

Diastereoselectivity in Mn(III)-Promoted 4-*exo-trig* Cyclization of Enamides to β -Lactams

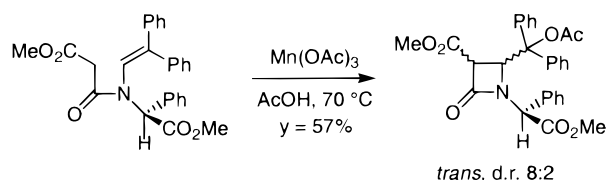
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Received December 16, 1999

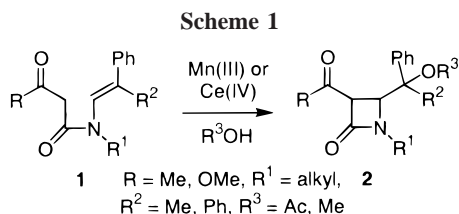
ABSTRACT



The effect of chiral substituents on the enamide nitrogen atom upon the diastereoselection of the Mn(III)-mediated 4-*exo-trig* cyclization to β -lactams was studied. A significant level of diastereoselectivity was achieved when an amino acid ester moiety was included into the enamidic skeleton. The structure of the major diastereoisomer was suggested by semiempirical calculations.

The synthesis of β -lactam skeletons by 4-*exo-trig* radical cyclization of suitable precursors is a well explored field, especially by Bu_3SnH -mediated methods.¹

Recently we have studied the transition-metal-promoted oxidative radical reactions of *N*-vinyl amides to azetidin-2-ones. We have reported some effective Mn(III)- and Ce(IV)-mediated procedures to obtain stereoselectively β -lactams **2**, *trans* at C-3 and C-4, from enamides **1**, bearing either an enolizable group close to the amidic functionality or some radical-stabilizing groups (such as phenyl) on the double bond (Scheme 1).²



The effect of substituents on the nitrogen atom upon the product yields has been extensively studied. Changing of

alkyl substituents at the nitrogen atom showed a marked effect on the cyclization outcome, and the best yields were obtained when the R¹ alkyl group presented a secondary or tertiary carbon close to the nitrogen. This could be due to the influence of R¹ on the geometry of the 4-*exo-trig* transition state.

This hypothesis suggested us to study the possibility of inducing diastereoselection in these reactions by placing suitable chiral substituents on the enamidic nitrogen atom; the preliminary results of this approach are reported in this communication.

The introduction of chiral groups onto the enamidic structure was easily accomplished by the usual enamide synthetic procedure described in the literature,³ i.e., imine

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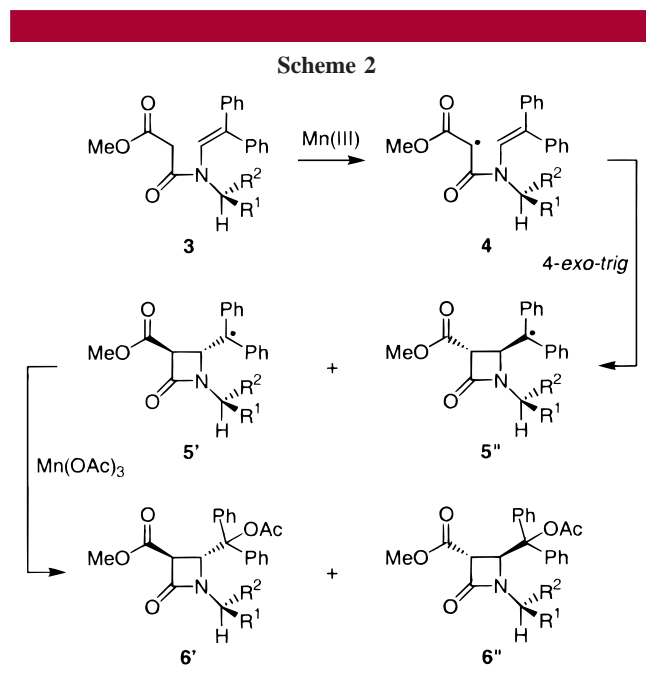
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formation by condensation of the suitable chiral amine with diphenylacetaldehyde, and subsequent reaction with methyl malonyl chloride. Then, enamides **3a–i** were reacted with $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ in glacial acetic acid (Scheme 2). Reactions



were carried out at 70 °C⁴ because of the prevalent formation of side-product mixtures at lower temperatures.

As expected, *trans* azetidinones **6** were obtained in good to high yields; the results are summarized in Table 1. As regards product stereochemistry, enamides **3a** and **3b** (obtained from (*R*)-(+)- and (*S*)-(–)-phenylethylamine, respec-

Table 1. Reactions of Chiral Enamides **3** with $\text{Mn}(\text{OAc})_3$

substrate	R ¹	R ²	product	yield (%) ^a	dr ^b
3a	Me	Ph	6a	78	54:46
3b	Ph	Me	6b	68	55:45
3c	cyclohexyl	Me	6c	79	61:39
3d	Me	naphthyl	6d	72	62:38
3e	CO ₂ Me	Me	6e	55	57:43
3f	CO ₂ Me	Bn	6f	72	50:50
3g	CO ₂ Me	Ph	6g	57	80:20
3h	CO ₂ Et	<i>i</i> -Pr	6h	63	80:20
3i	CO ₂ Me	<i>t</i> -Bu	6i	55	80:20

^a Yields were calculated on pure, chromatographically isolated products; ^b Diastereomeric ratios (dr) were calculated by NMR.

tively) gave no diastereoselective reaction at all. Slightly better, but not yet significant, stereochemical results were obtained in the case of enamides **3c** and **3d**, prepared from cyclohexyl and naphthylamine.

Searching for suitable, easily available chiral groups, we planned to use esters of α -amino acids to prepare the starting products. Enamides **3e–i** were thus prepared, and their reactions with $\text{Mn}(\text{III})$ showed a significant level of diastereoselection (ca. 80:20 dr) when the enamide chiral center was linked to a secondary or tertiary carbon as R².

Unfortunately, the structure of the prevalent oily diastereoisomers could not be ascertained by either normal spectral or X-ray diffraction data. Nevertheless, semiempirical molecular calculations suggested that, when a stereoselection is observed, the prevalent compound is the diastereoisomer **6''**. Details of calculations are reported in the Supporting Information.

Although these data are preliminary, we could certainly say that in the $\text{Mn}(\text{III})$ -mediated 4-*exo-trig* cyclization of enamides a good diastereoselection can be obtained by placing suitable chiral substituents on the nitrogen atom. Moreover, these data are a further example of the possibility, previously described by other authors,⁵ to carry out $\text{Mn}(\text{III})$ -mediated reactions stereoselectively.

Acknowledgment. We acknowledge financial support from CNR, MURST (1998–1999 grant for “Free Radicals and Radical Ions in Chemical and Biological Processes” and “New Methodologies and Strategies for the Synthesis of Biologically Interesting Compounds”), and both the University of Rome “La Sapienza” and the University of Bologna (1997–1999 funds for Selected Research Topics).

Supporting Information Available: Experimental procedures and full characterization (IR, ¹H and ¹³C NMR spectra) for compounds **3a–i** and **6a–i** and details of semiempirical calculations. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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