposes of stereocontrol.

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Supplementary Material Available: Representative experimental procedures and characterization data for **4a**, **4a'**, **4b**, **6**, **7**, **9**, **13**, **13'**, **14**, **14'**, and **15** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.