JOC Article

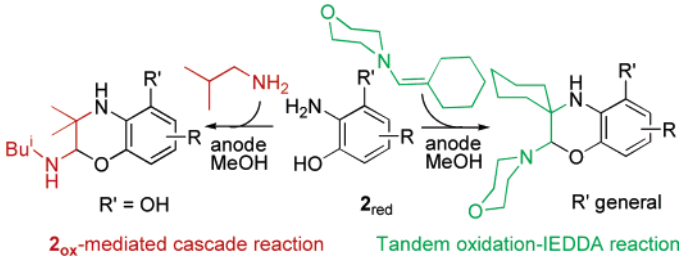
Electrochemically Induced Cascade Reaction for the Assembly of Libraries of Biologically Relevant 1,4-Benzoxazine Derivatives

Daiwang Xu,[†] Angèle Chiaroni,[‡] Maurice-Bernard Fleury,[†] and Martine Largeron*,[†]

UMR 8638 CNRS-Université Paris 5, Synthèse et Structure de Molécules d'Intérêt Pharmacologique, Faculté des Sciences Pharmaceutiques et Biologiques, 4 Avenue de l'Observatoire, 75270 Paris Cedex 06, France, and Institut de Chimie des Substances Naturelles, Centre National de la Recherche Scientifique, 1 Avenue de la Terrasse, 91198 Gif-sur-Yvette Cedex, France

martine.largeron@univ-paris5.fr.

Received March 2, 2006



The scope and mechanism of an electrochemically induced cascade reaction, which leads to highly substituted 1,4-benzoxazine derivatives, have been explored through the variation of the structure of the *o*-azaquinone mediator. This reaction sequence, wherein both cycloaddition partners are generated in situ, at room temperature, under metal-free conditions, allows the regiospecific inverse-electron-demand Diels−Alder (IEDDA) reaction of an *o*-azaquinone heterodiene and a secondary alkylenamine dienophile, two chemically nonaccessible unstable entities. The cascade reaction was found to be general with electron-poor *o*-azaquinone entities generated from substituted 2-aminoresorcinol substrates. In the case of *o*-aminophenol derivatives which lack the 2-hydroxyl group, the generated *o*-azaquinone species failed to catalyze the oxidation of the amine to the corresponding imine, precursor of the enamine dienophile, because the absence of an intramolecular hydrogen bond at the origin of a highly reactive Schiff base cyclic transition state. To overcome this problem, a tandem oxidation-IEDDA reaction, in which the *o*-azaquinone is generated in the presence of a preformed enamine, has been developed as an alternative. These one-pot methodologies, which offer the opportunity to introduce variations in both cycloaddition partners, should be particularly useful for the development of libraries of biologically relevant 1,4-benzoxazine derivatives.

Introduction

1,4-Benzoxazine derivatives have received great attention in chemical and medicinal research because of their natural occurrence and important biological activities. Some of them are central nervous system depressants, antipsychotic agents, calcium antagonists, and antibacterial agents, while others are potential drugs for treating neurodegenerative, inflammatory, autoimmune, cardiovascular, and diabetic disorders.[1]

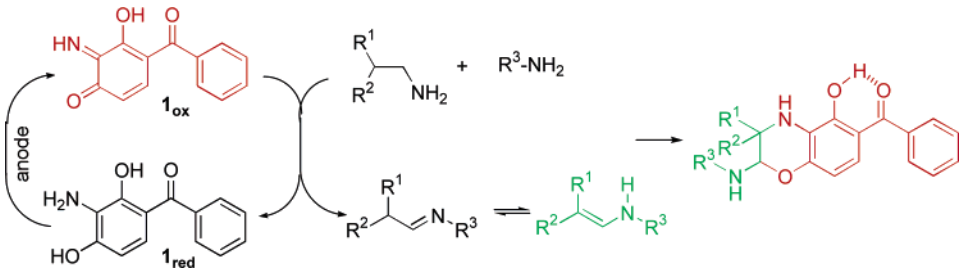
Past syntheses of 1,4-benzoxazine derivatives have relied predominantly upon multistep procedures, using 2-nitrophenols or 2-aminophenols as the starting materials. However, these methods suffered some limitations in the generation of molecular diversity.[2] The recent development of new synthetic strategies such as solid-state synthesis, use of palladium catalysis, or microwave irradiation, which allow one-pot multiple function-

[†] UMR 8638 CNRS-Université Paris 5.
[‡] Centre National de la Recherche Scientifique.

(1) For a recent review on biologically active 1,4-benzoxazine derivatives, see the following: (a) Achari, B.; Mandal, S. B.; Dutta, P. K.; Chowdhury, C. *Synlett* **2004**, 2449 and references therein. For some recent examples, see also the following: (b) Rybczynski, P. J.; Zeck, R. E.; Dudash, J.; Combs, D. W.; Burris, T. P.; Yang, M.; Osborne, M. C.; Chen, X.; Demarest, K. T. *J. Med. Chem.* **2004**, *47*, 196. (c) Yang, W.; Wang, Y.; Ma, Z.; Golla, R.; Stouch, T.; Seethala, R.; Johnson, S.; Zhou, R.; Güngör, T.; Feyen, J. H. M.; Dickson, J. K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2327. (d) Thomas, A.; Ross, R. A.; Saha, B.; Mahadevan, A.; Razdan, R. K.; Pertwee, R. G. *Eur. J. Pharmacol.* **2004**, *487*, 213. (e) Caliendo, G.; Perissutti, E.; Santagada, V.; Fiorino, F.; Severino, B.; Cirillo, D.; d'Emmanuele di Villa Bianca, R.; Lippolis, L.; Pinto, A.; Sorrentino, R. *Eur. J. Med. Chem.* **2004**, *39*, 815. (f) Dougherty K. J.; Bannatyne, B. A.; Jankowska, E.; Krutki, P.; Maxwell, D. J. *J. Neurosci.* **2005**, *25*, 584. (g) Stefanic Anderluh, P.; Anderluh, M.; Ilas, J.; Mravljak, J.; Sollner Dolenc, M.; Stegnar, M.; Kikelj, D. *J. Med. Chem.* **2005**, *48*, 3110. (h) Lee, H. J.; Ban, J. Y.; Seong, Y. H. *Life Sci.* **2005**, *78*, 294.

10.1021/jo060452f CCC: $33.50
Published on Web 07/15/2006

SCHEME 1. 1_{ox}-Mediated Cascade Reaction Leading To Highly Functionalized 1,4-Benzoxazine Derivatives



alization, has therefore reinforced the interest in the 1,4-benzoxazine core.[1a,2a] Because of its efficiency for introducing a high degree of diversity through the variation of the structure of both cycloaddition partners, the Diels−Alder reaction may also constitute an attractive strategy for the synthesis of the 1,4-benzoxazine scaffold.[3] Despite this potential, the synthetic scope of this reaction is limited by the requirement of *o*-azaquinone heterodienes, which are not readily accessible stable compounds. Most of the work has been mainly restricted to *o*-quinone monooximes[4] and *o*-quinonemonoimides.[5] To the best of our knowledge, only a few reports described the synthesis of 1,4-benzoxazine derivatives from in situ chemically generated *o*-azaquinone heterodienes.[5j,l]

A few years ago, we showed that electrogenerated 3,4-azaquinone $\mathbf{1}_{ox}$ (Scheme 1) behaved as an effective organic catalyst for the autorecycling oxidation of aliphatic primary amines. The catalytic cycle produced the reduced catalyst $\mathbf{1}_{red}$ and an imine as the product of amine oxidation.[6] However, in the case of $R^1R^2CHCH_2NH_2$ amines, the catalytic process ceased after a few turnovers, as the catalyst $\mathbf{1}_{ox}$ was trapped through inverse-electron-demand Diels−Alder (IEDDA) reaction with the simultaneously electrogenerated tautomeric enamine form of the alkylimine extruded during the catalytic process. This cascade sequence, wherein both cycloaddition partners were generated in situ, at room temperature, under metal-free conditions, allowed the rapid synthesis of polyfunctionalized 1,4-benzoxazine derivatives.[7a]

Although similar reactions with in situ chemically generated tertiary enamine are known,[8] the electrochemically induced enamine cycloaddition reaction represented uncharted terrain. Consequently, in a preceding work, we examined the scope of this cascade reaction, first with respect to the secondary enamine dienophile.[7b] Especially, to increase the molecular diversity, we generated enamines in 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 a second primary aliphatic amine R^3NH_2 (Scheme 1). Then, the $\mathbf{1}_{ox}$-mediated cascade reaction led to the construction of complex 1,4-benzoxazine derivatives in a regiospecific manner and allowing diastereospecific annellation.[7b] Interestingly, some of these compounds were found to be significant targets as neuroprotective agents both in vitro and in vivo.[7c, d]

At this stage, a sole heterodiene ($\mathbf{1}_{ox}$) was engaged in the cascade reaction with diverse enamine dienophiles. For a more comprehensive investigation of the scope of the cascade reaction, the variation of the heterodiene part proved to be essential. In this prospect, there were several challenges inherent to this reaction sequence which needed to be addressed. As a continuation of our preceding work,[7b] we present hereafter the results of new experiments aimed at exploring further the synthetic potential of this cascade reaction using a variety of electrogenerated *o*-azaquinone entities, with the ultimate goal of developing libraries of biologically relevant 1,4-benzoxazine derivatives.

Results and Discussion

The scope of the cascade reaction was investigated from newly synthesized *o*-aminophenol derivatives **2** (Table 1), under the optimum conditions previously reported[7b] which required a mercury anode, methanol as the solvent, tetraethylammonium

(2) For a recent review on the synthesis of 1,4-benzoxazine derivatives, see ref 1a; for a recent report, see (a) Ilas, J.; Stefanic Anderluh, P.; Sollner Dolenc, M.; Kikelj, D. *Tetrahedron* **2005**, *61*, 7325. See also (b) Teller, J. In *Houben-Weyl Methods of Organic Chemistry*; Schaumann, E.; Ed.; Georg Thieme: Stuttgart, Germany, 1997; Vol. E 9a, p 141. (c) Sainsbury, M. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W. Eds.; Oxford, 1984; Vol. 3, p 995.

(3) For reviews on hetero Diels−Alder reactions see (a) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869. (b) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781. (c) Boger, D. L.; Weinreb, S. M. In *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: San Diego, CA, 1987.

(4) (a) McKillop, A.; Sayer, T. S. B. *J. Org. Chem.* **1976**, *41*, 1079. (b) Nicolaides, D. N.; Awad, R. W.; Varella, E. A. *J. Heterocyclic Chem.* **1996**, *33*, 633. (c) Nicolaides, D. N.; Bezergiannidou-Balouctsi, C.; Awad, R. W.; Litinas, K. E.; Malamidou-Xenikaki, E.; Terzis, A.; Raptopoulou, C. P. *J. Org. Chem.* **1997**, *62*, 499.

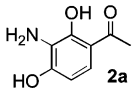
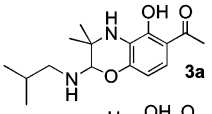
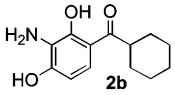
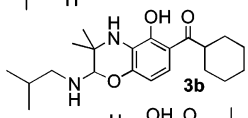
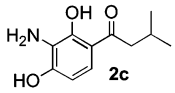
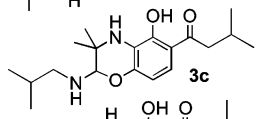
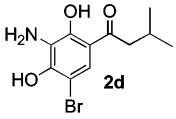
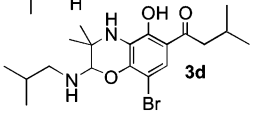
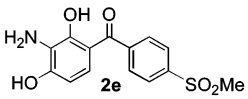
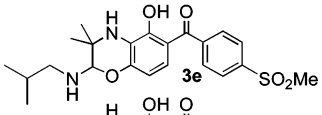
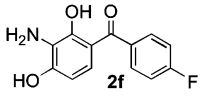
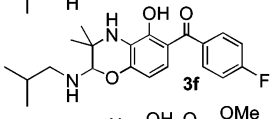
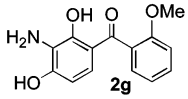
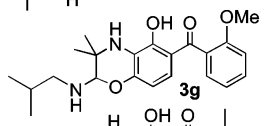
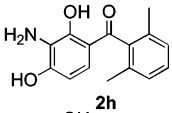
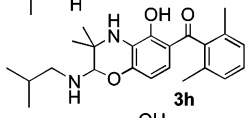
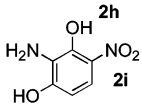
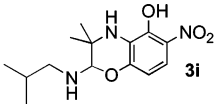
(5) (a) Heine, H. W.; Barchiesi, B. J.; Williams, E. A. *J. Org. Chem.* **1984**, *49*, 2560. (b) Black, D. S. C.; Craig, D. C.; Heine, H. W.; Kumar, N.; Williams, E. A. *Tetrahedron Lett.* **1987**, *28*, 6691. (c) Heine, H. W.; Olsson, C.; Bergin, J. D.; Foresman, J. B.; Williams, E. A. *J. Org. Chem.* **1987**, *52*, 97. (d) Heine, H. W.; Schairer, W. C.; Suriano, J. A.; Williams, E. A. *Tetrahedron* **1988**, *44*, 3181. (e) Heine, H. W.; Suriano, J. A.; Winkel, C.; Burik, A.; Taylor, C. M.; Williams, E. A. *J. Org. Chem.* **1989**, *54*, 5926. (f) Desimoni, G.; Faita, G.; Righeti, P. P. *Tetrahedron* **1991**, *47*, 5857. (g) Heine, H. W.; Williams, D. K.; Rutherford, J. L.; Ramphal, J.; Williams, E. A. *Heterocycles* **1993**, *35*, 1125. (h) Heine, H. W.; La Porte, M. G.; Overbaugh, R. H.; Williams, E. A. *Heterocycles* **1995**, *40*, 743. (i) Nicolaou, K. C.; Zhong, Y. L.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 622. (j) Nicolaou, K. C.; Baran, P. S.; Kranich, R.; Zhong, Y. L.; Sugita, K.; Zou, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 202. (k) Nicolaou, K. C.; Sugita, K.; Baran, P. S.; Zhong, Y. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 207. (l) Nicolaou, K. C.; Baran, P. S.; Zhong, Y. L.; Sugita, K. *J. Am. Chem. Soc.* **2002**, *124*, 2212. (m) Nicolaou, K. C.; Sugita, K.; Baran, P. S.; Zhong, Y. L. *J. Am. Chem. Soc.* **2002**, *124*, 2221.

(6) (a) Largeron, M.; Fleury, M.-B. *J. Org. Chem.* **2000**, *65*, 8874. (b) Largeron, M.; Neudörffer, A.; Fleury, M.-B. *Angew. Chem., Int. Ed.* **2003**, *42*, 1026.

(7) (a) Largeron, M.; Neudörffer, A.; Vuilhorgne, M.; Blattes, E.; Fleury, M.-B. *Angew. Chem., Int. Ed.* **2002**, *41*, 824. (b) Blattes, E.; Fleury, M.-B.; Largeron, M. *J. Org. Chem.* **2004**, *69*, 882. (c) Blattes, E.; Fleury, M.-B.; Largeron, M. *Electrochim. Acta* **2005**, *50*, 4902. (d) Blattes, E.; Lockhart, B.; Lestage, P.; Schwendimann, L.; Gressens, P.; Fleury, M.-B.; Largeron, M. *J. Med. Chem.* **2005**, *48*, 1282.

(8) For some examples of in situ chemically generated tertiary enamines, see: (a) Juhl, K.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1498. (b) Wabnitz, T. C.; Saaby, S.; Jorgensen, K. A. *Org. Biomol. Chem.* **2004**, *2*, 828. (c) Raw, S. A.; Taylor, R. J. K. *Chem. Commun.* **2004**, 508. (d) Raw, S. A.; Taylor, R. J. K. *J. Am. Chem. Soc.* **2004**, *126*, 12260. (e) Ramachary, D. B.; Barbas III, C. F. *Chem. Eur. J.* **2004**, *10*, 5323. (f) Sainz, Y. F.; Raw, S. A.; Taylor, R. J. K. *J. Org. Chem.* **2005**, *70*, 10086.

TABLE 1. 2_{ox}**-Mediated Cascade Reaction Affording 2-Alkylamino-1,4-benzoxazines 3a−i**[a]

Entry	Substrate	n[b]	Product	Yield%[c]
1	 **2a**	12	 **3a**	71
2	 **2b**	11	 **3b**	78
3	 **2c**	12	 **3c**	76
4	 **2d**	11	 **3d**	80
5	 **2e**	11	 **3e**	74
6	 **2f**	12	 **3f**	75
7	 **2g**	11	 **3g**	84
8	 **2h**	10	 **3h**	72
9	 **2i**	12	 **3i**	75

[a] Reagents and conditions for **2a**−**i**: 2 mM, (isobutylamine) = 40 mM, MeOH, room temperature, Hg anode (E = +50 mV vs SCE), 5−8 h. [b] Total number of electrons transferred per molecule of mediator. [c] Yields refer to chromatographically pure isolated products.

hexafluorophosphate (TEAHFP) as the supporting electrolyte, and 20.0 equiv of amine substrate per molecule of *o*-aminophenol derivative **2**. Under these conditions, the cyclic voltammogram of compound $\mathbf{2a}_{red}$ (2 mM), in deaerated MeOH containing isobutylamine (40 mM) chosen as an example of amine substrate, showed, at a dropping mercury electrode, an oxidation peak Pa at −50 mV versus SCE, due to a two-electron process, the sweep rate being 0.5 V s^{-1}. As can be seen in Figure 1, a cathodic peak Pc appeared on the reverse sweep at −160 mV versus SCE, illustrating the quasireversibility of the two-electron transfer that could be assigned to the *o*-aminophenol $\mathbf{2a}_{red}$/*o*-iminoquinone $\mathbf{2a}_{ox}$ redox couple.

When the controlled potential of the mercury pool was fixed at +50 mV versus SCE, which is at a potential for which $\mathbf{2a}_{red}$ could be oxidized to the iminoquinone form $\mathbf{2a}_{ox}$, the system of peaks (Pa, Pc) remained unchanged for a certain time, consistent with steady-state catalytic behavior (Figure 1). Accordingly, the anodic current remained constant over a certain time, while a value of 12 was found for the total number of electrons (n) transferred per molecule of $\mathbf{2a}_{red}$ in the catalytic process (six turnovers). These results indicated that the $\mathbf{2a}_{red}$/$\mathbf{2a}_{ox}$ system behaved as a redox mediator for the electrochemical oxidation of isobutylamine to the corresponding alkylimine (Scheme 1), according to the transamination mechanism previously reported.[6b] Further, the catalytic process ceased, and close inspection of the exhaustively oxidized solution revealed that

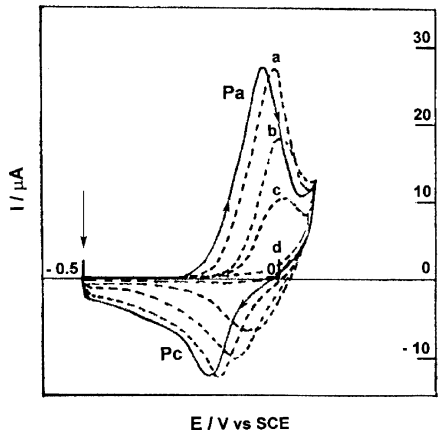


FIGURE 1. Voltammetric changes accompanying the electrochemical oxidation of **2a** (2 mM) at a mercury anode (E = +50 mV vs SCE), in deaerated MeOH containing tetraethylammonium hexafluorophosphate (20 mM) and isobutylamine (40 mM): continuous line, before electrolysis; dashed line, (a) 2−6, (b) 8, (c) 10, and (d) 12 mol of electrons. Arrowheads indicate the direction of the potential sweep; v = 0.5 V s^{-1}. The vertical arrow indicates the initial potential point.

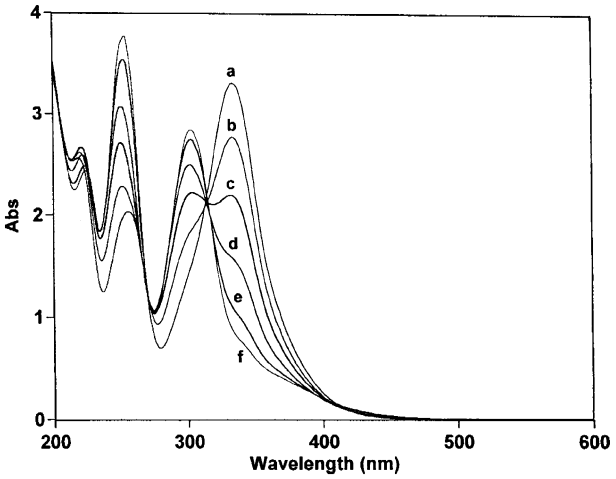


FIGURE 2. Spectrophotometric changes accompanying the electrochemical oxidation of **2a** (2 mM) at a mercury anode ($E = +50$ mV vs SCE), in deaerated MeOH containing tetraethylammonium hexafluorophosphate (20 mM) and isobutylamine (40 mM): (a) 0 (before electrolysis), (b) 8, (c) 9, (d) 10, (e) 11, and (f) 12 mol of electrons. Cell thickness is 0.1 cm.

electrogenerated *o*-azaquinone $\mathbf{2a}_{ox}$ was trapped with the tautomeric enamine form of the alkylimine, to give the substituted 2-alkylamino-1,4-benzoxazine **3a** in 71% yield (Table 1, entry 1).

The progress of the electrolysis was simultaneously followed by monitoring the UV−vis absorption spectrum. After application of the anodic potential ($E = +50$ mV vs SCE), no spectral changes were observed for a time, consistent with steady-state catalytic behavior (Figure 2). After the consumption of 7 F mol^{-1}, a decrease in the UV−vis absorption band shown by the monoanionic form of $\mathbf{2}_{red}$ at 334 nm (ϵ/mol^{-1} L cm^{-1} = 16500) was observed, while new bands at 302 and 254 nm developed. Spectral changes showed two isosbestic points at 313 and 268 nm, indicating that a simple equilibrium between two species was shifted. The new bands at 302 and 254 nm could be assigned to the 2-alkylamino-1,4-benzoxazine **3a**, as corroborated after recording the UV−vis absorption spectrum of the isolated product.

With the reliable set of conditions in hand, the electrochemically induced cascade reaction was investigated using different *o*-aminophenol substrates **2a**−**i**. Table 1 shows some examples of the molecular diversity that is accessible through this reaction sequence, which encompasses an IEDDA reaction between the electron-poor *o*-azaquinone heterodiene and the electron-rich secondary alkylenamine dienophile. This cycloaddition reaction occurred at room temperature, within 5−8 h, with complete regioselectivity. The more electron-rich carbon atom of the enamine dienophile added to the nitrogen atom of the *o*-azaquinone heterodiene. In all cases (Table 1, entries 1−9), the methodology was successful, producing the 1,4-benzoxazine derivatives in good yields. Interestingly, bromosubstituted 3,4-aminophenol derivative **2d** reacted effectively to furnish the desired cycloadduct **3d** in 80% yield (Table 1, entry 4).[9] In the specific case of 3,4-aminophenol derivatives bearing a benzophenone framework, the scope of the cascade reaction could be also extended by the attachment of substituents on the benzoyl moiety (Table 1, entries 5−8). Surprisingly, the yield of the cycloadduct was good regardless of the electronic and/or steric effects of the substituents. This outcome could be rationalized from X-ray crystallographic analyses of benzoxazines **3f**,**h**, which showed the presence of a hydrogen bond between the 2-hydroxyl substituent and the carbonyl group of the benzophenone skeleton (Figure 3). As a consequence, the substituted phenyl group twisted out of the plane,[10] then affecting the transmission of the substituent effects. Similarly, a hydrogen bond could be expected on the 3,4-azaquinone heterodiene which would produce the same effects.

A few other attempts to accomplish the cascade reaction which are not listed in Table 1 deserve special note. The electrochemical oxidation of 3,4-aminophenol derivatives **4a**,**b** (Table 2), which lack the 2-hydroxyl substituent, was performed under the experimental conditions reported above. However, as these substrates were oxidizable at a higher potential, the mercury anode, which has a low anodic decomposition potential, was replaced by a platinum anode. Then, the cyclic voltammogram of compound $\mathbf{4a}_{red}$ (2 mM) showed an oxidation peak Pa due to a two-electron process at + 200 mV versus SCE, the sweep rate being 0.1 V s^{-1} (Figure 4). On the reverse sweep, the lack of peak Pc illustrated the irreversibility of the overall two-electron oxidation process, indicating that the produced 3,4-azaquinone $\mathbf{4a}_{ox}$ was reactive enough to be engaged in a fast follow-up chemical reaction.

When the controlled potential of the Pt anode was fixed at + 350 mV versus SCE, which is at a potential for which $\mathbf{4a}_{red}$ could be oxidized to the 3,4-azaquinone form $\mathbf{4a}_{ox}$, a decrease in both anodic electrolysis current and Pa height was observed (Figure 4). At the same time, the solution became dark, while a coulometric value of 4.0 was found for *n*. These results indicated that the produced 3,4-azaquinone $\mathbf{4a}_{ox}$ was probably converted into a Michael adduct which, after a subsequent two-electron oxidation reaction, spontaneously decomposed to melanin-like polymers. Accordingly, no stable product could be detected at the end of the electrolysis. To evaluate the ability of the 2-substituent to prevent the competing formation of Michael adduct, 3,4-aminophenol **4b** (Table 2), bearing a 2-methyl group, was used as the substrate and treated under the same experimental conditions. Similarly, no stable product could be isolated at the end of the electrolysis.

At this point, it could be concluded that the presence of the 2-hydroxyl substituent was of overriding importance for the success of the cascade reaction. On the basis of the low value found for *n* using **4a** or **4b** as the substrate (4 instead of 10−12 in the case of examples collected in Table 1), we suspected that the requirement for a 2-hydroxyl group was mainly inherent to the catalytic process. So, to circumvent the limitation related to the catalytic process, we envisioned a variant of our initial procedure in which the *o*-azaquinone entity was electrogenerated in the presence of a preformed enamine. In other words, we sought to design an alternative procedure which could be generally applied to construct polyfunctionalized 1,4-benzoxazine derivatives, without the need to employ a 2-aminoresorcinol derivative as the starting material (Table 1).

We first performed the anodic controlled-potential electrolysis of 3,4-aminophenol **4a** (Table 2 and Scheme 2), in the presence of 4-cyclohexylidenemethylmorpholine. The optimized conditions required 5 equiv of enamine per molecule of **4a**. However, as the basicity of the alkylenamine was not sufficient to produce the phenolate anion of $\mathbf{4a}_{red}$, which is the sole form that can be oxidized to 3,4-azaquinone $\mathbf{4a}_{ox}$, 1 equiv of morpholine was added to the bulk solution as the ancillary base. Then, the

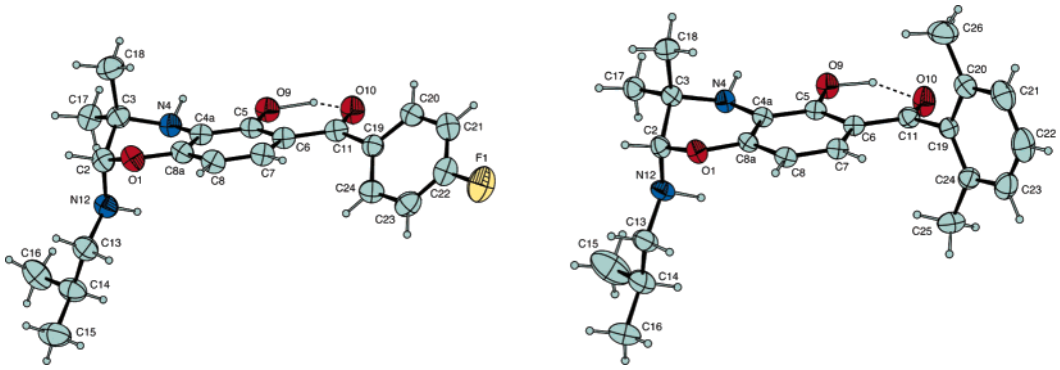


FIGURE 3. Ortep view of **3f** and **3h**. Displacement ellipsoids are drawn at the 30% probability level.

TABLE 2. Anodic Oxidation of Various *o*-Aminophenol Derivatives 4a−h and Trapping of the Electrogenerated *o*-Azaquinone Heterodiene by 4-Cyclohexylidenemethylmorpholine[a]

Entry	Substrate	Product	Yield%[b]
1	**4a**	**5a**	56
2	**4b**	**5b**	60
3	**4c**	**5c**	65
4	**4d**	**5d**	55
5	**4e**	**5e**	62
6	**4f**	**5f**	65
7	**4g**	**5g**	26
8	**4h**	**5h**	10

[a] Reagents and conditions for **4a**−**h**: 2 mM, (enamine) = 10 mM, MeOH, room temperature, Pt anode (E = + 450 mV vs SCE), 4 h; 1equiv of morpholine was added to the bulk solution for producing the phenolate anion of **4a**−**h**. [b] Yields refer to chromatographically pure isolated products.

reaction could go to completion by acid−base equilibrium displacement.

When E was fixed at +450 mV versus SCE, that is, at a potential for which $\mathbf{4a}_{red}$ could be oxidized to the 3,4-azaquinone form $\mathbf{4a}_{ox}$ (Figure 4), a coulometric value of 2.2 was found for n, consistent with a two-electron transfer. After applying the potential, a decrease in the UV−vis absorption bands shown by the major neutral form of $\mathbf{4a}_{red}$ at 343 and 244 nm was observed, while two new bands at 360 and 254 nm developed (Figure 5). Spectral changes showed two isosbestic points at 355 and 310 nm, indicating that a simple equilibrium between two species was shifted.

After 4 h, treatment of the exhaustively electrolyzed solution afforded the desired 2-alkylamino-1,4-benzoxazine derivative

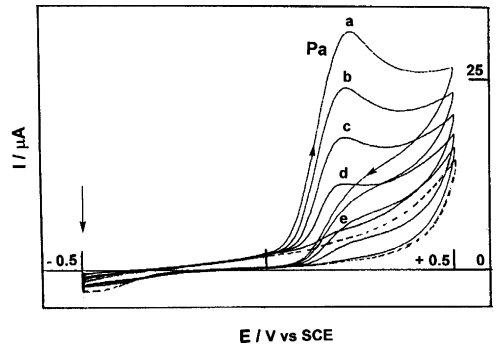
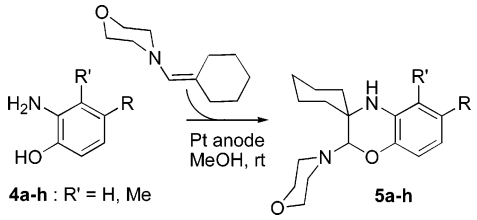


FIGURE 4. Voltammetric changes accompanying the electrochemical oxidation of **4a** (2 mM) at a platinum anode ($E = +450$ mV vs SCE), in deaerated MeOH containing tetraethylammonium hexafluorophosphate (20 mM) and isobutylamine (40 mM): (a) 0 (before electrolysis), (b) 1, (c) 2, (d) 3, and (e) 4; dashed line, 4.1 mol of electrons. Arrowheads indicate the direction of the potential sweep; $v = 0.1$ V s^{-1}. The vertical arrow indicates the initial potential point.

SCHEME 2. Tandem Oxidation−IEDDA Reaction Leading to 2-Alkylamino-1,4-benzoxazine Derivatives 5a−h



5a, in 56% yield, as a single regioisomer (Table 2, entry 1). Conclusive evidence of the structure of the regioisomer was provided by X-ray crystallographic analyses of the benzoxazine derivatives **5e**,**f** (Figure 6).[11]

The scope of the tandem oxidation-IEDDA reaction was then investigated using a series of *o*-aminophenol derivatives **4a**−**h**. As illustrated in Table 2, the method was sufficiently general to accommodate a variety of substituents.

As predicted for an IEDDA reaction, electrogenerated *o*-azaquinone heterodienes, with a pronounced electron-poor character, produced the desired cycloadduct in good yield (Table 2, entries 1−6), whereas introduction of an amide substituent resulted in lower yield (Table 2, entry 7). Anodic oxidation of 2-aminophenol generated a poor reactive *o*-iminoquinone heterodiene, which mainly decomposed to melanin-like polymers, giving only 10% of the desired cycloadduct (Table 2, entry 8).

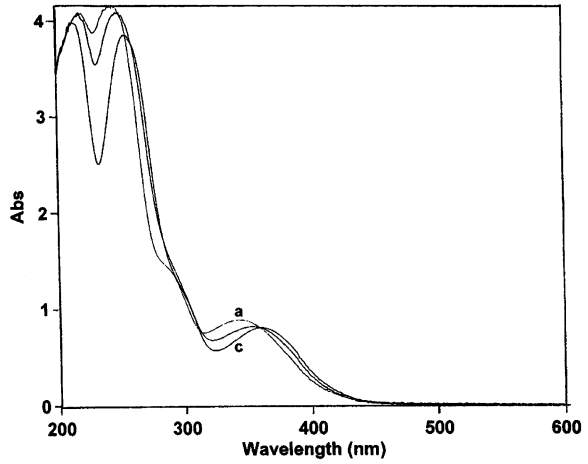
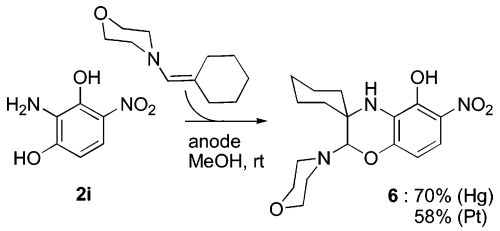


FIGURE 5. Spectrophotometric changes accompanying the electrochemical oxidation of **4a** (2 mM) at a platinum anode ($E = +450$ mV vs SCE), in deaerated MeOH containing tetraethylammonium hexafluorophosphate (20 mM), 4-cyclohexylidenemethylmorpholine (10 mM), and morpholine (2 mM): (a) 0 (before electrolysis), (b) 1, and (c) 2.2 mol of electrons. Cell thickness is 0.1 cm.

SCHEME 3. Tandem Oxidation−IEDDA Reaction using 2i as the Starting Material



In general, the tandem oxidation-IEDDA reaction produced slightly lower yields of cycloadducts than those yielded by the aforementioned cascade reaction, presumably because of the replacement of the Hg anode by a Pt anode rather than because of the lack of the 2-hydroxyl substituent. To ensure that, we carried out the anodic controlled-potential electrolysis of the 2-aminoresorcinol derivative **2i**, in the presence of 4-cyclohexylidenemethylmorpholine using the two anodes, alternatively (Scheme 3). Accordingly, we found that replacing the Hg anode by a Pt anode lowered the yield of cycloadduct **6** from 70 to 58%.

Note that *o*-azaquinone heterodienes displayed an interesting reactivity in the sense that the cycloaddition reactions were regiospecific, irrespective of the nature of the 2-substituent, thus ensuring their synthetic utility. These results contrast with our preceding observations concerning related *o*-quinone heterodienes, generated from pyrogallol derivatives, for which the 2-hydroxyl group is required for inducing the regiospecificity.[12] Although the *o*-quinone entities have been the most widely utilized for IEDDA reactions,[13] the *o*-iminoquinone species proved to be more versatile heterodienes which would merit further developments.

(9) Bromosubstituted aromatic rings are particularly attractive in diversity-oriented synthesis because they can be easily transformed into differently substituted aromatics by cross-coupling reactions.

(10) As shown in Figure 3, in both compounds, a strong intramolecular hydrogen bond is established between the hydroxyl groups O9−H and the oxygen atoms O10 (for **3f**, distances O9···O10 = 2.547(3) Å, O9−H = 1.27, HO9···O10 = 1.47 Å, angle O−H···O = 136.2°; for **3h**, distances O9···O10 = 2.603(3) Å, O9−H = 1.16, HO9···O10 = 1.59 Å, angle O−H···O = 141.2°), leading to respective shorter bonds C5−OH of 1.360(3) and 1.354(3) Å, and longer bonds C11−O10 of 1.247(3) and 1.245(3) Å. Torsion angle values and mean plane calculations show that the oxazine rings are in a half-chair conformation with atoms C2 and C3 deviated by, respectively, −0.349(3) and 0.435(2) Å in **3f** and by −0.373(2) and 0.446-(2) Å in **3h**, from the mean plane of the other four atoms. The mean planes of the benzoxazine and the phenyl ring at C11 are tilted by 132.5° in **3f** and 101.5° in **3h**.

(11) For the two enantiomers, torsion angle and mean plane calculations show that the oxazine rings exhibit a nearly C3 envelope conformation, with atom C3 deviated by −0.629(1) Å in **5e** and −0.690(2) Å in **5f** from the mean plane of the other five atoms. In **5f**, the nitro group lies in the mean plane of the benzoxazine (torsion angles C5−C6−N9−O10 = 5.7-(3)°, C7−C6−N9−O11 = 4.6(3)°). However, differences appear at the C2 atom where the morpholine ring is fixed in an axial position (H2 atom being equatorial) in **5e**, while it is the opposite in **5f**. Moreover, the cyclohexyl group at C3 is orientated differently.

(12) Xu, D.; Chiaroni, A.; Largeron, M. *Org. Lett.* **2005**, *7*, 5273.

(13) For a review on cycloaddition reactions of *o*-quinone heterodienes see Nair, V.; Kumar, S. *Synlett* **1996**, 1143 and references therein.

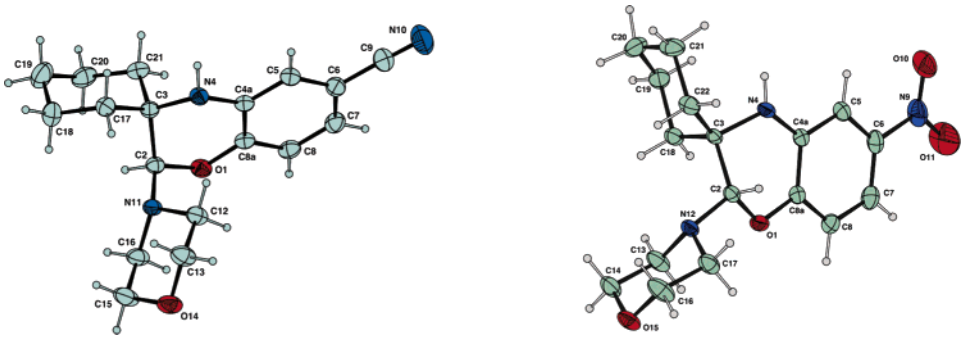
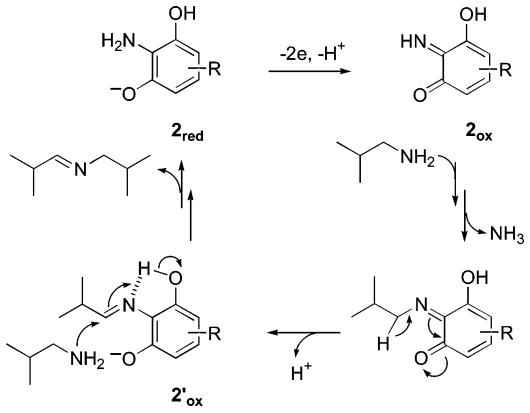


FIGURE 6. ORTEP view of **5e** and **5f**. Displacement ellipsoids are drawn at the 30% probability level.

SCHEME 4. Effect of 2-Hydroxyl Group on The Reaction Pathway



All these results indicated that, in the course of the cascade reaction, the presence of the 2-hydroxyl substituent constituted a prerequisite only to the development of the catalytic process. Then, we questioned about the exact role of the 2-hydroxyl substituent to convert a catalytic inert *o*-azaquinone species into a highly effective organic catalyst. For this purpose, we thoroughly reexamined the ionic transamination mechanism we have previously reported for the autorecycling oxidation of aliphatic amines.[6b] This process involves α-proton abstraction and the subsequent electron flow from the α-carbon to the *o*-azaquinone moiety, which aromatizes to the Schiff base $\mathbf{2'}_{ox}$ (Scheme 4). At this stage, the activation of the imine function for further nucleophilic attack of amine would be provided by an intramolecular hydrogen bond between the 2-hydroxyl group and the imine nitrogen, generating the highly reactive cyclic transition state $\mathbf{2'}_{ox}$. This activated nucleophilic attack of amine would constitute the driving force of the overall transamination mechanism, then preventing any competitive Michael addition reaction. Similar effects of 2-phenolic hydroxyl group on the reactivity of ketimine derivatives have been recently reported in the literature.[14]

Conclusion

New insights into the scope and mechanism of an electrochemically induced cascade reaction, which affords highly functionalized 1,4-benzoxazine derivatives, have been delineated through the variation of the structure of the *o*-azaquinone mediator. This cascade sequence, wherein both cycloaddition partners are generated in situ, under mild conditions, allows the IEDDA reaction of an *o*-azaquinone heterodiene and a secondary alkylenamine dienophile, two chemically nonaccessible unstable materials. The cycloaddition reaction proceeds with complete regioselectivity, ensuring its synthetic utility. The cascade reaction was found to be general with electron-poor *o*-azaquinone entities generated from substituted 2-aminoresorcinol substrates. Using *o*-aminophenol derivatives which lack the 2-hydroxyl group, the generated *o*-azaquinone species was devoid of catalytic efficiency toward the amine oxidation, then preventing the in situ formation of the enamine dienophile. To circumvent this limitation, a variant, in which the *o*-azaquinone heterodiene is generated in the presence of a preformed enamine, has been achieved. This tandem oxidation−IEDDA reaction, which tolerates diverse functional groups, completes the initial cascade sequence in terms of increasing the molecular diversity. These one-pot methodologies, which allow variations in both cycloaddition partners, should be particularly useful for the assembly of libraries of biologically relevant 1,4-benzoxazine derivatives. In this respect, the preparation of the new series of 1,4-benzoxazine derivatives **3** and **5** offers the opportunity to explore further the structural requirements for efficient neuroprotective activity, with the objective to identify the most promising targets.

Experimental Section

All apparatus, cells and electrodes were identical with those described previously.[15] Chemicals were commercial products of the highest available purity and were used as supplied. 2-Amino-4-nitrophenol **4f** and 2-aminophenol **4h** were commercially available compounds. Substituted *o*-aminophenol starting materials **2i**, **4a**, **4c**, and **4e** were synthesized through previously reported procedures.[16] The syntheses of new 2-aminoresorcinol derivatives **2a**−**h** together with *o*-aminophenol substrates **4b**, **4d**, and **4g**, are reported in the Supporting Information.

$\mathbf{2}_{ox}$-Mediated Cascade Reaction Leading to Benzoxazine Derivatives 3a−i. General Procedure A. *o*-Aminophenol substrate **2** (0.5 mmol) and excess isobutylamine (10 mmol) were dissolved in methanol (250 mL), which contained tetraethylammonium hexafluorophosphate (TEAHFP) as the supporting electrolyte (5 mmol). The resulting solution was then oxidized under nitrogen, at room temperature, at a mercury pool whose potential was fixed

(14) (a) Miyabe, H.; Yamaoka, Y.; Takemoto, Y. *Synlett* **2004**, 2597. (b) Miyabe, H.; Yamaoka, Y.; Takemoto, Y. *J. Org. Chem.* **2006**, *71*, 2099.

(15) Largeron, M.; Neudörffer, A.; Fleury, M.-B. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2721.

(16) (a) Lindner H. *Chem. Ber.* **1923**, *56*, 1870. (b) Tseitlin, G. M.; Tokarev, B. V.; Kulagin, V. N. *J. Org. Chem. USSR (Engl. Trans.)* **1982**, *18*, 931. (c) Edkins, L. *J. Pharm. Pharmacol.* **1936**, *75*, 102. (d) Caliendo, G.; Perissutti, E.; Santagada, V.; Fiorino, F.; Severino, B.; D'Emmanuele di Villa Bianca, R.; Lippolis, L.; Pinto, A.; Sorrentino, R. *Bioorg. Med. Chem.* **2002**, 10, 2663.

at +50 mV versus SCE (initial current 50 mA). After exhaustive electrolysis (5−8 h, $n = 10-12$), that is, when a negligible current was recorded (1 mA), the solution was neutralized with dry ice, and the solvent was removed under reduced pressure. The brown oil residue was then poured into diethyl ether (20 mL). Insoluble TEAHFP 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 derivatives.

[(*R*,*S*)-3,3-Dimethyl-5-hydroxy-2-isobutylamino-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl](4-fluorophenyl) Methanone 3f. Orange crystal: mp 134−136 °C (from diethyl ether and petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.63 (s, 1 H), 7.80−7.60 (m, 2 H), 7.30−7.10 (m, 2 H), 6.96 (d, $J = 9.0$ Hz, 1 H), 6.41 (d, $J = 9.0$ Hz, 1 H), 4.65 (s, 1 H), 4.02 (s, 1 H), 2.90−2.70 (m, 1 H), 2.60−2.40 (m, 1 H), 1.91 (bs, 1H), 1.80−1.60 (m, 1 H), 1.31 (s, 3 H), 1.23 (s, 3 H), 0.91 (d, $J = 6.0$ Hz, 3 H), 0.88 (d, $J = 9.0$ Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.0, 166.3, 162.9, 152.1, 147.6, 134.7, 131.5, 131.4, 123.7, 121.2, 115.5, 115.2, 112.5, 108.7, 93.0, 53.2, 50.4, 28.9, 26.4, 24.6, 20.4. MS (ES+): *m*/*z* 373 $[M + H]^+$, *m*/*z* 395 $[M + Na]^+$. X-ray analysis: A little plate of 0.35 mm × 0.30 mm × 0.10 mm was used. Empirical formula $C_{21}H_{25}FN_2O_3$, $M_r = 372.43$, $T = 293$ K. Monoclinic system, space group $P2_1/c$, $Z = 4$, $a = 14.022(13)$, $b = 10.920(9)$, $c = 12.843(12)$ Å, $\beta = 92.64(5)°$, $V = 1964$ Å^3, $d_{calcd} = 1.259$ g cm^{-3}, $F(000) = 792$, $\mu = 0.091$ mm^{-1}, λ(Mo Kα) = 0.71073 Å. A total of 9182 intensity data were measured with a Nonius Kappa-CCD diffractometer giving 7486 monoclinic reflections, of which 3929 unique. Refinement of 249 parameters on F^2 led to $R_1(F) = 0.0658$ calculated with 1836 observed reflections as $I \geq 2\sigma(I)$ and $wR_2(F^2) = 0.2129$ considering all the 3929 data. Goodness of fit = 1.022. CCDC deposition number: 298621.

[(*R*,*S*)-3,3-dimethyl-5-hydroxy-2-isobutylamino-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl](2,6-dimethylphenyl) Methanone 3h. Yellow crystal: mp 154−156 °C (from petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.82 (s, 1 H), 7.24 (t, $J = 9.0$ Hz, 1 H), 7.08 (d, $J = 9.0$ Hz, 2 H), 6.54 (d, $J = 9.0$ Hz, 1 H), 6.28 (d, $J = 9.0$ Hz, 1 H), 4.63 (s, 1 H), 3.98 (s, 1 H), 2.90−2.70 (m, 1 H), 2.60−2.40 (m, 1 H), 2.19 (s, 6 H), 1.88 (bs, 1H), 1.80−1.60 (m, 1 H), 1.31 (s, 3 H), 1.27 (s, 3 H), 0.91 (d, $J = 6.0$ Hz, 3 H), 0.88 (d, $J = 6.0$ Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.6, 151.7, 148.0, 138.7, 134.1, 128.8, 127.4, 122.8, 120.8, 113.9, 109.3, 93.0, 53.3, 50.4, 28.9, 26.5, 24.5, 20.4, 19.4. MS (ES+): *m*/*z* 383 $[M + H]^+$, *m*/*z* 405 $[M + Na]^+$. X-ray analysis: A bright yellow needle of 0.40 mm × 0.25 mm × 0.125 mm was used. Empirical formula $C_{23}H_{30}N_2O_3$, $M_r = 382.49$, $T = 293$ K. Monoclinic system, space group $C2/c$, $Z = 8$, $a = 31.003(13)$, $b = 7.393(4)$, $c = 20.004(8)$ Å, $\beta = 112.19(3)°$, $V = 4245$ Å^3, $d_{calcd} = 1.197$ g cm^{-3}, $F(000) = 1648$, $\mu = 0.079$ mm^{-1}, λ(Mo Kα) = 0.71073 Å. A total of 17704 data was measured with a Nonius Kappa-CCD diffractometer reduced to 7921 monoclinic reflections, of which 4764 unique. Refinement of 260 parameters on F^2 led to $R_1(F) = 0.0623$ calculated with the 2470 observed reflections having $I \geq 2\sigma(I)$ and $wR_2(F^2) = 0.1944$ considering all the 4764 data. Goodness of fit = 1.030. CCDC deposition number: 298622.

Tandem Oxidation-IEDDA Reaction Leading to Benzoxazine Derivatives 5a−h. General Procedure B. Freshly distilled 4-cyclohexylidenemethylmorpholine (2.5 mmol) and morpholine (0.5 mmol) were added to a 0.02 M solution of TEAHFP in MeOH. Then, *o*-aminophenol **4** (0.5 mmol) was added to the solution which was oxidized at a platinum anode whose potential was fixed at +450 mV versus SCE, under nitrogen, at room temperature. After exhaustive electrolysis (4 h, $n = 2$), the solution was treated as above (general procedure A) to give the 1,4-benzoxazine derivatives **5a**−**h**.

[(*R*,*S*)-2-Morpholino-3-spiro-1′-cyclohexyl-3,4-dihydro-2H-1,4-benzoxazin-6-yl] Nitrile 5e. Colorless crystal: mp 174−176 °C (from diethyl ether). 1H NMR (300 MHz, $CDCl_3$): δ 6.98 (d, $J = 9.0$ Hz, 1 H), 6.83 (s, 1 H), 6.81 (d, $J = 9.0$ Hz, 1 H), 4.59 (s, 1 H), 4.05 (s, 1 H), 3.75−3.55 (m, 4 H), 3.40−3.25 (m, 2 H), 2.65−2.50 (m, 2 H), 1.80−1.00 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.3, 132.4, 123.7, 119.8, 117.9, 115.8, 103.5, 95.6, 67.1, 52.5, 48.9, 35.1, 34.0, 25.2, 21.4, 21.2. MS (ES+): *m*/*z* 314 $[M + H]^+$, *m*/*z* 336 $[M + Na]^+$. X-ray analysis: A little plate of 0.70 mm × 0.40 mm × 0.10 mm was used. Empirical formula $C_{18}H_{23}N_3O_2$, $M_r = 313.39$, $T = 293$ K. Monoclinic system, space group $P2_1/c$, $Z = 4$, $a = 10.734(4)$, $b = 10.465(4)$, $c = 15.663(6)$ Å, $\beta = 107.34(2)°$, $V = 1679$ Å^3, $d_{calcd} = 1.239$ g cm^{-3}, $F(000) = 672$, $\mu = 0.082$ mm^{-1}, λ(Mo Kα) = 0.71073 Å. A total of 18442 intensity data were measured with a Nonius Kappa-CCD diffractometer giving 8335 monoclinic reflections, of which 4489 unique. Refinement of 208 parameters on F^2 led to $R_1(F) = 0.0483$ calculated with 2923 observed reflections as $I \geq 2\sigma(I)$ and $wR_2(F^2) = 0.1286$ considering all the 4489 data. Goodness of fit = 1.031. CCDC deposition number: 298623

(*R*,*S*)-2-Morpholino-3-spiro-1′-cyclohexyl-6-nitro-3,4-dihydro-2*H*-1,4-benzoxazine 5f. Yellow crystal: mp 210−212 °C (from diethyl ether and chloroform). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (dd, $J = 9.0$ and 3.0 Hz, 1 H), 7.50 (d, $J = 3.0$ Hz, 1 H), 6.82 (d, $J = 9.0$ Hz, 1 H), 4.63 (s, 1 H), 4.18 (s, 1 H), 3.80−3.60 (m, 4 H), 3.40−3.20 (m, 2 H), 2.70−2.40 (m, 2 H), 1.80−1.00 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.3, 141.5, 131.8, 115.6, 114.9, 110.1, 96.0, 67.1, 52.5, 48.9, 35.1, 33.9, 25.2, 21.4, 21.2; MS (ES+): *m*/*z* 334 $[M + H]^+$, *m*/*z* 356 $[M + Na]^+$. X-ray analysis: A little prismatic crystal of 0.40 mm × 0.25 mm × 0.125 mm was used. Empirical formula $C_{17}H_{23}N_3O_4$, $M_r = 333.38$, $T = 293$ K. Triclinic system, space group $P1$, $Z = 2$, $a = 9.373(6)$, $b = 9.802(5)$, $c = 10.391(8)$ Å $\alpha = 71.79(4)$, $\beta = 70.18(4)$, $\gamma = 72.29(4)°$, $V = 832$ Å^3, $d_{calcd} = 1.331$ g cm^{-3}, $F(000) = 356$, $\mu = 0.096$ mm^{-1}, λ(Mo Kα) = 0.71073 Å. A total of 4474 reflections was measured with a Nonius Kappa-CCD diffractometer of which 3327 unique. Refinement of 220 parameters on F^2 led to $R_1(F) = 0.0504$ calculated with the 2629 observed reflections having $I \geq 2\sigma(I)$ and $wR_2(F^2) = 0.1377$ considering all the 3327 data. Goodness of fit = 1.022. CCDC deposition number: 298624.

Acknowledgment. This work is dedicated to the memory of Professor Pierre Potier. D.X. thanks Paris 5 University and the MRT for a postdoctoral grant.

Supporting Information Available: Typical experimental procedures and spectroscopic data for new starting materials **2a**−**h**, **4b**,**d**,**g**; analytical data for compounds **3a**−**e**,**g**,**i**, **5a**−**d**,**g**,**h** and **6**, including ^{1}H and ^{13}C NMR spectra of all 1,4-benzoxazine derivatives **3a**−**i**, **5a**−**h** and **6** together with crystallographic files (CIF) for compounds **3f**,**h** and **5e**,**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060452F