

Diastereoselective Kinetically and Thermodynamically Controlled Additions of (*R*)-(+)-Methyl *p*-Tolyl Sulphoxide Anion to Imines (Tolyl = C₆H₄Me)

Stephen G. Pyne* and Branko Dikic

Department of Chemistry, University of Wollongong, Wollongong, N.S.W. 2500, Australia

The anion of (*R*)-(+)-methyl *p*-tolyl sulphoxide reacts diastereoselectively with imines to give chiral β -amino sulphoxides.

Chiral β -amino sulphoxides are useful compounds for asymmetric synthesis.¹⁻⁸ We have previously reported the total synthesis of (*R*)-(+)-carnegine⁴ and (*R*)-(+)-canadine⁵ from chiral isoquinoline precursors prepared *via* the intramolecular conjugate addition of amines to chiral vinyl sulphoxides. The diastereoselectivity of these reactions, however, were modest (diastereoisomeric excess of 68%). We now report a highly efficient and diastereoselective method for preparing β -amino sulphoxides from the addition of the lithium anion of (*R*)-(+)-methyl *p*-tolyl sulphoxide (**2B**) to imines. (Tolyl = C₆H₄Me).

In 1973, Tsuchihashi² reported that the addition of (**2B**) to benzylideneaniline (**1a**) at -10 to -20 °C was a highly diastereoselective process; the generality of this method, however, was not demonstrated. Our initial studies focused on the addition of the anion of racemic methyl phenyl sulphoxide (**2A**) to (**1a**). The addition of (**2A**) to (**1a**) at -78 °C occurred smoothly over a period of 5 h giving a mixture of the diastereoisomeric adducts (**3a**) and (**4a**) with modest dia-

stereoselection (Table 1). An identical product diastereoselection was realized when a solution of (**2A**) and (**1a**) was prepared at -78 °C and then held at -45 °C for 2 h or 0 °C for 5 min. Longer reaction times (0.5-12 h) at 0 °C resulted in very poor diastereoselection suggesting that equilibration had occurred between the diastereoisomeric adducts (**3'a**) and (**4'a**). A similar trend was observed when analogous reactions were performed with the anion of (*R*)-(+)-methyl *p*-tolyl sulphoxide⁹ (**2B**) and the imine (**1a**) or benzylidenemethylamine (**1b**). The reaction of (**2B**) with (**1c**) was also highly diastereoselective under kinetically controlled conditions (0 °C, 10 min). The relative stereochemistry of (**3; b,c**) and (**4; b,c**) was determined by ¹H n.m.r. spectroscopic analysis using (**3a**) and (**4a**) of known absolute stereochemistry as reference compounds.²

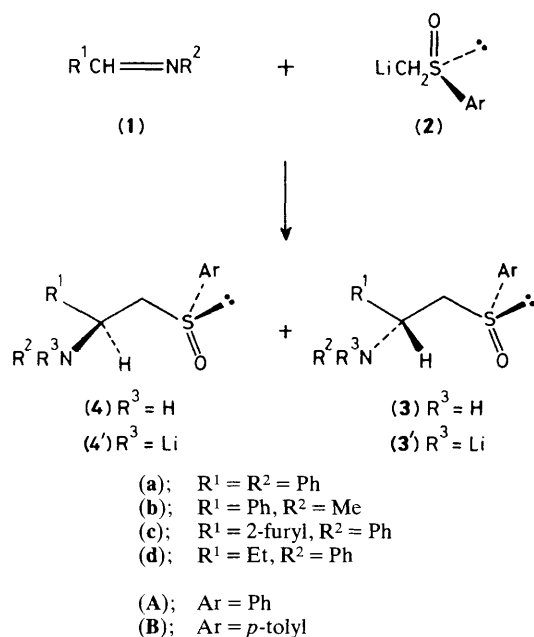
The addition of (**2B**) to 3,4-dihydro-6,7-dimethoxyisoquinoline (**6**) under kinetically controlled conditions [-78 to -45 °C (2 h)] gave a mixture of (**7**) and (**8**) in which the former product was favoured. At 0 °C, however, a high and much

Table 1. Addition of anion (2) to imines (1).

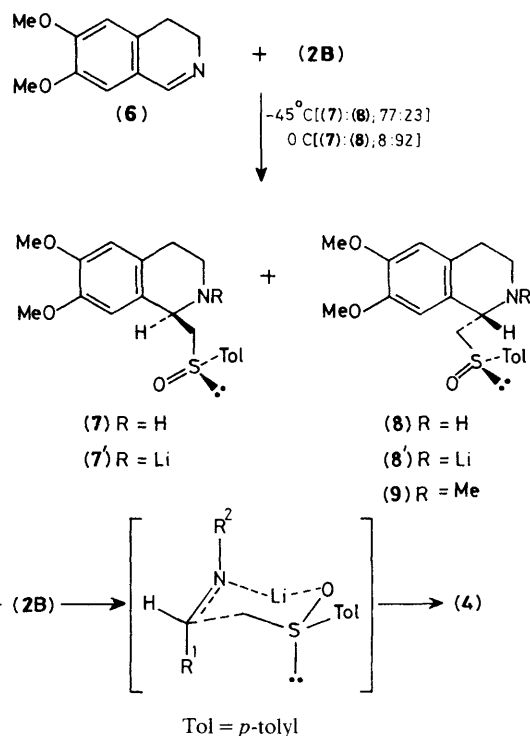
Imine	Anion	Temp. ^a /°C	Time	Yield ^b /%	(3):(4) ^c
(1a)	(2A)	-78	5 h	96	18:82
(1a)	(2A)	-45	2 h	^d	18:82
(1a)	(2A)	0	5 min	^d	18:82
(1a)	(2A)	0	0.5 h	^d	30:70
(1a)	(2A)	0	1 h	95	42:58
(1a)	(2B)	0	5 min	95	14:86
(1a)	(2B)	0	12 h	95	43:57
(1b)	(2B)	0	10 min	89	9:91
(1b)	(2B)	0	12 h	89	49:51
(1c)	(2B)	0	10 min	96	9:91
(6)	(2B)	-45	2 h	64	77(7):23(8)
(6)	(2B)	0	12 h	92	8(7):92(8)
(1d)	(2B)	-45	2 h	85	20:80

^a Tetrahydrofuran solutions of the imine and (2) were mixed at -78°C and then warmed slowly to the designated temperatures.

^b Yield after chromatography. ^c Determined on crude reaction mixtures by ¹H n.m.r. spectroscopy (400 MHz). ^d 90–95% from ¹H n.m.r. spectral analysis.



improved product diastereoselection was observed and (8) was the major diastereomeric product. A similar product diastereoselection was observed when a mixture of (6) and (2B) was held at -45°C for 2 h and then warmed to 0°C (12 h). It is clear that the diastereoisomeric adducts (3'; a,b) and (4'; a,b) and (7') and (8') interconvert, presumably via a retro addition reaction to (1) or (6) and (2B), at 0°C. In general the product diastereoselection is poor under equilibrium control compared to that from kinetic control. The reaction of (6) with (2B) was unique in that the most favourable product diastereoselection was observed under equilibrium controlled conditions. The exact reasons for this high diastereoselectivity

**Scheme 1**

are unclear at this stage. The absolute stereochemistry of (8) was unequivocally determined by its conversion to (1*S*,*R*_s)-(+)(9) [m.p. 71°C, lit.⁴ 70–72°C, [α]_D²³ +206° (c 1.1, CHCl₃)] by reductive methylation (82% yield).¹⁰ We have previously converted (9) to (*R*)-(+)-carnegine by reductive desulphurization.⁴

We suggest the chair transition state (Scheme 1) to account for the preference of the diastereoisomeric adduct (4) over (3). The application of this methodology to alkaloid synthesis is currently under investigation.

We thank the Australian Research Council for financial support and Chris Dixon for performing the initial experiments.

Received, 10th February 1989; Com. 9/006551

References

- D. J. Abbot, S. Colonna, and C. J. M. Stirling, *J. Chem. Soc., Chem. Commun.*, 1971, 471.
- G. I. Tsuchihashi, S. Iriuchijam, and K. Maniwa, *Tetrahedron Lett.*, 1973, 3389.
- J. J. Hansen and A. Kjaer, *Acta Chem. Scand., Ser. B*, 1974, **28**, 418.
- S. G. Pyne and S. L. Chapman, *J. Chem. Soc., Chem. Commun.*, 1986, 1688.
- S. G. Pyne, *Tetrahedron Lett.*, 1987, **28**, 4737.
- S. G. Pyne, R. Griffith, and M. Edwards, *Tetrahedron Lett.*, 1988, **29**, 2089.
- M. Hiram, H. Hioki, S. Ito, and C. Kabuto, *Tetrahedron Lett.*, 1988, **29**, 3121.
- T. Satoh, T. Oohara, and K. Yamakawa, *Tetrahedron Lett.*, 1988, **29**, 4093.
- G. Solladie, *Synthesis*, 1981, 185.
- R. F. Borch and A. I. Hassid, *J. Org. Chem.*, 1972, **37**, 1673.