Tetrahedron Letters, Vol 33, No. 25, pp. 3575-3578, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .
Pergamon Press Ltd

Diastereoselective Azomethine Ylide Cycloadditions to Unsaturated, Chiral Bicyclic Lactams

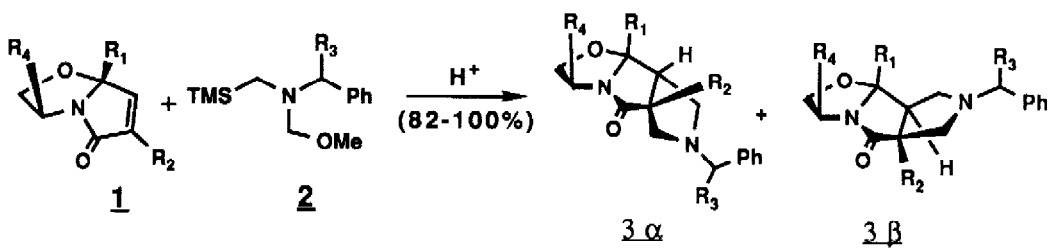
Andrew H. Fray and A. I. Meyers*

Department of Chemistry, Colorado State University, Fort Collins, Colorado, 80523, U S A

Abstract: *The levels of diastereoselection resulting from the 1,3-dipolar cycloaddition of chiral and achiral azomethine ylides* ***2(a-c)*** *to chiral, unsaturated bicyclic lactams* ***1(a-f)*** *are described in terms of steric factors.*

Although azomethine ylide cycloadditions have been studied and reviewed in detail,[1] the asymmetric variant of this useful reaction has not been as extensively explored Generally, the level of stereoselection achieved for intermolecular azomethine ylide cycloadditions has been variable and dependent upon the proper combination of chiral dipolarophile[2] or chiral dipole.[3] Furthermore, to our knowledge, the prospect of obtaining high diastereoselectivities in these processes via double asymmetric induction[4] has not been previously explored.

We now report our preliminary results concerning the diastereofacial addition of chiral and achiral azomethine ylide precursors **2** to non-racemic, unsaturated bicyclic lactams **1**. The latter have previously been shown to be valuable templates for asymmetric [2+2][5], [2+1][6], and [4+2][7] cycloadditions. Optimum parameters for cycloaddition to the unsaturated bicyclic lactams were achieved by employing the azomethine ylide precursors **2** utilizing conditions described by Achiwa.[8] The levels of diastereoselection resulting from both single and double asymmetric additions to lactams **1** were then examined The chiral dipoles were each derived from R(+) and S(-)-α-methylbenzylamines using the method reported by Padwa.[9] In this process, a catalytic amount of trifluoroacetic acid was used to generate the azomethine ylides in the presence of the unsaturated lactams producing diastereomeric mixtures of the pyrrolidine-fused tricyclic lactams **3** (α,β) in excellent yields (82-100%).[10]



1 2 3 α 3 β

Table 1. Cycloaddtion of Chiral and Achiral Dipoles to Chiral Bicyclic Lactams, **1**.

				Dipole **2a** (R_3=H)	(*R*) Dipole **2b** (R_3=Me)	(*S*) Dipole **2c** (R_3=Me)
Lactam	R_1	R_2	R_4	3α:β [a]	3α:β [a]	3α:β [a]
1a	Me	CO_2Me	i-Pr	71:29[b]	87:13[b]	59:41[b]
1b	Me	CO_2t-Bu	i-Pr	72:28	92·8	51:49
1c	Ph	CO_2Me	i-Pr	74:26	87:13[b]	69:31[b]
1d	Me	H	i-Pr	91·9	94:6	91 9
1e	Me	H	Ph	94:6	----	----
1f	H	H	Ph	17:83	----	----

[a] determined by ^{1}H NMR of the crude products and corroborated by GC or isolation.
[b] separable by flash chromatography (EtOAc/hexanes).

The diastereoselectivities observed by the reactions of chiral bicyclic lactams **1(a-f)** with dipoles **2(a-c)** are summarized in Table 1. Generally, the direction of cycloaddition was found to be dependent upon the steric requirement of the angular substituent (R_1) present in **1**. Thus, predominant α-approach of the 1,3-dipole was observed when R_1=Me, Ph and β-approach was observed when R_1=H (Fig. 1).

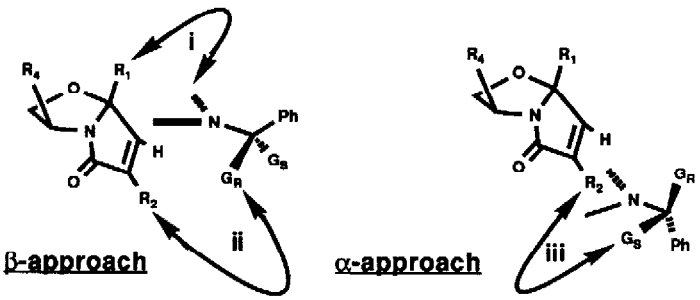
The extent of diastereofacial selectivity was seen to be a function of the non-bonded interactions between the benzylic substituent (R_3) of the dipole and the α-substituent (R_2) on the bicyclic lactam As shown in Figure 1, the phenyl group may be oriented to allow antiperiplanar approach to the lactam as the pi-systems of the two partners approach each other within two parallel planes.[3a] β-Approach of both chiral and achiral dipoles is hindered by the presence of steric interactions (**I**) between the angular substituent (R_1) of lactams **1(a-e)** and the planar pi-system of the dipole. However, for the (*R*)-dipole, β-approach is further hindered by steric interactions (**II**) that exist between the methyl substituent (G_R) of that dipole and the ester moiety (R_2) of unsaturated lactams **1(a-c)**. These major steric factors encountered as the transition state is approached probably account for the enhanced diastereofacial preferences observed for α-approach (74-84% d.e.). Conversely, α-approach is also subject to hindrance by steric interactions (**III**) between the methyl substituent (G_S) of the (*S*)-dipole and the ester moiety (R_2) of unsaturated lactams **1(a-c)**. This, therefore, would tend to destabilize this transition state relative to that for β-approach and accounts for the poor diastereofacial preferences (2-38% d.e) observed for this pair of reactants.

Figure 1.

(*R*)-Dipole: (G_R = Me, G_S = H)

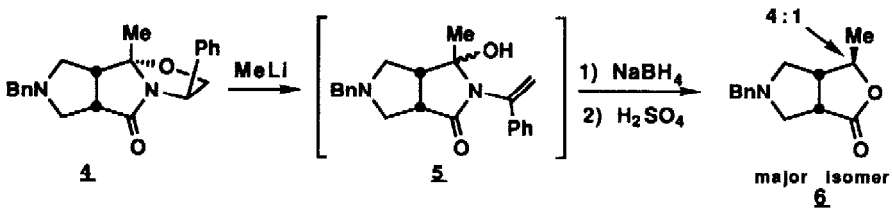
(*S*)-Dipole: (G_R = H, G_S = Me)

Achiral Dipole: (G_R = G_S = H)



Consistent with this proposal that the degree of diastereofacial selectivity (favoring the α cycloadducts) is determined by the presence or absence of significant steric interactions **ii** and **iii** (Fig. 1) is the observation that reactions involving α-unsubstituted lactams **1d** and **1e** (R_2 = H) with chiral or achiral dipoles gave similar diastereoselectivities (82-88% d.e., Table 1).[11]

An example of the synthetic utility of tricyclic lactams (**3**, R=Ph) is shown below. Lactam **4** was observed to give non-racemic bicyclic hydroxylactams **5** as a consequence of benzylic proton abstraction[12] by MeLi, followed by oxazolidine C-O bond cleavage. Conversion of **5** to a 4:1 mixture of bicyclic lactones[13] was accomplished using published procedures[14] in 51% overall yield from **4**. The major lactone **6** (*R*) was shown to be 93.7% e.e. by chiral stationary phase HPLC analysis.



4 5 6

In conclusion, high yielding 1,3-dipolar cycloadditions of a readily available azomethine ylide derived from *R*(+)-α-methylbenzylamine to α-carboalkoxyl, unsaturated lactams derived from (*S*)-valine give good diastereofacial selectivities (75-85% d.e) as a consequence of matched double diastereoselection. Unsubstituted bicyclic lactams derived from (*S*)-valine or (*S*)-phenylglycine react with both chiral or achiral azomethine ylides to afford the corresponding tricyclic derivatives with high diastereoselectivity (82-88% d.e). Further studies are in progress to convert these cycloadducts into non-racemic polysubstituted pyrrolidine derivatives.

ACKNOWLEDGEMENTS: The authors are grateful to the National Institutes of Health for financial support of our program. A Department of Education Fellowship (to AHF) is also warmly acknowledged.

REFERENCES.

1. Huisgen, R. '1,3-Dipolar Cycloaddition-Introduction, Survey, and Mechanism', Vol. 1, 1-163, and Lown, J.W. 'Azomethine Ylides', Vol. 1, 653-731, in '1,3-Dipolar Cycloaddition Chemistry', ed. Padwa, A.; Wiley, New York, **1986**; Tsuge, O and Kanemasa, S. 'Recent Advances in Azomethine Ylide Chemistry' in *Advances in Heterocyclic Chemistry* **1989**, *45*, 232. Ed. Katritzky, A.
2. Use of chiral dipolarophiles: a) Takahashi, T ; Kitano, K.; Hagi, T.; Nihonmatsu, H.; Koizumi, T. *Chem. Lett.* **1989**, 597. b) Kanemasa, S.; Yamamoto, H. *Tetrahedron Lett.* **1990**, *31*, 3633. c) Garner, P.; Ho, W. B. *J. Org. Chem.***1990**, *55*, 3973. d) Barr, D. A.; Dorrity, M. J.; Grigg, R.; Malone, J. F.; Montgomery, J.; Rajviroongit, S ; Stevenson, P. *Tetrahedron Lett* **1990**, *31*, 6569.e) Coulter, T ; Grigg, R.; Malone, J. F.; Sridharan, V. *Tetrahedron Lett.* **1991**, *32*, 5417.
3. Use of chiral dipoles: a) Padwa, A.; Chen, Y. Y.; Chiacchio, U. and Dent, W. *Tetrahedron* **1985**, *41*, 3529.b) Garner, P.; Sunitha, K.; Shanthilal, T. *Tetrahedron Lett.***1988**, *29*, 3525. c) Deprez, P.; Rouden, J.; Chiaroni, A.; Riche, C.; Royer, J.; Husson, H P *Tetrahedron Lett.* **1991**, *32*, 7531.
4. Masamune, S.; Petersen, J.S.; Sita, L R., *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1-30.
5. Meyers, A.I. and Fleming, S.A.; *J. Am. Chem. Soc.*, **1986**, *108*, 306.
6. Meyers, A.I.; Romo, D.; Romine, J.L.; and Midura, W. *Tetrahedron*, **1990**, *46*, 4951; Meyers, A.I. and Romo, D. *Tetrahedron Lett.*, **1989**, *30*, 1745; Meyers, A.I.; Romine, J.L. and Fleming, S.A., *J. Am. Chem. Soc.*, **1988**, *110*, 7245.
7. Busacca, C.A. and Meyers, A.I., *J. Chem. Soc. Perkin Trans I* **1991**, 2299.
8. Achiwa, K.; Terao, Y.; Kotaki, H and Imai, K *Chem. Pharm. Bull.* **1985**, *33*, 2762.
9 Padwa, A. and Dent, W. *J. Org. Chem.* **1987**, 52, 235.
10. Stereochemical assignments were made on the basis of NOE, 2D (^{13}C-^{1}H) correlation techniques, and comparison of the ^{13}C chemical shifts of the angular substituents of corresponding α and β cycloadducts. Since ^{13}C chemical shifts are moved significantly upfield by steric compression effects (γ-gauche effect, Ref 15), it was determined that the major isomers had the α-configuration.
11. The high diastereoselection observed in cycloadditions with **1d** and **1e** is in accord with the Hammond postulate (Ref 16). The lesser reactive α-unsubstituted dipolarophiles **1d** and **1e** proceed through more product-like transition states in which the steric effect of the angular substituent (R_1) is magnified; therefore, an enhanced preference of the unsaturated lactam for α-approach of the 1,3-dipoles is observed.
12. β-Lithiations of acyclic carboxamides have been shown to occur in preference to α-lithiations : Beak, P.; Kerrick, S.; Wallin, A.P. and Lutz, G.P. *J. Org. Chem.* **1991**, *56*, 4938.
13. Stereochemical assignments of these bicyclic lactones are based upon the upfield shift of the ^{13}C NMR methyl group signal of the minor isomer versus that of the major isomer. We attribute this upfield shift to steric compression of the methyl group *syn* to the pyrrolidine ring (Ref 15).
14. Mukaiyama, T.; Yamashita, H. and Asami, M. *Chem. Lett.* **1983**, 385; Speckamp, W.N. and deBoer, J.J.J. *Tetrahedron Lett.* **1975**, *46*, 4039.
15. Wehrli, F.W. and Wirthlin, T., *Interpretation of Carbon-13 NMR Spectra.* Heyden & Son, Ltd. pp 27-28, 37.
16. Hammond, G.S., *J. Am. Chem. Soc.* **1955**, *77*, 334.

(Received in USA 20 March 1992)