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# **Oxidative Deamination of Benzylamine by Electrogenerated Quinonoid Systems as Mimics of Amine Oxidoreductases Cofactors.**

**Martine Largeron and Maurice-Bernard Fleury\***

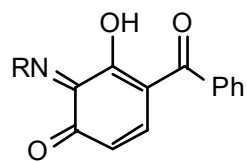
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### Oxidative Deamination of Benzylamine by Electrogenerated Quinonoid Systems as Mimics of Amine Oxidoreductases Cofactors

Martine Largeron and Maurice-Bernard Fleury\*



**3<sub>ox</sub>** : R = CH<sub>2</sub>Ph

**4<sub>ox</sub>** : R = H

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**Abstract** : The reactions of a new type of quinonoid systems with benzylamine have been investigated in methanol in order to mimic the reactions occurring in the course of the enzymatic oxidation of amines by quinone cofactors. Under strictly anaerobic conditions, unstable quinonoid species **1<sub>ox</sub>-4<sub>ox</sub>** have been selectively electrogenerated using anodic controlled potential electrolysis. Thus, we have demonstrated that 3,4-quinone **1<sub>ox</sub>** is incapable of deaminating benzylamine, while 3,4-iminoquinone species **3<sub>ox</sub>** and **4<sub>ox</sub>** act as efficient catalysts for the autorecycling oxidation of benzylamine : the reaction efficiency reached 64 turnovers. Additional mechanistic investigations reveal that the oxidation of benzylamine by our quinonoid model cofactors proceeds unambiguously via a transamination mechanism as suggested for many enzymatic systems.

## Introduction

Copper amine oxidases and bacterial amine dehydrogenases are enzymes containing a covalently bound quinone cofactor. These enzymes catalyze the oxidative deamination of a primary amine to produce the corresponding aldehyde and ammonia, concomitant with a two-electron reduction of dioxygen to hydrogen peroxide.<sup>1</sup> For instance, the active carbonyl cofactor used by mammalian copper amine oxidases is the quinone form (TPQ) of an active site 2,4,5-trihydroxyphenylalanine (TOPA) residue.<sup>2</sup> Likewise, the bacterial methylamine dehydrogenase has been shown to contain an active site tryptophan tryptophylquinone (TTQ). It is also well known that pyrroloquinoline quinone (PQQ) behaves as a catalyst of amine oxidation, although PQQ is now recognized not to be the cofactor of amine oxidases.<sup>3</sup>

The design of artificial catalysts that begin to approach the reactivity of amine oxidoreductases cofactors is a challenging problem, that could provide further insight into the function of the quinonoid cofactors in amine oxidation. Several synthetic models of naturally occurring quinones have been developed and model reactions of amine oxidoreductases were examined.<sup>4-9</sup> In particular, substantial informations have been obtained through catalytic aerobic deamination of benzylamine mediated by model cofactors, providing relevant insight into the enzyme catalysis. All the ionic mechanisms proposed so far involve a carbinolamine intermediate (Scheme 1). The most popular pathway is akin to the transamination reaction of pyridoxal phosphate with amino-acids. This involves a tautomerization of the benzyliminoquinone species to the product Schiff base, which is then hydrolysed to yield the aldehyde product and the aminophenol. The latter is autoxidized to the iminoquinone species, which is in turn hydrolysed to the quinone and ammonia. The alternative is an addition-elimination mechanism proposed first for PQQ, in which the carbinolamine is directly converted into the quinol and benzylimine without generating aminophenol intermediate.<sup>5</sup> The quinol is then autoxidized to regenerate the quinone. The observation of catalytic turnover did not permit a distinction between transamination and addition-elimination mechanisms. Furthermore, attempts to distinguish under anaerobic single-turnover between these two mechanisms through product analysis, (aminophenol from transamination or quinol from addition-elimination), were thwarted by the occurrence of redox

interchange reactions that scrambled the initial cofactor reduction product.<sup>7</sup> Nonetheless, in the case of the TPQ and TTQ-catalyzed amine oxidation reaction, solutions were found to circumvent these problems allowing to demonstrate a preferred transamination mechanism.<sup>10,11</sup>

In the course of our search for new neuroprotective agents, we recently reported the one-pot electrochemical syntheses of two novel classes of derivatives exhibiting potent neuroprotective activities close to that of standard  $\alpha$ -tocopherol.<sup>12,13</sup> The key step consisted of the reactivity of the highly electrophilic electrogenerated 3,4-quinone  $\mathbf{1_{ox}}$  (Chart 1) with amino-alcohols. Depending on the nature of the condensed amino-alcohols, attack at the 2-position led to 3-substituted-1,4-benzoxazin-8-one derivatives, while attack at the 3-position gave substituted alkylaminophenols.<sup>14,15</sup> The C(3) reactivity of the electrogenerated 3,4-quinone  $\mathbf{1_{ox}}$  was further extended to amines. At the outset, we believed that 3,4-quinone  $\mathbf{1_{ox}}$  efficiently catalysed the oxidative deamination of benzylamine, in deaerated  $\text{CH}_3\text{OH}$ , in a way reminiscent of that reported for PQQ, TTQ and TPQ model cofactors.

This paper describes our efforts to provide an unambiguous conclusion based on an electrochemical approach. Through controlled potential electrolysis, whose advantages derive from the possibility of realizing selective oxidation by varying the potential applied to the working anode, we will endeavor to demonstrate that 3,4-quinone  $\mathbf{1_{ox}}$  is incapable of deaminating benzylamine, while 3,4-iminoquinone species  $\mathbf{3_{ox}}$  and  $\mathbf{4_{ox}}$  act as a new type of efficient cofactor for the autorecycling oxidation of benzylamine.

## Results and Discussion

**Reaction of the electrogenerated 3,4-quinone  $\mathbf{1_{ox}}$  with benzylamine.** The cyclic voltammogram of compound  $\mathbf{1_{red}}$  (2mM), in deaerated  $\text{CH}_3\text{OH}$  containing  $\text{LiClO}_4$  as the supporting electrolyte and an excess of benzylamine (100 mM), at a dropping mercury electrode, showed an oxidation peak  $\text{Pa}_1$ , due to a diffusion controlled two-electron process, at - 140 mV vs SCE, the sweep rate  $\nu$  being  $0.5 \text{ Vs}^{-1}$ . As can be seen in Figure 1 (curve a), a cathodic peak  $\text{Pc}_1$  appeared on the reverse sweep, at - 190 mV vs SCE, illustrating the partial reversibility of the two-electron transfer that could be assigned to the 3,4-quinol  $\mathbf{1_{red}}$  / 3,4-quinone  $\mathbf{1_{ox}}$  redox couple.

However, the redox potential  $E^0$  could not be accurately evaluated, under our experimental conditions, as the system ( $Pa_1$ ,  $Pc_1$ ) did not fulfill all the diagnostic criteria required for a reversible process, at least when  $v$  was  $\leq 500 \text{ Vs}^{-1}$ : the ratio of the height of  $Pa_1$  over that of  $Pc_1$  never reached unity ( $i_{Pc_1}/i_{Pa_1} \sim 0.8$ ) and the value of  $E_{Pa_1} - E_{Pc_1}$  ( $E$  being the peak potential) was found to be higher than 30 mV. Note that, in the reverse sweep, a second reduction peak was recorded at a more negative potential (- 1720 mV vs SCE), due to the irreversible two-electron reduction of the carbonyl group of the benzophenone skeleton.<sup>16</sup> From the results of preparative electrolyses, two different anodic behaviors could be distinguished depending on the selected potential.

*When the controlled potential  $E$  of the mercury pool was fixed at - 180 mV vs SCE*, i.e. at a potential for which the quinol **1<sub>red</sub>** could be oxidized exclusive of the reaction products **2<sub>red</sub>**-**4<sub>red</sub>** (Chart 2), a coulometric value of  $2.1 \pm 0.1$  was found for the number of electrons ( $n$ ) involved in the oxidation of one molecule of **1<sub>red</sub>**. As the electrolysis proceeded, a decrease in the  $Pa_1$  and  $Pc_1$  intensities was observed, while a new system of peaks ( $Pa_2$ ,  $Pc_2$ ) developed at a 100 mV more positive potential, due to a partially reversible two-electron transfer. The lack of peak  $Pc_1$  in the voltammogram of the oxidized solution clearly indicated that the electrochemical oxidation of **1<sub>red</sub>** was followed by a chemical reaction involving the produced 3,4-quinone **1<sub>ox</sub>**. The height of  $Pa_2$  was found to be roughly identical to that of the initial peak  $Pa_1$ , and the voltammogram of the oxidized solution exhibited a well defined cathodic peak  $Pc_3$  at - 1 300 mV vs SCE (Figure 1, curve c). This corresponded to the reduction of N-benzylidenebenzylamine ( $\text{PhCH=NCH}_2\text{Ph}$ ), as further confirmed after recording the cyclic voltammogram of an authentic sample. The progress of the electrolysis was simultaneously followed by monitoring the UV-vis absorption spectrum. After applying the potential  $E$ , no spectral changes were observed : the UV-vis spectrum shown by the oxidized solution was nearly identical with that of the monoanionic form of the quinol **1<sub>red</sub>** with  $\lambda_{\text{max}}$  at 348 nm, suggesting a similarity in their chromophoric groups. The preparative electrolysis was stopped after consumption of 2.1 Faraday (F).  $\text{mol}^{-1}$ , when a negligible value of the current was recorded, allowing the isolation of two benzylaminophenols **2<sub>red</sub>** (16% yield) and **3<sub>red</sub>** (5% yield) as the minor products, along with aminophenol **4<sub>red</sub>** (62% yield) as the major product (See experimental section). The structure of products **2<sub>red</sub>**-**4<sub>red</sub>** justified, in the cyclic voltammogram of the oxidized solution, the presence of the system of peaks ( $Pa_2$ ,  $Pc_2$ ) that could

be assigned to the oxidation/reduction of the aminophenol/iminoquinone redox couples. These structures were also consistent with the analogy existing between the UV-vis absorption spectrum of the oxidized solution and that of the starting quinol **1<sub>red</sub>**.

At that point it could be deduced that, when the controlled potential  $E$  of the mercury working electrode was fixed at  $-180$  mV vs SCE, i.e. at a potential for which the quinol **1<sub>red</sub>** could be electrochemically oxidized whereas the reaction products **2<sub>red</sub>**-**4<sub>red</sub>** remained nonoxidizable, no catalytic behavior was observed. Accordingly, PhCH=NCH<sub>2</sub>Ph (quantified in terms of benzaldehyde phenylhydrazone obtained upon workup of the oxidized solution with phenylhydrazine) was isolated in equimolar amount based on **1<sub>red</sub>** initial concentration.

These results demonstrated that, under our experimental conditions, the electrogenerated quinone **1<sub>ox</sub>** was incapable of deaminating benzylamine, whatever the nature of the mechanism (path A or path B in Scheme 1). Consequently, the primary identification of **1<sub>ox</sub>** as an efficient catalyst for benzylamine oxidation proved to be unfounded.

In contrast, *when  $E$  was fixed at  $+100$  mV vs SCE*, i.e. at a potential following the peak Pa<sub>2</sub> for which the reaction products **2<sub>red</sub>**-**4<sub>red</sub>** could be oxidized to the iminoquinone forms **2<sub>ox</sub>**-**4<sub>ox</sub>**, a different anodic behavior was observed. After the consumption of  $2F \cdot \text{mol}^{-1}$ , the system of peaks (Pa<sub>2</sub>, Pc<sub>2</sub>) remained unchanged over a long time, a result in agreement with a steady-state catalytic behavior, while a significant increase in the cathodic peak Pc<sub>3</sub> intensity was observed (Figure 2). At the same time, a new absorption band at 250 nm markedly increased, its height being much higher than the absorption band at 348 nm. The electrolysis proceeded further until a coulometric value of  $55 \pm 1$  was found for  $n$ . It could be noted that a) during the last part of the anodic electrolysis ( $n > 40$ ) a new cathodic peak Pc<sub>4</sub> developed at a more negative potential ( $-1550$  mV vs SCE), that could be assigned to the reduction of PhCHO, as corroborated after recording the cyclic voltammogram of an authentic sample ; b) the voltammogram given by the exhaustively oxidized solution no longer exhibited the pair of peaks (Pa<sub>2</sub>, Pc<sub>2</sub>).

As benzylamine was present in large amount compared with that of the quinonoid forms, these results supported the suggestion that benzylamine suffered catalytic oxidation. The turnover yield was firstly determined in terms of the benzaldehyde phenylhydrazone which was isolated in 2600% turnover yield, based on **1<sub>red</sub>** initial concentration (Table 1). In order to quantify more



accurately the products of benzylamine anodic oxidation, these were isolated after subsequent electrochemical reduction of the exhaustively oxidized solution conducted at a potential fixed at -1.600 mV vs SCE, *i.e.* at a potential immediately following the peak  $Pc_4$ . The results of the exhaustive cathodic electrolyses are summarized in Table 2. They indicated that the main product of benzylamine oxidation was  $PhCH=NCH_2Ph$ , whereas  $PhCHO$  was present as a minor product. As earlier reported,<sup>17</sup> dibenzylamine **5** resulted from a two-electron reduction process, while dimers **6** and **7**, isolated as meso and (D,L) forms, arised from a one-electron reduction mechanism. The formation of imidazolidine **8** could be reasonably regarded as proceeding through a tandem two-electron oxidation-cyclisation reaction of a dimer form, during isolation or upon column chromatography. (Scheme 2). Interesting enough, the isolation of mixed dimer **9** constituted a proof of the presence, in the exhaustively oxidized solution, of benzaldehyde as the minor product. Mixed dimer **9** resulted obviously from the condensation reaction of radicals formed consecutively to the one-electron reduction of both  $PhCHO$  and  $PhCH=NCH_2Ph$ .<sup>17</sup>

Therefore, we were encouraged to think that one of the iminoquinone systems  $2_{ox}$ - $4_{ox}$  could be effective in benzylamine oxidative deamination. Consequently, in order to clarify the substantial role of each iminoquinone form in supporting the catalytic efficiency, the electrochemical oxidation of compounds  $2_{red}$ - $4_{red}$  was separately performed, in deaerated  $CH_3OH$ , in the presence of benzylamine excess. With  $2_{red}$  as the starting material, the catalytic process ceased after 16 turnovers, and the yield of benzaldehyde phenylhydrazone did not exceed 800% (Table 1). As a consequence,  $2_{ox}$  could not be considered as responsible for the potent catalytic efficiency (2600% turnover yield) in deaminating benzylamine. So, we focused our attention on the catalytic potential of iminoquinone derivatives  $3_{ox}$  and  $4_{ox}$  which proved to be equivalent.

**Reaction of the electrogenerated 3,4-benzyliminoquinone  $3_{ox}$  with benzylamine.** The cyclic voltammogram of  $3_{red}$  (2mM), in deaerated  $CH_3OH$  containing  $LiClO_4$  as the supporting electrolyte and an excess of benzylamine (100 mM), at a dropping mercury electrode, exhibited an oxidation peak  $Pa_1$  at -70 mV vs SCE, in agreement with the two-electron oxidation of  $3_{red}$  to  $3_{ox}$ . The partial reversibility of the two electron transfer was illustrated by the appearance of a cathodic peak  $Pc_1$ , on the reverse sweep, at -120 mV vs SCE.

When E was fixed at + 100 mV vs SCE, a decrease in the Pa<sub>1</sub> and Pc<sub>1</sub> intensities was observed simultaneously, while a new system of peaks (Pa<sub>2</sub>, Pc<sub>2</sub>) developed at a 30 mV more positive potential, due to a partially reversible two-electron transfer. Simultaneously, the cathodic peak Pc<sub>3</sub> characteristic of the reduction of PhCH=NCH<sub>2</sub>Ph developed at - 1 300 mV vs SCE.

In the *first procedure*, the anodic electrolysis was allowed to go to completion. As the electrolysis proceeded, the system of peaks (Pa<sub>2</sub>, Pc<sub>2</sub>) remained unchanged for a long time, consistent with a steady-state catalytic behavior, while the cathodic peak Pc<sub>3</sub> continuously increased. Finally, a coulometric value of  $70 \pm 1$  was found for n, and benzaldehyde phenylhydrazone was isolated in 3200% turnover yield (Table 1).

In the *second procedure*, the anodic electrolysis was spontaneously stopped after consumption of  $2F \cdot mol^{-1}$ . Then, 3,4-aminophenol **4<sub>red</sub>** was isolated in 70% yield along with 6% of the recovered starting material **3<sub>red</sub>**, a result in agreement with a transamination mechanism which implied the 3,4-iminoquinone species **4<sub>ox</sub>** as the efficient catalyst in deaminating benzylamine.

The hypothesis that **4<sub>ox</sub>** might play a crucial role in the oxidative deamination of benzylamine was further substantiated when considering the specific behavior of **4<sub>red</sub>**, under the same experimental conditions.

**Reaction of the electrogenerated 3,4-iminoquinone 4<sub>ox</sub> with benzylamine.** The cyclic voltammogram of **4<sub>red</sub>** (2mM), in deaerated CH<sub>3</sub>OH containing LiClO<sub>4</sub> as the supporting electrolyte and an excess of benzylamine (100 mM), at a dropping mercury electrode, showed an oxidation peak Pa at - 40 mV vs SCE, characteristic of the two-electron oxidation of **4<sub>red</sub>** to **4<sub>ox</sub>**. When E was fixed at + 100 mV vs SCE, the intensity of the anodic peak at - 40 mV vs SCE remained unchanged, in agreement with a steady-state catalytic behavior. When the electrolysis was stopped after consumption of  $2F \cdot mol^{-1}$ , 76% of the starting material **4<sub>red</sub>** was recovered without evidence of other products. When the controlled potential electrolysis was pursued beyond  $2F \cdot mol^{-1}$ , the catalytic efficiency was identical to that previously described from **3<sub>red</sub>**. The results of these experiments are collected in Tables 1 and 2.

### **Mechanism of benzylamine oxidation.**

On the basis of the results given by the controlled potential electrolyses, we can formulate the following assumptions about the mechanism of benzylamine oxidative deamination. Electrogenerated 3,4-iminoquinone species  $3_{ox}$  and  $4_{ox}$  turned out to be efficient catalysts in deaminating benzylamine, producing 3200% turnover yield. The fact that, starting from  $3_{red}$ ,  $4_{red}$  was isolated in 70% yield after a single turnover ( $2F \cdot mol^{-1}$ ), clearly demonstrated that the oxidative catalytic deamination of benzylamine proceeded via a transamination mechanism. This involved  $\alpha$ -proton abstraction and the subsequent electron flow from the  $\alpha$ -carbon to the quinone moiety, to produce the Schiff base intermediate  $3'_{ox}$ , the driving force being the tendency to restore aromaticity within the 3,4-iminoquinone ring. The proposed mechanism (Scheme 3) is the analog of path B in Scheme 1 which is the accepted mechanism for catalytic deamination by quinonoid cofactors.

Although the structure of our model compounds markedly differs from that of naturally occurring quinones, the reaction displays two features that are most often associated with enzymatic systems: a) the reactions seems to be enhanced through the participation of neighboring substituents, here, the benzoyl and 2-hydroxyl substituents, as they prevented the competing formation of Michael adducts. b) the presence of an active hydroxyl proton at the 2-position very probably is an essential component of the catalytic activity. It can be remembered that similar active hydrogens (pyrrole proton 1-NH of PQQ and hydroxyl proton 2-OH of TPQ) were found to be essential for optimal catalytic activity.<sup>4,7</sup> In this connection, further analogs development would be useful to confirm the substantial role of both the benzoyl and 2-hydroxyl groups in enhancing the reactivity of the iminoquinone ring.

### **Concluding remarks**

In this paper, the catalytic efficiency of a new type of quinonoid cofactors was investigated towards the oxidation of benzylamine. Contrary to previous studies on related redox cofactors, in our work the unstable quinonoid species were electrogenerated. Under strictly anaerobic conditions, the use of controlled potential electrolysis enabled us to modulate the oxidative strength by a simple variation of the potential applied to the working anode. On this basis, we have

established that electrogenerated 3,4-quinone **1<sub>ox</sub>** was incapable of deaminating benzylamine, while electrogenerated 3,4-iminoquinone species **3<sub>ox</sub>** and **4<sub>ox</sub>** behaved as effective catalysts. Under our experimental conditions, the reaction efficiency reached 64 turnovers.

Finally, using **3<sub>red</sub>** as the starting material, we were led to conclude that the deamination mechanism of benzylamine was akin to the transamination reaction reported earlier for quinone cofactors of amine oxidoreductases. We are currently conducting experiments to explore the ability of our model system **4<sub>ox</sub>** to catalyze the oxidative deamination of unactivated aliphatic primary amines.

## Experimental Section

Chemicals were commercial products of the highest available purity and were used as supplied. All apparatus, cells and electrodes were identical with those described previously.<sup>18</sup>

**Preparation of 4-benzylamino-2,3-dihydroxybenzophenone  $2_{\text{red}}$ , 3-benzyl-amino-2,4-dihydroxybenzophenone  $3_{\text{red}}$  and 3-amino-2,4-dihydroxybenzophenone  $4_{\text{red}}$  from electrochemical oxidation of  $1_{\text{red}}$  in the presence of benzylamine. Method A.**

A solution of 2,3,4-trihydroxybenzophenone  $1_{\text{red}}$  (115 mg, 0.5 mmol), LiClO<sub>4</sub> (5.30 g, 50 mmol) and benzylamine (2.67 g, 25 mmol) in CH<sub>3</sub>OH (250 mL) was oxidized under N<sub>2</sub>, at room temperature, at a mercury pool working electrode (E = - 180 mV vs SCE). After exhaustive oxidation (2F.mol<sup>-1</sup>), i.e. when a negligible value of the current was recorded, the methanolic solution was poured into a molar citric acid buffered aqueous solution of pH  $\approx$  3 (100 mL). The resulting hydroalcoholic solution was concentrated to remove CH<sub>3</sub>OH and extracted with ether (100 mL). After the extract was dried over MgSO<sub>4</sub>, evaporation of the solvent gave a dark yellow residue from which aminophenols  $2_{\text{red}}$ ,  $3_{\text{red}}$  and  $4_{\text{red}}$  were isolated in 16%, 5% and 62% yields, respectively, by flash column chromatography [SiO<sub>2</sub>, toluene-acetone gradient from (100:0) to (95:5)].

$2_{\text{red}}$  (recrystallized from ether) mp 124-126°C; <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>)  $\delta$  4.45 (d, 2H, J = 5 Hz), 6.10 (d, 1H, J = 9 Hz), 6.85 (d, 1H, J = 9 Hz), 6.90 (t, 1H, J = 5 Hz), 7.20-7.35 (m, 5H), 7.40-7.55 (m, 5H), 8.95 (s, br, 1H), 12.70 (s, br, 1H); <sup>13</sup>C NMR (75MHz, DMSO-d<sub>6</sub>)  $\delta$  46.2, 103.1, 110.0, 127.8, 128.0, 128.3, 129.3, 129.5, 131.9, 130.4, 139.2, 140.8, 146.0, 151.5, 197.0. MS DCI *m/z* 320 (MH<sup>+</sup>). Anal. Calcd for C<sub>20</sub>H<sub>17</sub>NO<sub>3</sub> C, 75.23; H, 5.33; N, 4.39. Found : C, 74.97; H, 5.37; N, 4.36.

$3_{\text{red}}$  (recrystallized from ether) mp 149-151°C dec; <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>)  $\delta$  4.50 (d, 2H, J = 5 Hz), 6.40 (d, 1H, J = 9 Hz), 6.85 (d, 1H, J = 9 Hz), 7.20-7.35 (m, 5H), 7.50-7.65 (m, 5H), 12.80 (s, br, 1H); <sup>13</sup>C NMR (75MHz, DMSO-d<sub>6</sub>)  $\delta$  50.1, 108.8, 113.1, 125.1, 126.9, 127.6, 128.5, 129.2, 129.4, 129.7, 132.4, 139.2 and 142.6, 155.3, 155.7, 201.0. MS DCI *m/z* 320 (MH<sup>+</sup>). Anal. Calcd for C<sub>20</sub>H<sub>17</sub>NO<sub>3</sub> C, 75.23; H, 5.33; N, 4.39. Found : C, 74.93; H, 5.35; N, 4.37.

$4_{\text{red}}$  (recrystallized from CH<sub>2</sub>Cl<sub>2</sub>) mp 186-188°C dec; Spectroscopic data for product  $4_{\text{red}}$  have been reported earlier.<sup>15</sup>

**Catalytic oxidation of benzylamine from electrogenerated 3,4-quinone  $1_{\text{ox}}$ . Method B.** A solution of 2,3,4-trihydroxybenzophenone  $1_{\text{red}}$  (115 mg, 0.5 mmol), LiClO<sub>4</sub> (5.30 g, 50 mmol) and benzylamine (2.67 g, 25 mmol) in CH<sub>3</sub>OH (250 mL) was oxidized under N<sub>2</sub>, at room temperature,

at a mercury pool working electrode ( $E = + 100 \text{ mV vs SCE}$ ). After exhaustive oxidation ( $55\text{F}\cdot\text{mol}^{-1}$ ), phenylhydrazine (2.70g, 25 mmol) and 100 mL of a molar acetic buffered aqueous solution of  $\text{pH} \sim 3.5$  were added to the reaction mixture. The resulting hydroalcoholic solution was concentrated to remove  $\text{CH}_3\text{OH}$  and allowed to come to room temperature. The solid was collected by filtration, washed with  $\text{H}_2\text{O}$ , and dried in a vacuum dessicator. Benzaldehyde phenylhydrazone was then isolated as a colorless solid in 53% yield, based on  $\text{PhCH}_2\text{NH}_2$  initial concentration. mp  $156\text{-}158^\circ\text{C}$  (recrystallized from toluene). Spectroscopic data of benzaldehyde phenylhydrazone have been reported earlier.<sup>19,20</sup>

**Method C.** A solution of 2,3,4-trihydroxybenzophenone **1<sub>red</sub>** (115 mg, 0.5 mmol),  $\text{LiClO}_4$  (5.3 g, 50 mmol) and benzylamine (2.67 g, 25 mmol) in  $\text{CH}_3\text{OH}$  (250 mL) was oxidized using method B. After exhaustive oxidation ( $55\text{F}\cdot\text{mol}^{-1}$ ), the resulting methanolic solution was immediately reduced after the potential of the mercury pool was switched to  $- 1600 \text{ mV vs SCE}$ . After exhaustive cathodic electrolysis, the solution was poured into  $\text{H}_2\text{O}$  (100 mL). The resulting hydroalcoholic solution was concentrated to remove  $\text{CH}_3\text{OH}$  and extracted with  $\text{CH}_2\text{Cl}_2$  (100 mL). After the extract was dried over  $\text{MgSO}_4$ , evaporation of the solvent gave a pale yellow oil from which pure dimer product **6** (meso form) was isolated after washing with ethanol in 12% yield, based on  $\text{PhCH}_2\text{NH}_2$  initial concentration. The resulting ethanolic layer was concentrated to remove ethanol leading to a crude product which was purified by flash column chromatography ( $\text{SiO}_2$ , toluene-acetone gradient (100:0) 200 mL, (95:5) 200 mL, (90:10) 200 mL). Dibenzylamine **5**, dimer **7** (D,L form), imidazolidine **8** and mixed dimer **9** were then isolated in 11%, 10%, 5% and 2% yields, respectively.

**Dibenzylamine 5** : colorless oil. Spectroscopic data of dibenzylamine have been reported earlier.<sup>21</sup>  
**N,N'-dibenzyl-1,2-diphenyl-1,2-diaminoethane 6 (meso form)** : white solid recrystallized from ethanol mp  $149\text{-}151^\circ\text{C}$ .  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.70 (s, br, 2H), 3.30 (d, 2H,  $J = 14 \text{ Hz}$ ), 3.55 (d, 2H,  $J = 14 \text{ Hz}$ ), 3.75 (s, 2H), 7.00-7.35 (m, 20H);  $^{13}\text{C NMR}$  (75MHz,  $\text{CDCl}_3$ )  $\delta$  50.9, 67.1, 126.6, 127.6, 127.8, 128.1, 128.3, 128.5, 140.2, 140.7. MS DCI  $m/z$  393 ( $\text{MH}^+$ ). Anal. Calcd for  $\text{C}_{28}\text{H}_{28}\text{N}_2$  C, 85.71; H, 7.14; N, 7.14. Found : C, 85.77; H, 7.19; N, 7.11.

**N,N'-dibenzyl-1,2-diphenyl-1,2-diaminoethane 7 (D, L form)** : colorless oil.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  2.40 (s, br, 2H), 3.50 (d, 2H,  $J = 13 \text{ Hz}$ ), 3.75 (d, 2H,  $J = 13 \text{ Hz}$ ), 3.80 (s, 2H),

7.10-7.40 (m, 20H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  51.3, 68.3, 126.7, 126.9, 127.9, 128.0, 128.3, 140.6, 141.1. MS DCI  $m/z$  393 ( $\text{MH}^+$ ).

**3-Benzyl-2,4,5-triphenylimidazolidine 8** : colorless oil.  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  2.05 (1H, broad s, NH,  $\text{D}_2\text{O}$  exchanged), 3.65 (2H, AB,  $J = 16$  Hz,  $\text{CH}_2\text{-N}$ ), 3.80 (1H, d,  $J = 8$  Hz, H-4), 4.42 (1H, d,  $J = 8$  Hz, H-5), 4.88 (1H, s, H-2), 6.95 (2H, broad d,  $J = 8$  Hz, ortho Ph-3), 7.20 (2H, broad d,  $J = 8$  Hz, ortho Ph-5), 7.25 to 7.40 (12H, m, aromatic proton), 7.45 (2H, broad d,  $J = 8$  Hz, ortho Ph-4), 7.70 (2H, broad d,  $J = 8$  Hz, ortho Ph-2);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  53.5 ( $\text{CH}_2\text{-N}$ ), 69.8 (C-5), 75.6 (C-4), 81.3 (C-2), 127.2 to 130.4 (CH, aromatic carbon), 136.3, 140.5 and 142.7 ( $\text{C}_\text{Q}$ , aromatic). HRMS (LC TOF, reserpine as the lock mass)  $m/z$  391.2185 ( $\text{MH}^+$ ) Calcd for  $\text{C}_{28}\text{H}_{27}\text{N}_2$  391.2174.

The relative stereochemistry of the three asymmetric centres was determined through a 2D NOESY experiment (mixing time = 250 ms). NOE cross peaks were observed between H-2 and H-4, ortho Ph-5, on the one hand, while correlations were obtained between H-5 and ortho Ph-4, ortho Ph-2, on the other. The carbon type (methyl, methylene, methide or quaternary) was determined by DEPT experiments.

**N-benzyl-1,2-diphenyl-aminoethanol 9** : white solid recrystallized from ethanol mp 156-158 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.70 (s, 1H), 3.00 (s, 1H), 3.55 (d, 1H,  $J = 13$  Hz), 3.75 (d, 1H,  $J = 13$  Hz), 3.95 (d, 1H,  $J = 13$  Hz), 4.85 (d, 1H,  $J = 6$  Hz), 7.10-7.35 (m, 15H);  $^{13}\text{C}$  NMR (75MHz,  $\text{CDCl}_3$ )  $\delta$  51.0, 67.8, 76.7, 126.8, 126.9, 127.6, 127.7, 127.8, 128.0, 128.2, 128.3, 128.4, 139.1 139.8 and 140.3. MS DCI  $m/z$  304 ( $\text{MH}^+$ ). Anal. Calcd for  $\text{C}_{21}\text{H}_{21}\text{NO}$  C, 83.17; H, 6.93; N, 4.62. Found : C, 82.87; H, 6.97; N, 4.60.

**Catalytic oxidation of benzylamine by electrogenerated 4,3-benzyliminoquinone 2<sub>ox</sub>**. The above described method A, replacing **1<sub>red</sub>** by **2<sub>red</sub>**, with  $E = +100$  mV vs SCE and  $n = 2$ , led, after flash column chromatography [ $\text{SiO}_2$ , toluene-acetone 98:2], to the recovered starting material in 75% yield.

The above described method B, replacing **1<sub>red</sub>** by **2<sub>red</sub>**, allowed, after consumption of  $18\text{F}\cdot\text{mol}^{-1}$ , to the isolation of benzaldehyde phenylhydrazone in 16% yield, based on  $\text{PhCH}_2\text{NH}_2$  initial concentration.

**Catalytic oxidation of benzylamine by electrogenerated 3,4-benzyliminoquinone  $3_{ox}$ .** The above described method A, replacing  $1_{red}$  by  $3_{red}$ , with  $E = + 100$  mV vs SCE and  $n = 2$  afforded, after flash column chromatography [ $SiO_2$ , toluene-acetone 90:10], compound  $4_{red}$  in 70% yield, along with 6% of the recovered starting material  $3_{red}$ .

The above described method B, replacing  $1_{red}$  by  $3_{red}$ , allowed, after consumption of  $70F.mol^{-1}$ , to the isolation of benzaldehyde phenylhydrazone in 64% yield, based on the  $PhCH_2NH_2$  initial concentration.

**Catalytic oxidation of benzylamine by electrogenerated 3,4-iminoquinone  $4_{ox}$ .** The above described method A, replacing  $1_{red}$  by  $4_{red}$ , with  $E = + 100$  mV vs SCE and  $n = 2$ , led, after flash column chromatography [ $SiO_2$ , toluene-acetone 90:10], to the recovered starting material  $4_{red}$  in 76% yield.

The above described method B, replacing  $1_{red}$  by  $3_{red}$ , allowed, after consumption of  $70F.mol^{-1}$ , to the isolation of benzaldehyde phenylhydrazone in 64% yield, based on  $PhCH_2NH_2$  initial concentration.

The above described method C, replacing  $1_{red}$  by  $4_{red}$ , afforded dibenzylamine **5** (13% yield), dimer compounds **6** (12% yield, meso form) and **7** (10% yield, D,L form), imidazolidine **8** (4% yield) and mixed dimer **9** (2% yield).

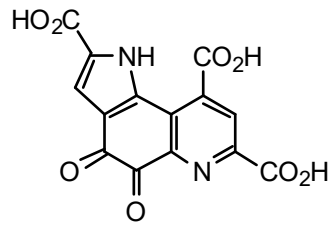
**Acknowledgements :** The authors are indebted to Marc Vuilhorgne for HRMS and stereochemical attribution of compound **8**.



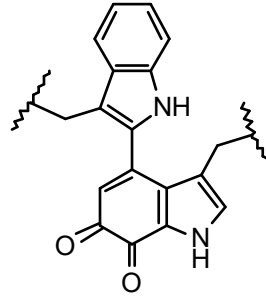
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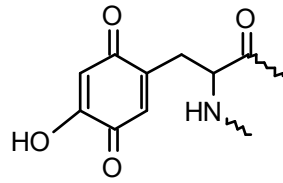
## Chart 1



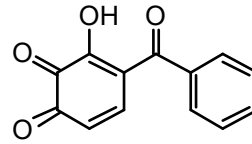
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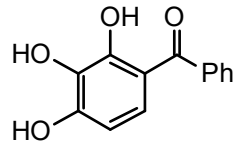
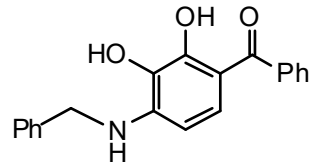
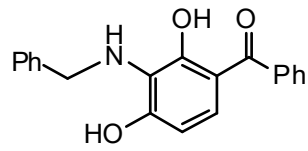
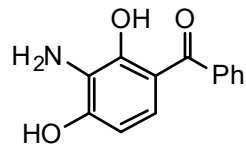


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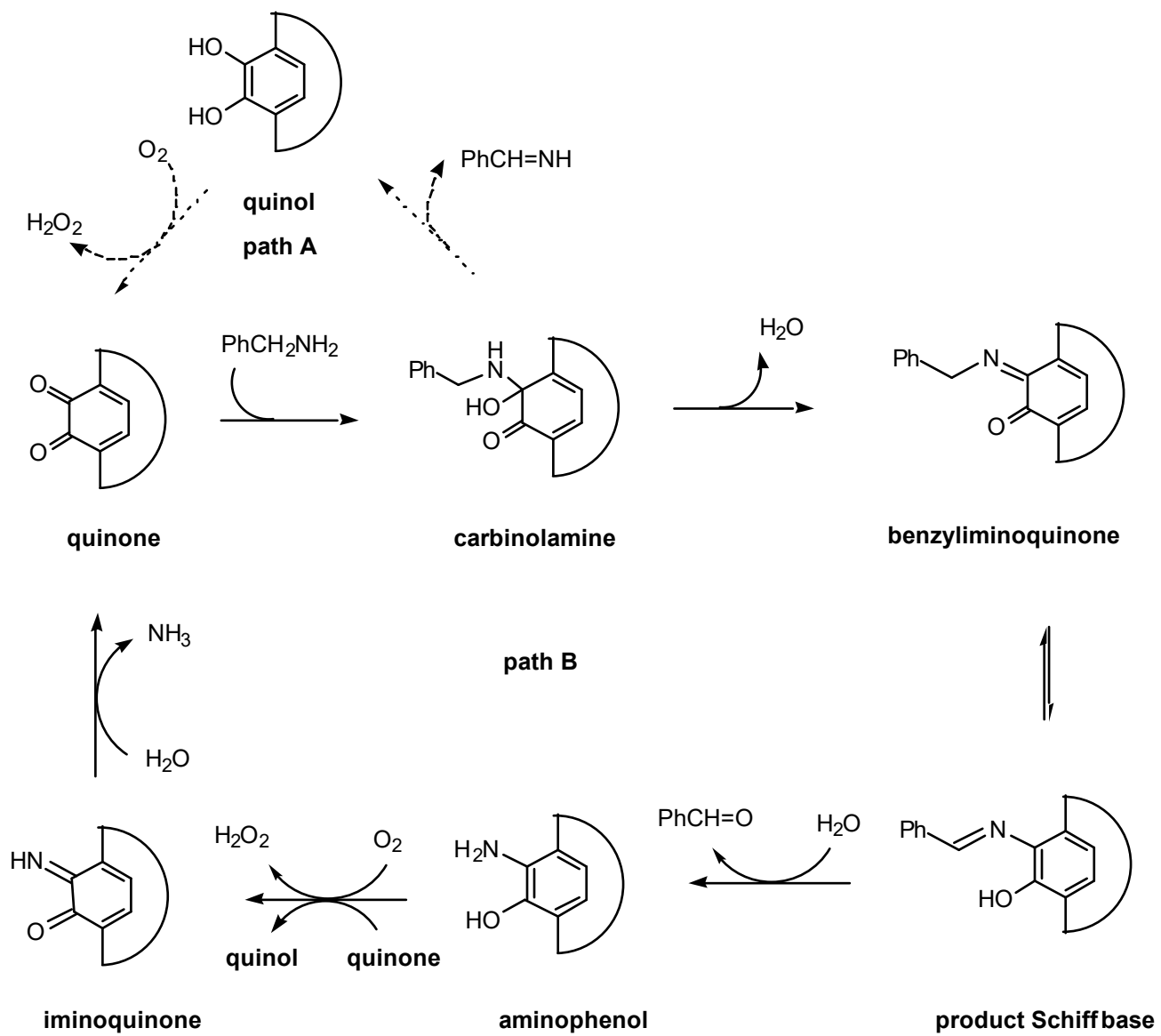


1 ox

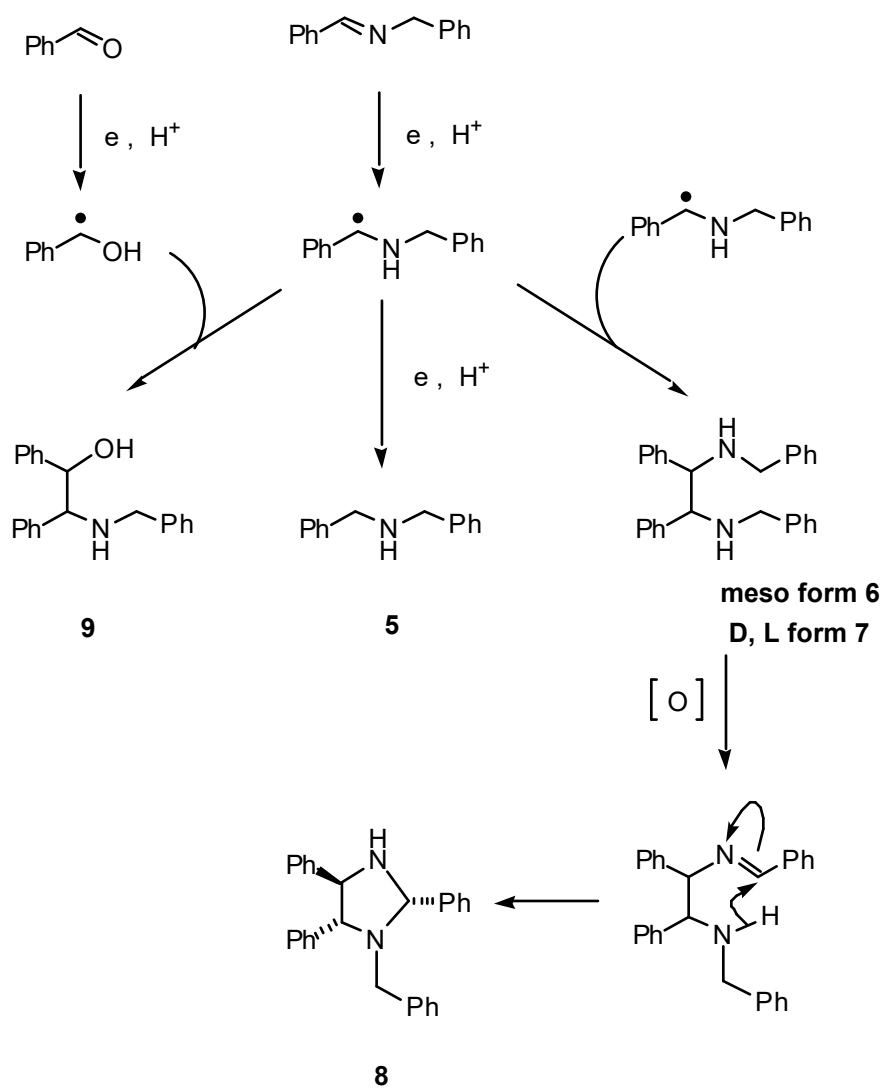
## Chart 2

1<sub>red</sub>2<sub>red</sub>3<sub>red</sub>4<sub>red</sub>

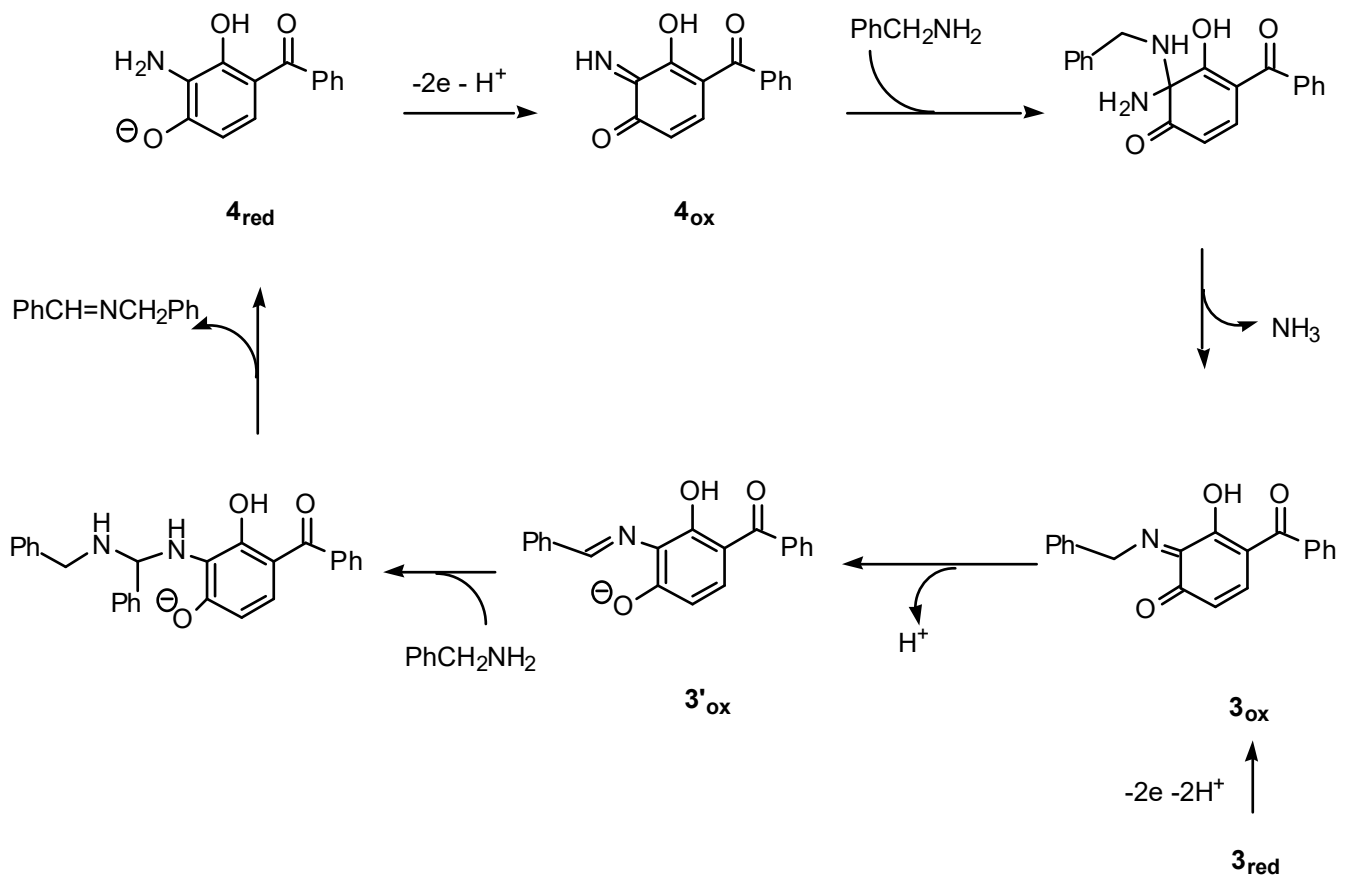
## Scheme 1



## Scheme 2



## Scheme 3

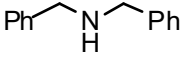
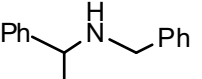
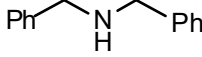
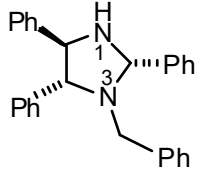
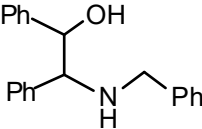


**Table 1. Yields of Catalytic Deamination of Benzylamine Mediated by Electrogenerated Model Quinonoid Cofactors in Deaerated CH<sub>3</sub>OH.**

Substrate	Yield (%)	
	(a)	(b)
<b>1<sub>red</sub></b>	2600	53
<b>2<sub>red</sub></b>	800	16
<b>3<sub>red</sub></b>	3200	64
<b>4<sub>red</sub></b>	3200	64

Electrochemical oxidation of the substrate was performed at a mercury pool ( $E = + 100$  mV vs SCE), [substrate] = 2 mM, [PhCH<sub>2</sub>NH<sub>2</sub>] = 100 mM, under N<sub>2</sub>, in CH<sub>3</sub>OH. Control studies indicated that the amount of PhCHO produced either from simple autoxidation or from electrochemical oxidation of benzylamine in the absence of catalyst was negligible. Yields represent mol% of isolated benzaldehyde phenylhydrazone based on the substrate initial concentration (a), and on PhCH<sub>2</sub>NH<sub>2</sub> initial concentration (b).

**Table 2. Products and Yields of Cathodic Controlled Potential Electrolysis Consecutive to Catalytic Electrochemical Oxidation of Benzylamine in Deaerated CH<sub>3</sub>OH.**

Product		Yield %	
		(a)	(b)
	<b>5</b>	11	13
	<b>6</b> (meso form)	12	12
	<b>7</b> (D, L form)	10	10
	<b>8</b>	5	4
	<b>9</b>	2	2

$E_{an} = +100$  mV vs SCE;  $E_{cath} = 1600$  mV vs SCE.

Yields represent mol% of isolated product based on PhCH<sub>2</sub>NH<sub>2</sub> initial concentration; [substrate] = 2 mM, [PhCH<sub>2</sub>NH<sub>2</sub>] = 100 mM, under N<sub>2</sub>, in CH<sub>3</sub>OH. <sup>a</sup> **1<sub>red</sub>** was used as the substrate; <sup>b</sup> **4<sub>red</sub>** was used as the substrate.



### Figure Captions

**Figure 1.** Progress of the cyclic voltammogram in the course of anodic controlled potential electrolysis of **1<sub>red</sub>** (2mM) at a mercury working electrode ( $E = - 180 \text{ mV vs SCE}$ ), in deaerated  $\text{CH}_3\text{OH}$  containing  $\text{LiClO}_4$  (200 mM) and benzylamine (100 mM). Curve a (—), before electrolysis; curve b (---), after consumption of 1 Faraday per mole of substrate; curve c (-·-), after exhaustive electrolysis ( $2.1 \text{ F}\cdot\text{mol}^{-1}$ ). Arrowheads indicate the direction of the potential sweep;  $v = 0.5 \text{ Vs}^{-1}$ . The vertical arrow indicates the initial potential point.

**Figure 2.** Progress of the cyclic voltammogram in the course of anodic controlled potential electrolysis of **1<sub>red</sub>** (0.4mM) at a mercury working electrode ( $E = + 100 \text{ mV vs SCE}$ ), in deaerated  $\text{CH}_3\text{OH}$  containing  $\text{LiClO}_4$  (40 mM) and benzylamine (20 mM). Curve a (—), before electrolysis; curve b (---), after consumption of 2 Faraday per mole of substrate; curve c (-·-), after consumption of  $10\text{F}\cdot\text{mol}^{-1}$ ; curve c is superimposed on curve b in the anodic domain. Arrowheads indicate the direction of the potential sweep;  $v = 0.5 \text{ Vs}^{-1}$ . The vertical arrow indicates the initial potential point.