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Generation of strong, homochiral bases by electrochemical reduction of phenazine derivatives†

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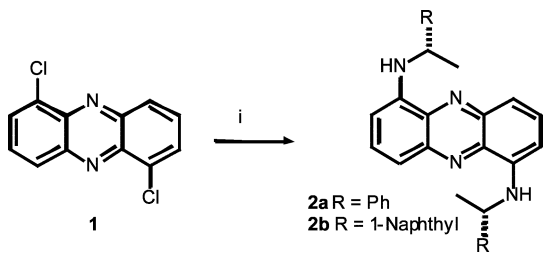
Electrochemical reduction of enantiomerically pure amino- and alkoxy-phenazine derivatives forms strongly basic radical anions which give asymmetric induction in the conversion of 3,4-epoxytetrahydrothiophene-1,1-dioxide 7 into the allylic ester 9 with facile regeneration of the phenazine.

Electrochemical reduction of neutral substrates ('probases') generates radical-anions and dianions which may be used as bases in synthetic transformations.[1] Previous studies have shown that the radical-anion of phenazine is able to deprotonate phosphonium ions such as $Ph_3PCH_3^+$ at conveniently measurable rates.[2] There have not hitherto been any descriptions of the use of electrogenerated bases in asymmetric reactions. We now report the synthesis of some C_2-symmetric homochiral phenazine derivatives, the radical-anions of which exhibit enantioselectivity in the rearrangement of a prochiral epoxide.

The known[3] 1,6-dichlorophenazine **1** underwent palladium-catalysed amination with chiral amines to give enantiomerically pure 1,6-diaminophenazine derivatives **2** (Scheme 1).

Readily available[4] 1,6-dimethoxyphenazine underwent quantitative conversion into 1,6-dihydroxyphenazine **3** using hot BBr_3. Cyclophane systems were obtained by alkylation of **3** using terminal diiodides under conditions of high dilution (Schemes 2 and 3). Thus the planar chiral compound **4** was initially obtained as a racemate, as shown by chiral HPLC; resolution of **4** was achieved through flash chromatographic separation of the diastereoisomeric *N*-acyldihydrophenazines, **5a** and **5b**, followed by acid hydrolysis and re-aromatisation. Use of an enantiomerically pure bis-alkylating agent derived from (*R*,*R*)-cyclohexane-1,2-diol, followed by chromatographic separation, gave the two bridged phenazines **6a** and **6b** as pure stereoisomers. Single crystal X-ray diffraction studies were performed on compounds (−)-(p*S*)-**4**, **5b**, **6a** and **6b** and the sense of planar chirality in these substances was thus defined relative to the established central chirality, which is derived from (*R*,*R*)-cyclohexane-1,2-diol and (*R*)-α-methoxyphenylacetic acid.‡

Cyclic voltammetry in aprotic solvents showed the phenazine derivatives to be reduced in two one-electron steps, the first being chemically reversible at modest scan rates (< 1 V s^{-1}) and the second becoming reversible at higher scan rates (up to 100 V s^{-1}).



Scheme 1 *Reagents and conditions*: (i) $RCH(Me)NH_2$ (2.2 equiv.), *t*-BuONa (2.4 equiv.), $Pd_2(dba)_3$ (2 mol%), (*R*)-(−)-BINAP (5 mol%), toluene, 99% (R = Ph) or 55% (R = 1-naphthyl).

† Electronic supplementary information (ESI) available: procedure for conversion of **7** into **9** using electrochemical reduction of **6a** to generate the chiral base; crystallographic data for (p*S*)-**4**, **5b**, **6a** and **6b**. See http://www.rsc.org/suppdata/cc/b3/b313995f/

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The first and second E^0 values of −1.10 and −2.05 V in DMSO *vs.* SCE, observed for compound **6a**, are typical and indicate the feasibility of generating phenazine radical anions in the presence of other reactants.

Reaction between an added carbon acid such as $Ph_3PCH_3^+$ and the radical-anion formed at the first reduction potential results in loss of reversibility of the first peak and a consequent doubling of the peak height. This is characteristic of the well established DISP mechanism, set out in steps (1) to (4) as follows, in which the second electron transfer (step 3) involves a second equivalent of the radical-anion.

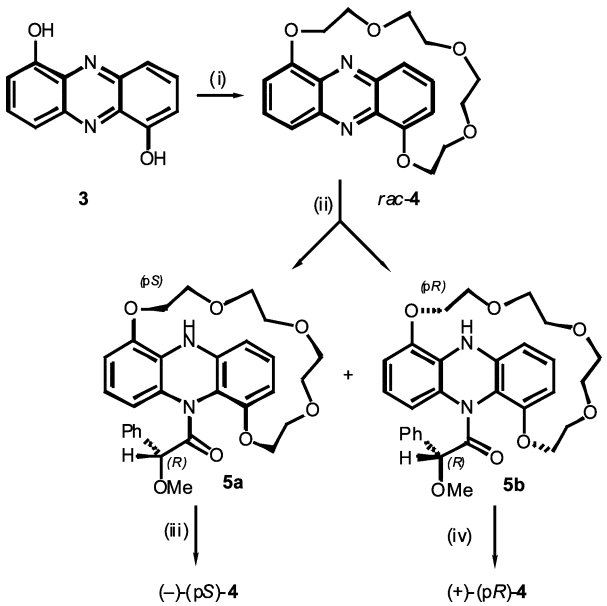
$$\text{Phen} + e^- \rightarrow \text{Phen}^{\cdot -} \quad (1)$$

$$\text{Phen}^{\cdot -} + \text{HA} \rightarrow \text{HPhen}^{\cdot} + A^- \quad (2)$$

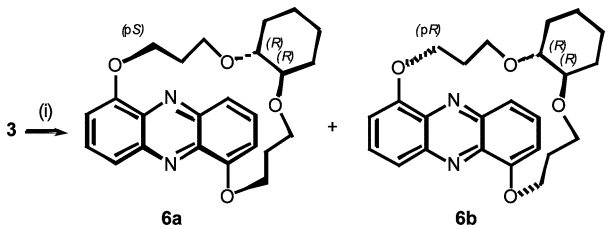
$$\text{HPhen}^{\cdot} + \text{Phen}^{\cdot -} \rightarrow \text{HPhen}^- + \text{Phen} \quad (3)$$

$$\text{HPhen}^- + \text{HA} \rightarrow H_2\text{Phen} + A^- \quad (4)$$

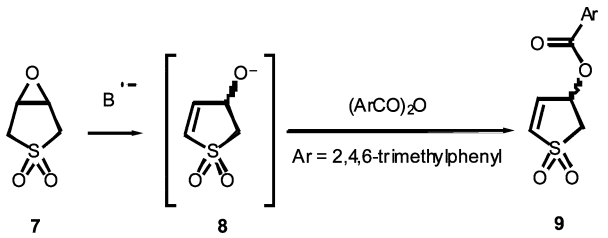
It is of note that although each phenazine undergoes reduction to a 5,10-dihydrophenazine product in the course of acting as an



Scheme 2 *Reagents and conditions*: (i) $I[CH_2CH_2O]_3CH_2CH_2I$, K_2CO_3, DMF, 80 °C, 30 h, 14%; (ii) H_2 (balloon), 10% Pd–C, CH_2Cl_2, 20 °C, 30 min; then (*R*)-α-methoxyphenylacetyl chloride (3.1 equiv.), pyridine (3.8 equiv.), 14% for **5a** and 19% for **5b**; (iii) 1.3 M HCl, EtOH–H_2O (2 : 1), reflux, 3 d, 31%; (iv) 6.7 M HCl, EtOH–H_2O (2 : 1), reflux, 7 d, 34%.



Scheme 3 *Reagents and conditions*: (i) (*R*,*R*)-1,2-bis(3-iodopropoxy)-cyclohexane, K_2CO_3, DMF, 80 °C, 30 h, 5% for **6a** and 5% for **6b**.



Scheme 4

Table 1 Conversion of epoxide **7** into ester **9** using electrogenerated bases[a]

Probase	Additive[b]	Yield of **9**	ee[c] of **9**	Recovery of probase
(*R*,*R*)-**2a**	—	50[d]	+8	72
(*S*,*S*)-**2a**	—	50[d]	−8	
(*R*,*R*)-**2b**	—	63	+18	74
(+)-(p*R*)-**4**	—	33	< 10	71
(+)-(p*R*)-**4**	$LiClO_4$	53	+20	78
(−)-(p*S*)-**4**	—	38	< 10	57
6a	—	43	+34	100
6a	$LiClO_4$	77	+28	100
6a	—	39	+32	100
6a	—	48[d]	+28	67
6a	$Yb(OTf)_3$	0		
6b	—	63	+16	100
6b	$LiClO_4$	72	+24	80
6b	$Mg(OTf)_2$	19	< 10	100

[a] Experiments were conducted in DMSO with Bu_4NPF_6 as supporting electrolyte unless indicated otherwise. [b] 3 equiv. relative to probase. [c] Determined by chiral HPLC on Daicel Chiralpak OT-(+) eluted with 9 : 1 hexane : propan-2-ol; a positive ee value indicates an excess of the (*R*)-enantiomer, which we have synthesised independently and found to have a longer retention time than the (*S*)-form. [d] DMF was used as solvent.

electrogenerated base, regeneration of the initial phenazine is efficiently achieved by brief air oxidation. This means that investment in the synthesis of relatively complex phenazine derivatives is not wasted and they can be recovered from product mixtures.

Cyclic voltammetry and digital simulation, assuming the DISP mechanism, allow the measurement of rate constants for the rate-limiting proton transfer step (step 2). Self-consistent rate constant data, which will be discussed elsewhere, were obtained over a variety of experimental conditions (concentration of phenazine derivative and carbon acid, cyclic voltammetric sweep speed).

The rearrangement of the epoxide **7** to the isomeric allylic alcohol was used to test the ability of the electrogenerated chiral bases to effect enantioselective deprotonation. This epoxide rearrangement is known to occur in the presence of moderate bases such as barium carbonate.[5] Therefore the intermediate alkoxide **8**, which might have acted as an alternative base, was trapped by *in situ* acylation (Scheme 4). 2,4,6-Trimethylbenzoic anhydride was used for this purpose, since unlike the less hindered benzoic anhydride, it did not react with the phenazine radical ions under the reaction conditions. The ester product **9** was isolated by flash chromatography and its ee was determined by chiral HPLC (Table 1). Phenazine derivatives were recovered by air oxidation and chromatography.

We have established the principle that bases formed by electrochemical reduction of chiral phenazines with either amino or alkoxy substitution are able to effect rearrangement of the epoxide **7** with modest, but significant, enantiomeric excess. Greatest selectivity is seen with the bridged compounds **6a** and **6b**, although the data suggest that the stereochemical outcome is controlled more by the presence of chiral centres than by the planar chirality. Addition of Lewis acidic metal salts was examined: Li^+ increased the yields of rearrangement product but did not improve the best ee values, whereas Mg^{2+} and Yb^{3+} salts were unhelpful, perhaps because they introduced water as a competing proton source.

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Notes and references

‡ *Crystal data for* (−)-(p*S*)-**4**. $C_{20}H_{22}N_2O_5$, M = 370.40, Orthorhombic, a = 10.0266(3), b = 11.8433(4), c = 14.9627(5) Å, α = 90.00, β = 90.00, γ = 90.00°, V = 1776.79(10) Å^3, space group $P2_12_12_1$, Z = 4, D_c = 1.385 Mg m^{-3}, μ = 0.100 mm^{-1}, reflections measured 14029, reflections unique 4047 with R_{int} = 0.0493, T = 120(2) K, final R indices [$I > 2\Sigma(I)$] $R1$ = 0.0412, $wR2$ = 0.0841 and for all data $R1$ = 0.0661, $wR2$ = 0.0927. *Crystal data for* **5b**. $C_{29}H_{31}N_2O_7$, M = 519.56, Monoclinic, a = 8.429(7), b = 15.650(14), c = 9.980(9) Å, α = 90.00, β = 105.40(4), γ = 90.00°, V = 1269.2(19) Å^3, space group $P2_1$, Z = 2, D_c = 1.271 Mg m^{-3}, μ = 0.098 mm^{-1}, reflections measured 3776, reflections unique 3408 with R_{int} = 0.0063, T = 160(2) K, final R indices [$I > 2\Sigma(I)$] $R1$ = 0.0457, $wR2$ = 0.1151 and for all data $R1$ = 0.0541, $wR2$ = 0.1210. *Crystal data for* **6a**. $C_{24}H_{28}N_2O_4$, M = 408.48, Monoclinic, a = 7.436(11), b = 17.116 (12), c = 8.713(13) Å, α = 90.00, β = 105.712(14), γ = 90.00°, V = 1068(2) Å^3, space group $P2_1$, Z = 2, D_c = 1.271 Mg m^{-3}, μ = 0.087 mm^{-1}, reflections measured 3892, reflections unique 2938 with R_{int} = 0.0171, T = 160(2) K, final R indices [$I > 2\Sigma(I)$] $R1$ = 0.0329, $wR2$ = 0.07580 and for all data $R1$ = 0.0485, $wR2$ = 0.0818. *Crystal data for* **6b**. $C_{24}H_{28}N_2O_4$, M = 408.48, Orthorhombic, a = 13.3625(4), b = 16.2726(5), c = 19.4817(7) Å, α = 90.00, β = 90.00, γ = 90.00°, V = 4236.2(2) Å^3, space group $P2_12_12_1$, Z = 8, D_c = 1.281 Mg m^{-3}, μ = 0.087 mm^{-1}, reflections measured 20623, reflections unique 8921 with R_{int} = 0.0818, T = 120(2) K, final R indices [$I > 2\Sigma(I)$] $R1$ = 0.0844, $wR2$ = 0.1970 and for all data $R1$ = 0.1842, $wR2$ = 0.2376. CCDC 223727–223730. See http://www.rsc.org/suppdata/cc/b3/b313995f/ for crystallographic data in .cif or other electronic format.

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