Diastereoselective Kinetically and Thermodynamically Controlled Additions of (*R*)-(+)-Methyl *p*-Tolyl Sulphoxide Anion to Imines (Tolyl = C_6H_4Me)

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*)-(+)-carnegine[4] and (*R*)-(+)-canadine[5] 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 = C_6H_4Me).

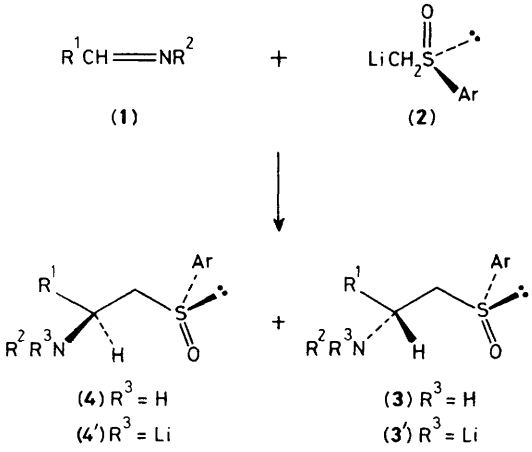
In 1973, Tsuchihashi[2] reported that the addition of (**2B**) to benzylideneaniline (**1a**) at −10 to −20 °C was a highly diastereoselective process; the generality of this method, however, was not demonstrated. Our initial studies focused on the addition of the anion of racemic methyl phenyl sulphoxide (**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 diasteroisomeric adducts (**3a**) and (**4a**) with modest diastereoselection (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 sulphoxide[9] (**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 ^{1}H 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

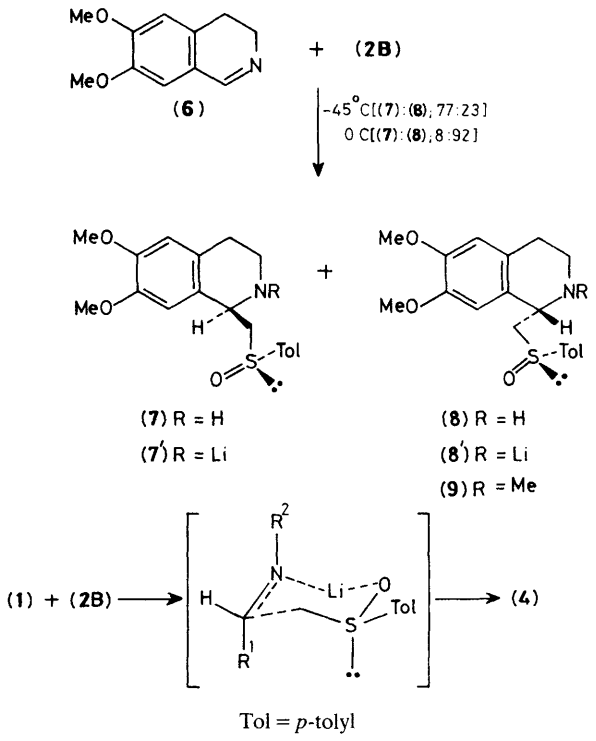
[a] Tetrahydrofuran solutions of the imine and (**2**) were mixed at −78 °C and then warmed slowly to the designated temperatures. [b] Yield after chromatography. [c] Determined on crude reaction mixtures by ^{1}H n.m.r. spectroscopy (400 MHz). [d] 90—95% from ^{1}H n.m.r. spectral analysis.



(**a**); $R^1 = R^2 = Ph$
(**b**); $R^1 = Ph$, $R^2 = Me$
(**c**); $R^1 = 2$-furyl, $R^2 = Ph$
(**d**); $R^1 = Et$, $R^2 = Ph$

(**A**); Ar = Ph
(**B**); Ar = *p*-tolyl

improved product diastereoselection was observed and (**8**) was the major diastereoisomeric 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



Tol = *p*-tolyl

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, $[\alpha]_D^{23}$ +206° (*c* 1.1, $CHCl_3$)] 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.

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