

Enantioselective Cathodic Reduction of Some Prochiral Ketones in the Presence of (1*R*,2*S*)-(–)-*N,N*-Dimethylephedrinium Tetrafluoroborate at a Mercury Pool Cathode

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The enantioselective cathodic reduction of some prochiral ketones viz. acetophenone (I), propiophenone (II), butyrophenone (III), valerophenone (IV), isobutyrophenone (V), and pivalophenone (VI) has been accomplished at a mercury pool cathode in *N,N*-dimethylformamide (DMF)–water (90:10) using tetrabutylammonium fluoroborate (TBA·BF₄) as a supporting electrolyte in the presence of (1*R*,2*S*)-(–)-*N,N*-dimethylephedrinium tetrafluoroborate (DET). Cyclic voltammetric investigations have been carried out and a probable mechanism of the process has been presented.

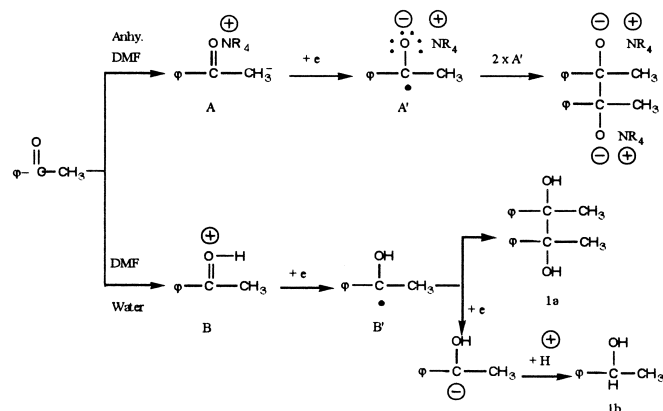
Enantioselective synthesis using a chiral heterogeneous catalyst has been a fascinating area and has attracted tremendous interest.^{1–4} A survey of the literature reveals that the variants applied in enantioselective electrosynthesis are: chirally modified electrodes,^{5–7} the use of a chiral solvent,⁸ a chiral supporting electrolyte,⁶ and cathodic reduction in the presence of optically active compounds,^{2,3,6,9} crown ethers¹⁰ etc. Our work is intended to explore the preparativescale enantioselective cathodic reduction of some prochiral ketones, I–VI, in DMF–H₂O (90:10) containing 0.1 M TBA·BF₄, at a mercury pool

cathode using DET as a chiral auxiliary. Pinacols (racemic/meso) viz. Ia–VIa and corresponding alcohols viz. Ib–VIb were obtained, which were separated on a silicagel column (60–150 mesh) by eluting with benzene–ethyl acetate/distillation under reduced pressure, their optical purity (ee) was calculated, and their absolute configuration was determined.

Results and Discussion

A preliminary investigation on the cathodic reduction of acetophenone has shown that in the presence of anhydrous DMF (aprotic media), containing 0.1 M TBA·BF₄ and 10 mM of DET, pinacol Ia was obtained in 93% yield. However, if a proton source, e.g. water, was added to it, the formation of alcohol, ie. Ib, increased at the expense of Ia. In our experiments, we obtained compounds Ia/Ib in 75%/15%, 60%/33%, 45%/46%, and 30%/62% yields when the cathodic reduction of I was carried out at a mercury pool at a potential of –1.48 V vs Ag–AgCl in DMF:Water, i.e. 99:1, 95:5, 90:10, and 80:20, respectively. The ee of alcohol Ib was found to be 17%, 34%, 55%, and 35%, respectively. These results indicate that the DMF–Water (90:10) is suitable for our purpose. The above observations also suggest that the electron transfer from the cathode to ketone I is not direct, but occurs to a tetrabutylammonated ketone in an anhydrous DMF/protonated ketone in DMF–Water. In the former case, dimerization (of A') is the main reaction, while in later case some radicals (B') undergo dimerization to give pinacol Ia, and also some radical B' undergoes one electron transfer followed by protonation to yield alcohol Ib (Scheme 1).

The reduction potential of ketones I–VI were determined by CV studies, and the preparativescale cathodic reduction was carried out at mercury pool at potentials of –1.48 V, –1.65 V, –1.72 V, –1.90 V, –2.00 V, and –2.10 V (Vs, Ag – AgCl in all cases), respectively, in DMF–Water (90:10) containing 0.1 M TBA·BF₄ and 10 mM DET. Pt foil was used as an anode in DMF–Water (90:10) containing 0.1 M TBA·BF₄. The charge was transferred corresponding to 2 F Mol^{–1}. The obtained products were pinacol Ia–VIa (racemic/meso) in 45%, 40%, 38%, 35%, 25%, and 18% yields, along with alcohols Ib–VIb in 46%, 54%, 52%, 54%, 60%, and 70% yields. The enantiomeric excess were assayed by comparing with known values of



Scheme 1.

the maximum rotation of each chiral alcohol¹¹ $[\alpha]_D^{20} -0.439^\circ$ (neat, $l = 0.01$) for (S)-**Ib**^{11a}; $[\alpha]_D^{20} -45.45^\circ$ (c 5.15, chloroform) for (S)-**IIb**^{11b}; $[\alpha]_D^{22} -45.2^\circ$ (c 4.8, benzene) for (S)-**IIIb**^{11a}; $[\alpha]_D^{22} -0.200^\circ$ (neat, $l = 0.01$) for (S)-**IVb**^{11a}; $[\alpha]_D^{25} -24.6^\circ$ (neat) for S-**Vb**^{11c}; $[\alpha]_D^{22} +25.9^\circ$ (c 2.2, benzene) for (R)-**Vb**^{11d}. The absolute configuration of alcohols **Ib**–**Vb** was found to be *S*.

Preliminary CV studies on the reduction of **I** at mercury film coated on a Pt wire (freshly prepared) in DMF containing 0.1 M TBA·BF₄ showed a reduction peak at $E_p -1.52$ V vs Ag/AgCl ($i_p = 8.75$ μ A). Upon the addition of 10 mM DET, when CV was recorded two peaks appeared, viz $E_{p1} -1.14$ V (peak current, $i_{p1} = 4.50$ μ A) and at $E_{p2} -1.48$ V ($i_{p2} = 13.25$ μ A). The first peak at $E_{p1} -1.14$ disappeared in repeated scans, and was thus identified as being due to the adsorption of DE⁺. The second peak i.e. $E_{p2} -1.48$, due to the reduction of compound **I**, was slightly shifted anodically with an increase in i_{p2} , indicating that the transfer of an electron from the cathode to a ketone becomes more facile upon the addition of DET. The effect of the concentration of DET on the cathodic reduction of **I** was then studied in DMF–Water (90:10) at a mercury pool at a potential of -1.48 V vs Ag–AgCl using 0.1 M TBA·BF₄ by passing charge corresponding to 2 F mol^{−1}. **Ia**/**Ib** was obtained in 50%/42%, 45%/46%, 48%/48%, and 46%/49% at DET concentrations 1 mM, 5 mM, 10 mM, and 20 mM, respectively. Compound **Ib** was found to have ee in 40%, 50%, 55%, 51%, and 45%, respectively, establishing that the inductor concentration, viz DET, does not significantly effect the yield of **Ia** and its optical yield and thus suggesting strong adsorption of DET on the surface of the cathode.¹²

Based on the above mentioned preliminary investigations, it appears that the DET is adsorbed on the surface of the cathode in a certain specific orientation, such that the H of –OH (of DE⁺) remains towards the catholyte, and the oxygen of the protonated k-etone ($>C=O^+-H \leftrightarrow >C^+-O-H$) forms a hydrogen bridge with H (of –OH) of the adsorbed DET. Upon electron transfer the intermediates (A' and B') are formed. Intermediate A' (ion pair) undergoes dimerization exclusively in DMF to give racemic/meso **Ia**. The radical B' either undergoes further electron transfer to give a carbanion (the electron is transferred to nearest p orbital as ketone (s) is in certain specific orientation towards cathode) or dimerization. The addition of a proton to carbanion in such a situation yields, the *S*-isomer selectively. The above preposition finds further support from an observation in the case of the reduction of ketone **VI**, where the corresponding alcohol **Vb** shows a loss of considerable enantioselectivity (5%), as the bulky group –C(CH₃)₃ appears to create a hinderance for a specific orientation on the surface of the cathode.

Detailed mechanistic studies of the process are being conducted and will be addressed later.

Experimental

Electrochemical studies were carried out on a Wenking potentiostat LB 72 M, a voltage scan generator VSG 72 and a Rikadenki X–Y recorder (model 101 T). The chiral auxillary viz. DET was synthesized by first refluxing (1*R*,2*S*) - ephedrine with methyl iodide (1:2) in alcohol for 10 h to give *N,N*-dimethylephedrinium

bromide. The TBA·BF₄ and DET were prepared by reported methods,^{13,14} and were dried under a vacuum and kept in a desiccator. DMF was dried by a reported method^{15a} and kept over activated molecular sieves (4 Å) under nitrogen gas.

A typical preparativescale electroreduction of acetophenone has been described as under: 1.2 g acetophenone in 40 mL DMF + H₂O (90:10) containing 0.1 M TBA·BF₄ and 10 mM DET·BF₄ was taken as a catholyte. A porous diaphragm was used as a cell divider, and to it 20 mL DMF–H₂O (90:10) containing 0.1 M TBA·BF₄ was added, which served as an anolyte. A Hg pool (36 cm²) was used as a cathode and Pt foil (9 cm²) served as an anode. A charge corresponding to 2 F mol^{−1} was transferred at an applied potential of -1.48 V vs Ag–AgCl.

After electrolysis, the solvent was removed under pressure (50 °C, 35 mm). To it water (~30 mL) was added, and the organic product(s) were extracted with ether (3 × 30 mL). The combined ethereal layer was dried over anhydrous sodium sulfate, filtered, and the solvent was removed. Distillation of mass under reduced pressure, 79–83 °C at 3 mm Hg (reported^{15b} 79 °C at 3 mm Hg), afforded 540 mg of pure **Ib** (yield 46%, mp 46–47 °C) $[\alpha]_D^{22} -0.240^\circ$ (neat, $l = 0.01$) in 55% ee assigned by a comparison of the known rotation value, $[\alpha]_D^{20} -0.439^\circ$ (neat, $l = 0.01$)^{11a}. The remaining mass upon recrystallization afforded pinacol **Ia** (45%).

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