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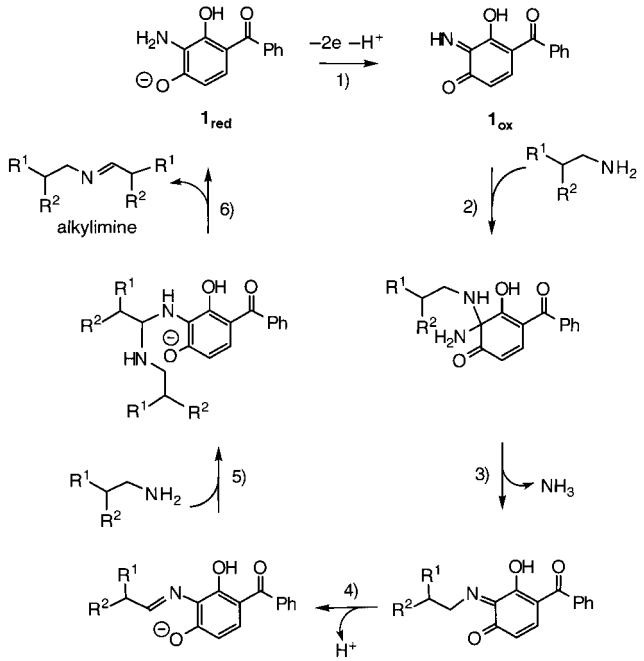
Regiospecific Inverse-Electron-Demand Diels–Alder Reaction of Simultaneously Electrogenerated Diene and Dienophile: An Expeditious Route to Polyfunctionalized 1,4-Benzoxazine Derivatives

Martine Largeron,* Anne Neudorffer, Marc Vuilhorgne, Estelle Blattes, and Maurice-Bernard Fleury

Quinonoid systems are powerful intermediates for organic synthesis and constitute potential precursors to numerous naturally occurring substances.[1] However, the synthesis of quinonoid entities, particularly *o*-quinones and *o*-azaquinones, which are usually unstable and very prone to polymerization, is not highly developed.[2] The facile generation of *o*-quinone-type structures by the electrochemical oxidation of related *o*-quinols and their well-known ability to react with nucleophiles[3] prompted us to investigate the reaction of highly reactive electrogenerated *o*-quinone species with amino alcohols, and we recently described the one-pot electrochemical synthesis of substituted 1,4-benzoxazine derivatives, a novel class of potent neuroprotective agents.[4]

We also revealed a new mode of reactivity of these quinonoid systems,[5] in which electrogenerated 3,4-azaquinone $\mathbf{1_{ox}}$ (Scheme 1) acts as an efficient catalyst for the



Scheme 1. Mechanism of catalytic oxidation of primary aliphatic amines mediated by electrogenerated model quinonoid cofactor $\mathbf{1_{ox}}$.

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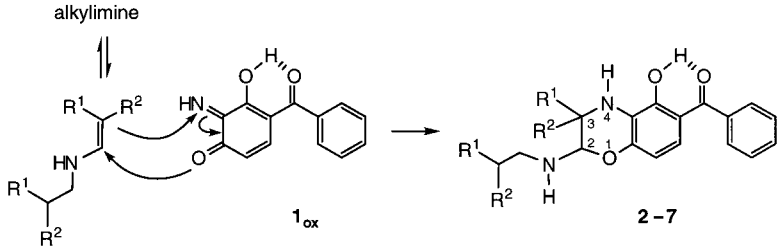
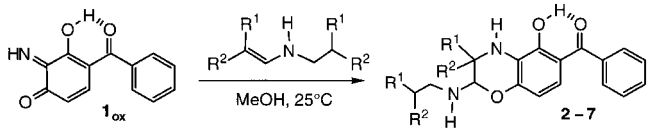
autorecycling oxidation of benzylamine, in a way reminiscent of that reported for amine oxidoreductase model cofactors; the reaction efficiency reached 64 turnovers. Through electrochemical investigations, we established that the deamination mechanism of benzylamine by our model cofactor $\mathbf{1}_{ox}$ was related to the transamination reaction of pyridoxal phosphate with amino acids. The catalytic cycle produced the reduced catalyst $\mathbf{1}_{red}$ and *N*-benzylidenebenzylamine as the product of benzylamine oxidation (Scheme 1). The potent reactivity of $\mathbf{1}_{ox}$ was extended further to unactivated primary aliphatic amines. In several cases (e.g. isopentylamine), the reaction efficiency reached 50 turnovers. Such a reactivity has not yet been reported with other existing amine oxidoreductase model cofactors under similar conditions.[6] In contrast, in the case of isobutylamine, the reaction efficiency did not exceed 8 turnovers, which agrees with an untimely deterioration of the catalyst $\mathbf{1}_{ox}$. Herein, we demonstrate that *o*-azaquinone $\mathbf{1}_{ox}$ is a willing partner in inverse-electron-demand Diels–Alder reactions with simultaneously electrogenerated putative enamines (Scheme 2). To the best of our knowledge, this reaction is the first example of an intermolecular Diels–Alder reaction[7] of electron-rich dienophiles with an *o*-quinone imine, though similar reactions with *o*-quinone monoimides[8] and *o*-quinone monooximes[9] are known. This unexpected reaction, in which the diene and the dienophile are simultaneously electrogenerated, provides an expeditious route to new polyfunctionalized 1,4-benzoxazine derivatives.

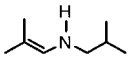
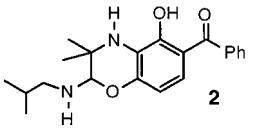
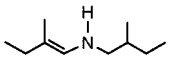
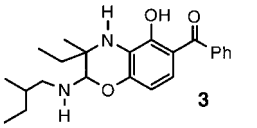
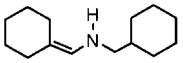
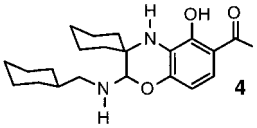
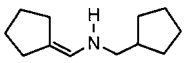
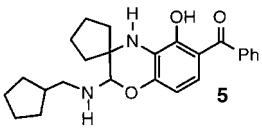
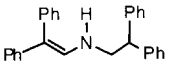
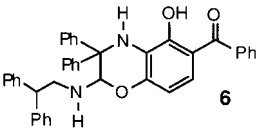
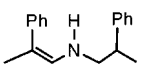
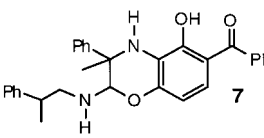


Scheme 2. Diels–Alder reaction of enamine dienophiles with *o*-azaquinone diene $\mathbf{1}_{ox}$, electrogenerated simultaneously, to give polyfunctionalized 1,4-benzoxazine derivatives.

3,4-Iminoquinone $\mathbf{1}_{ox}$ was electrogenerated from 3,4-aminophenol $\mathbf{1}_{red}$, by using anodic-controlled potential electrolysis, at a mercury electrode, in methanol that contained excess primary aliphatic amine $NH_2CH_2CHR^1R^2$. At the potential at which the 3,4-aminophenol $\mathbf{1}_{red}$ could be oxidized to the iminoquinone form $\mathbf{1}_{ox}$ (see Experimental Section), the anodic current remained unchanged for some time, which is consistent with steady-state catalytic behavior. This indicated that our catalyst $\mathbf{1}_{ox}$ was able to oxidize unactivated primary aliphatic amines to the corresponding alkylimines, according to the transamination mechanism shown in Scheme 1.[5] However, the catalytic process ceased after 6 to 8 turnovers. Close inspection of the exhaustively oxidized solution revealed that electrogenerated 3,4-iminoquinone $\mathbf{1}_{ox}$ was trapped with the tautomeric enamine form of the alkylimine extruded during the catalytic process (Scheme 1, step 6), to give the substituted 1,4-benzoxazine derivatives in good to high yields (52–77%). Table 1 shows some examples of the molecular diversity that is accessible through this reaction, which is an inverse-electron-demand controlled Diels–Alder reaction between the LUMO of the *o*-azaquinone heterodiene and the HOMO of the enamine. This uncatalyzed cycloaddition reaction occurs at room temperature, within 8 h, with complete regiospecificity. The more electron-rich carbon atom of the enamine dienophile adds to the nitrogen atom of the heterodiene system $\mathbf{1}_{ox}$ (Scheme 2, Table 1). Accordingly, alkylenamines with a pronounced electron-rich character led to the formation of the expected cycloadduct in high yields (Table 1, entries 1–4), whereas enamines that bear phenyl substituents resulted in somewhat lower yields (Table 1, entries 5 and 6).

Table 1. Inverse-electron-demand Diels–Alder reactions of simultaneously electrogenerated diene and enamine dienophile.



Entry	Enamine	Product	Yield [%]
1		 **2**	71
2		 **3**	70[a]
3		 **4**	77
4		 **5**	70
5		 **6**	55
6		 **7**	52[a]

[a] Obtained as a mixture of two unassigned diastereoisomers (ca. 1:1 ratio).

No subsequent elimination of the alkylamino chain was observed, in contrast to what has been previously reported for similar cycloadditions of enamines with heterodienes.[10] This feature is of synthetic interest since the methodology we describe herein represents the first synthesis of 1,4-benzoxazine derivatives that bear alkylamino substituents on the oxazine ring.

In a second series of experiments aimed at increasing the molecular diversity, we attempted to generate enamines in

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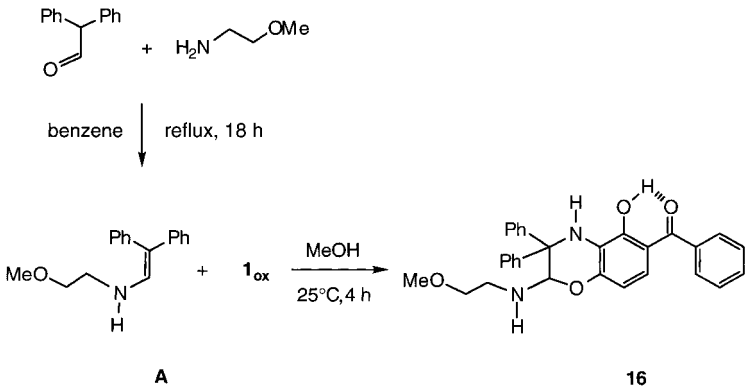
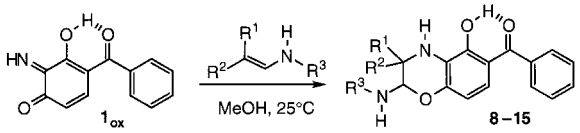
which the substituents on the amino group were different from those linked to the double bond. For this purpose, the amine $R^1R^2CHCH_2NH_2$ was catalytically oxidized by *o*-azaquinone $\mathbf{1_{ox}}$ in the presence of another primary aliphatic amine R^3NH_2. Table 2 gives some examples of 1,4 benzoxazine derivatives produced in this way. The choice of amines proved to be important for the outcome of the reaction, which is affected by steric and electronic effects exerted by the substituents R^1, R^2, and R^3. In particular, the most nucleophilic amine was oxidized, except when prevented by steric hindrance (Scheme 1, step 2). In all cases, both reacting amines were used in equimolar quantities and no efforts were made to optimize the yield. Further investigations would be necessary to establish the optimal reaction conditions.

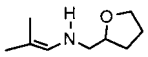
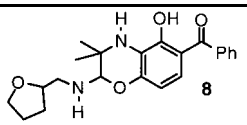
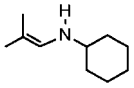
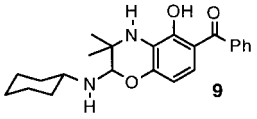
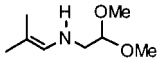
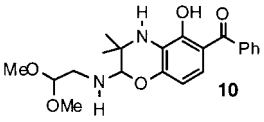
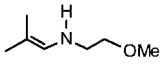
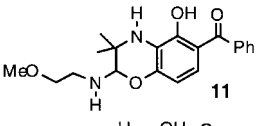
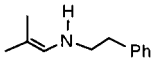
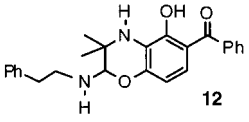
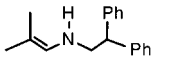
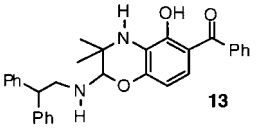
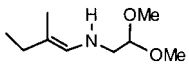
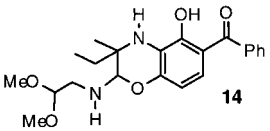
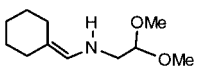
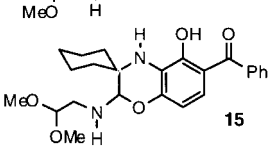


A 16

Scheme 3. Cycloaddition of enamine **A** and the electrogenerated *o*-azaquinone diene $\mathbf{1_{ox}}$, prepared separately.

Table 2. Catalytic oxidation of amine $R^1R^2CHCH_2NH_2$ by *o*-quinone imine $\mathbf{1_{ox}}$ in the presence of a second amine R^3NH_2.



Entry	Enamine	Product	Yield [%]
1		 **8**	70[a]
2		 **9**	50
3		 **10**	68[b]
4		 **11**	33
5		 **12**	60
6		 **13**	41
7		 **14**	66[a,b]
8		 **15**	62[b]

[a] Obtained as a mixture of two unassigned diastereoisomers (ca. 1:1 ratio). [b] Beside benzoxazines **10**, **14**, and **15**, benzoxazines **2**, **3**, and **4** were isolated as minor products, in yields of 5, 10, and 20%, respectively.

Finally, the reaction of a separately prepared enamine with the electrogenerated *o*-azaquinone diene $\mathbf{1_{ox}}$ was demonstrated in a control experiment. For this purpose, 2,2-diphenylacetaldehyde and 2-methoxyethylamine were condensed to produce enamine **A** (Scheme 3). This was reactive enough to combine with the fairly labile electrogenerated azaquinone $\mathbf{1_{ox}}$ before its oligomerization, thus allowing the isolation of the 1,4-benzoxazine derivative **16** in 51% yield (see Experimental Section). Interestingly, this methodology that uses a separately prepared enamine should expand the scope of the reaction as it would no longer be limited to the enamine part that originates from the more nucleophilic amine (Table 2).

In summary, we have demonstrated that putative enamines[11] and unstable *o*-azaquinone $\mathbf{1_{ox}}$, which are simultaneously accessible by an electrochemical process, cyclize at room temperature with complete regiospecificity in the absence of catalyst, to afford new polyfunctionalized 1,4-benzoxazine derivatives in a one-pot synthesis. As a result of their structural similarity with 1,4-benzoxazines reported earlier,[4] these compounds could be considered as target structures for the design of novel neuroprotective agents.

Experimental Section

General procedure: Controlled-potential electrolysis was carried out in a cylindrical, three-electrode, divided cell (9 cm diameter) by using an electronic potentiostat. In the main compartment, a mercury pool electrode (60 cm^2 area) served as the anode (working electrode). Alternatively, a platinum grid (6 cm diameter) could be used as the anode, except with phenyl substituted aliphatic amines, due to a platinum electrode fouling problem. A platinum sheet was placed in the concentric cathodic compartment (counter electrode), which was separated from the main compartment with a glass frit. The reference electrode was an aqueous saturated calomel electrode (SCE), which was isolated from the bulk solution in a glass tube with a fine-porosity frit. The electrolyte solution (0.02 mol L^{-1} tetraethylammonium perchlorate (TEAP) in methanol) was poured into the anodic and the cathodic compartments, as well as into the glass tube that contained the SCE electrode. 3,4-Aminophenol $\mathbf{1_{red}}$ (0.5 mmol) and excess primary aliphatic amine $R^1R^2CHCH_2NH_2$ (10 mmol), or a mixture of amine $R^1R^2CHCH_2NH_2$ (5 mmol) and amine R^3NH_2 (5 mmol), were added to the solution in the main compartment (250 mL), and the resulting solution was then oxidized under nitrogen, at room temperature, at +50 mV vs SCE (initial current 50 mA), that is, at a potential following the anodic peak observed in cyclic voltammetry, characteristic of the two-electron oxidation of $\mathbf{1_{red}}$ to $\mathbf{1_{ox}}$. After exhaustive electrolysis (8–10 h, 12 to 16 Faraday mol^{-1}), that is, when a negligible value of the current was recorded (1 mA), the solution was neutralized with dry ice and the solvent

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was removed under reduced pressure. The brown oil residue was then poured into diethyl ether (20 mL). Insoluble TEAP was filtered off and the filtrate was evaporated under reduced pressure, at 30 °C. Flash chromatography of the residue on silica gel afforded the expected 1,4-benzoxazine derivative.

16: A mixture of 2,2-diphenylacetaldehyde, 2-methoxyethylamine (slight excess), and toluene-*p*-sulfonic acid (catalytic amount) was heated at reflux in benzene for 18 h. The water was removed initially by means of a Dean–Stark separator, and then by using a molecular sieve. The solvent was removed under reduced pressure and the residue distilled. The freshly distilled enamine **A** (2.5 mmol) was dissolved in methanol (250 mL) that contained TEAP as the supporting electrolyte (5 mmol). 3,4-Aminophenol $\mathbf{1}_{red}$ (0.5 mmol) was then added to the resulting solution, along with 2-methoxyethylamine (0.5 mmol). The addition of the latter was necessary to produce the monoanionic species of $\mathbf{1}_{red}$, which is the sole form that can be oxidized to *o*-azaquinone $\mathbf{1}_{ox}$.[5] The resulting solution was then oxidized, under nitrogen, at room temperature, at a mercury pool whose potential was fixed at +50 mV vs. SCE. After exhaustive electrolysis (4 h, 2.1 Faraday mol^{-1}), the solution was treated as above (general procedure) to give the 1,4-benzoxazine derivative **16** in 51 % yield.

2: M.p. 133 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.85$ (d, $J = 6$ Hz, 3H), 0.90 (d, $J = 6$ Hz, 3H), 1.25 (s, 3H), 1.30 (s, 3H), 1.70 (m, $J = 6$ Hz, 1H), 1.90 (s, 1H), 2.50 (m, 1H), 2.80 (m, 1H), 4.00 (s, 1H), 4.65 (s, 1H), 6.40 (d, $J = 9$ Hz, 1H), 7.00 (d, $J = 9$ Hz, 1H), 7.50 (m, 3H), 7.65 (m, 2H), 12.8 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 20.3$, 24.5, 26.3, 28.8, 50.2, 53.0, 92.9, 108.5, 112.6, 120.9, 124.0, 128.0, 128.8, 131.2, 138.4, 146.9, 152.0, 198.5; UV/Vis (methanol): λ_{max} (ε) = 258 (21 850), 320 (17 150); MS-DCI: *m*/*z*: 355 [*M*H$^+$].

10: M.p. 110 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.25$ (s, 3H), 1.30 (s, 3H), 2.10 (s, 1H), 2.90 (dd, $J = 6$ Hz and $J = 13$ Hz, 1H), 3.10 (dd, $J = 6$ Hz and $J = 13$ Hz, 1H), 3.35 (s, 6H), 4.00 (s, 1H), 4.45 (t, $J = 6$ Hz, 1H), 4.70 (s, 1H), 6.40 (d, $J = 9$ Hz, 1H), 7.00 (d, $J = 9$ Hz, 1H), 7.50 (m, 3H), 7.65 (m, 2H), 12.70 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 24.5$, 26.3, 47.1, 50.2, 53.4, 54.1, 92.5, 104.2, 108.5, 112.8, 121.0, 123.9, 128.1, 128.9, 131.2, 138.5, 147.1, 152.1, 201.0; UV/Vis (methanol): λ_{max} (ε) = 258 (21 670), 319 (17 050); MS-DCI: *m*/*z*: 387 [*M*H$^+$].

16: M.p. 190 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.50$ (s, 1H), 3.00 (m, 1H), 3.10 (m, 1H), 3.20 (s, 3H), 3.35 (t, $J = 6$ Hz, 2H), 5.20 (s, 1H), 5.80 (s, 1H), 6.35 (d, $J = 9$ Hz, 1H), 6.95 (d, $J = 9$ Hz, 1H), 7.20 to 7.55 (m, 13H), 7.65 (m, 2H), 12.90 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 45.0$, 58.6, 62.4, 72.6, 89.7, 108.8, 112.8, 120.8, 124.6, 126.6, 126.9, 127.0, 128.1, 128.2, 128.4, 128.9, 131.3, 143.0, 144.3, 147.2, 152.3, 200.6; UV/Vis (methanol): λ_{max} (ε) = 258 (21 950), 319 (17 200); MS-DCI *m*/*z*: 481 [*M*H$^+$].

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Voltage-Driven Changes in Molecular Dipoles Yield Negative Differential Resistance at Room Temperature**

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The effect of negative differential resistance (NDR), discovered by Esaki[1] in Ge p–n diodes, forms the basis for a variety of high-speed semiconductor devices.[2] As future generations of electronics may rely on molecules as part of intelligent and/or nanoscopic devices,[3] much attention is given to the idea of molecular NDR. Experimentally only a few NDR devices utilizing molecules as the active component, have been reported.[4–10] Except for one,[10] all were effective only at low temperature ($T < 78$ K) and under high-vacuum conditions. Herein we report molecule-controlled, room-temperature NDR in a metal/molecular layer/semiconductor diode in ambient atmosphere.

The diodes use a series of relatively simple molecules of the type depicted in Figure 1. Hg was used as the metal and p-Si as the semiconductor because:

1) Disulfide molecules are electrochemically active once adsorbed on Hg.[11]

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