JOC*Note*

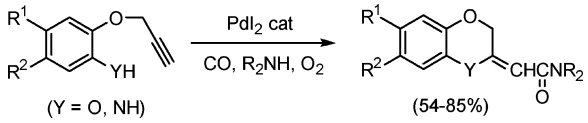
A New Synthesis of 2,3-Dihydrobenzo[1,4]dioxine and 3,4-Dihydro-2*H*-benzo[1,4]oxazine Derivatives by Tandem Palladium-Catalyzed Oxidative Aminocarbonylation−Cyclization of 2-Prop-2-ynyloxyphenols and 2-Prop-2-ynyloxyanilines

Bartolo Gabriele,*[,†] Giuseppe Salerno,[‡] Lucia Veltri,[‡] Raffaella Mancuso,[‡] Zhiyu Li,[‡,§] Alessandra Crispini,[‡] and Anna Bellusci[‡]

Dipartimento di Scienze Farmaceutiche, Università della Calabria, 87036 Arcavacata di Rende (Cosenza), Italy, and Dipartimento di Chimica, Università della Calabria, 87036 Arcavacata di Rende (Cosenza), Italy

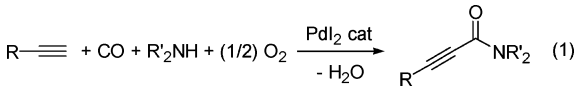
b.gabriele@unical.it

Received June 14, 2006



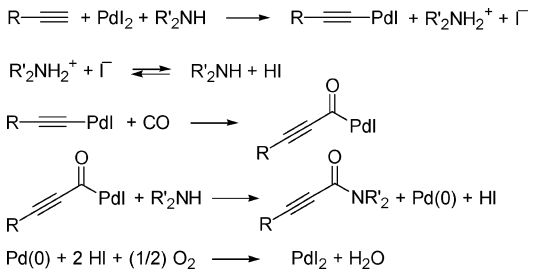
2-[(Dialkylcarbamoyl)methylene]-2,3-dihydrobenzo[1,4]dioxine and 3-[(dialkylcarbamoyl)methylene]-3,4-dihydro-2*H*-benzo-[1,4]oxazine derivatives (**3** and **5**, respectively) were synthesized for the first time starting from readily available 2-prop-2-ynyloxyphenols **1** and 2-prop-2-ynyloxyanilines **4**, respectively, through tandem oxidative aminocarbonylation of the triple bond−intramolecular conjugate addition. Reactions were carried out in the presence of catalytic amounts of PdI_2 in conjunction with an excess of KI in *N*,*N*-dimethylacetamide (DMA) as the solvent at 80−100 °C and under 20 atm (at 25 °C) of a 4:1 mixture of CO−air. The reaction showed a significant degree of stereoselectivity, the *Z* isomers being formed preferentially or exclusively. The configuration around the double bond of the major stereoisomers was unequivocally established by X-ray diffraction analysis.

The PdI_2-catalyzed oxidative aminocarbonylation of the triple bond is an excellent tool for synthesizing 2-ynamides directly from terminal alkynes (eq 1).[1] The reaction occurs through the formation of an alkynylpalladium complex as the key intermediate, which then inserts carbon monoxide and undergoes nucleophilic displacement by the secondary amine used as nucleophile (Scheme 1).

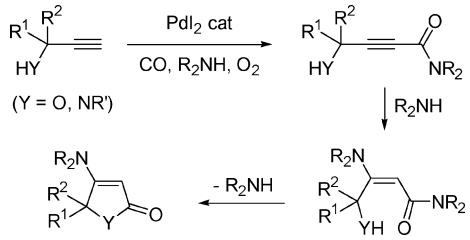


(1)

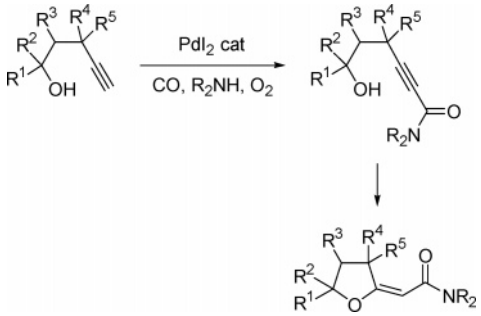
SCHEME 1



SCHEME 2



SCHEME 3



This reactivity can be exploited for synthesizing functionalized heterocycles when applied to alkynes bearing a suitably placed nucleophilic group. In this context, we have recently reported the synthesis of 4-dialkylamino-5*H*-furan-2-ones[2] and 4-dialkylamino-1,5-dihydropyrrol-2-ones,[3] starting from propynyl alcohols or amines, respectively, by a sequential oxidative aminocarbonylation−intermolecular conjugate addition−cyclization route (Scheme 2), as well as the synthesis of 2-[(dialkylcarbamoyl)methylene]tetrahydrofuran derivatives starting from 4-yn-1-ols,[4] by an oxidative aminocarbonylation−intramolecular conjugate addition sequence (Scheme 3).

We now wish to report a useful extension of this kind of reactivity, which allows an easy preparation of 2-[(dialkylcarbamoyl)methylene]-2,3-dihydrobenzo[1,4]dioxines and 3-[(dialkylcarbamoyl)methylene]-3,4-dihydro-2*H*-benzo[1,4]-oxazines starting from readily available 2-prop-2-ynyloxyphenols or 2-prop-2-ynyloxyanilines, respectively, according to Scheme 4.[5]

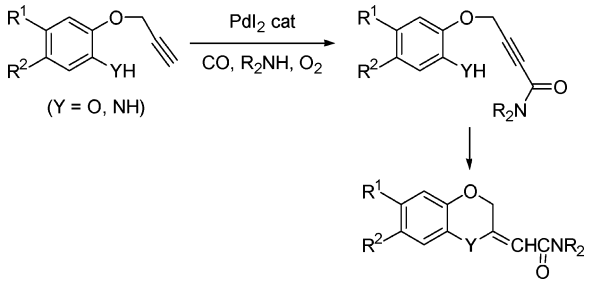
To our knowledge, this protocol represents the first example of a direct synthesis of 2,3-dihydrobenzo[1,4]dioxine and 3,4-

† Dipartimento di Scienze Farmaceutiche.
‡ Dipartimento di Chimica.
§ Present address: Department of Medicinal Chemistry, China Pharmaceutical University, Nanjing 210009, PRC China.

(1) Gabriele, B.; Salerno, G.; Veltri, L.; Costa, M. *J. Organomet. Chem.* **2001**, *622*, 84−88.
(2) Gabriele, B.; Salerno, G.; Plastina, P.; Costa, M.; Crispini, A. *Adv. Synth. Catal.* **2004**, *346*, 351−358.
(3) Gabriele, B.; Plastina, P.; Salerno, G.; Costa, M. *Synlett* **2005**, 935−938.
(4) Gabriele, B.; Salerno, G.; Plastina, P. *Lett. Org. Chem.* **2004**, *1*, 134−136.

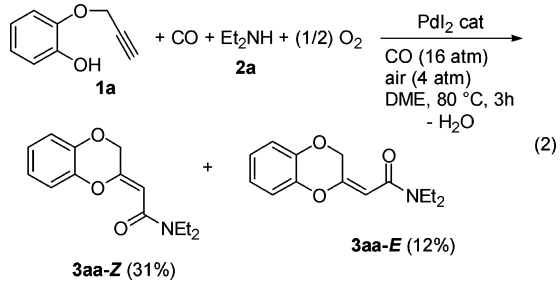
10.1021/jo061229l CCC: $33.50
Published on Web 09/08/2006

SCHEME 4



dihydro-2*H*-benzo[1,4]oxazine derivatives by direct carbonylation of acyclic substrates.[6−8] The development of new, selective, and atom-economical synthetic methodologies for the direct preparation of functionalized 2,3-dihydrobenzo[1,4]-dioxines and 3,4-dihydro-2*H*-benzo[1,4]oxazines starting from simple building blocks through an ordered sequence of steps is of particular interest, also in view of the wide range of biological activities shown by many derivatives of these classes of heterocycles.[9,10]

The oxidative carbonylation of 2-prop-2-ynyloxyphenol **1a** was initially carried out under conditions similar to those employed for the oxidative aminocarbonylation of 4-yn-1-ols and propargyl alcohols, i.e., in DME as the solvent at 80 °C under 20 atm (at 25 °C) of a 4:1 mixture of CO−air in the presence of catalytic amounts of PdI_2 in conjunction with KI and using diethylamine **2a** as the amine (PdI_2/KI/**1a**/**2a** molar ratio = 1:10:200:400, **1a** concentration = 0.5 mmol per mL of DME). After 3 h, we observed the formation of a *Z*/*E* mixture of 2-benzo[1,4]dioxin-2-ylidene-*N*,*N*-diethylacetamide **3aa** in 43% total yield (*Z*/*E* = 72:28) at 63% conversion of **1a** (eq 2) (Table 1, entry 1, see the Supporting Information).



(2)

The stereochemistry around the double bond of the major stereoisomer was established to be *Z* by single-crystal X-ray diffraction analysis (see the Supporting Information for details). The *Z*/*E* ratio reflected the relative stability of the diastereomers under the reaction conditions, as shown by blank experiments.[11]

In an attempt at improving this initial result, we carried out several experiments under different conditions (Table 1, entries 2−9). The use of an equimolar amount of **2a** with respect to **1a** led to a lower conversion of **1a** and to a lower yield of the final product (30%, entry 2). On the other hand, working with

(5) Formation of the 2-ynamide intermediates shown in Scheme 4 is strongly suggested on the basis of what we have already demonstrated in the case of aminocarbonylation of 2-yn-1-ols leading to 4-dialkylamino-5*H*-furan-2-ones (Scheme 2)[2] and of 4-yn-1-ols leading to 2-[(dialkylcarbamoyl)methylene]tetrahydrofurans (Scheme 3).[4] In those cases, we were able to isolate the corresponding 2-ynamide intermediates, which were shown to convert into the final products under the reaction conditions in the absence of the metal catalyst (this also proves that the conjugate addition step is not catalyzed by palladium).[2,4] In the present case, unfortunately, all the attempts to isolate the 2-ynamide intermediates shown in Scheme 4 were unsuccessful. It is, however, interesting to note that the intramolecular conjugate addition in very similar intermediates, such as 4-(2-hydroxyphenoxy)but-2-ynoic acid methyl ester, 4-(2-hydroxyphenoxy)but-2-ynoic acid methyl ester, 4-(2-hydroxyphenylsulfanyl)but-2-ynoic acid methyl ester, and 4-(2-mercaptophenoxy)but-2-ynoic acid methyl ester (formed in situ by the reaction between 1,2-benzenediol, 2-methylaminophenol, or 2-mercaptophenol with 4-chlorobut-2-ynoic acid methyl ester), has been described in the literature.[6a] Moreover, the fact that 2-prop-2-ynyloxyphenols or 2-prop-2-ynyloxyanilines bearing an internal triple bond were unreactive under our reaction conditions is another indirect proof of the validity of the mechanism shown in Scheme 4, which clearly can be at work only starting from substrates bearing a terminal triple bond.

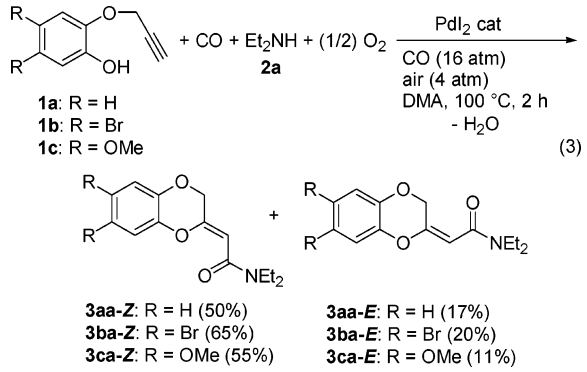
(6) The synthesis of (4*H*-benzo[1,4]oxazin-3-ylidene)acetic esters and benzo[1,4]dioxin-2-ylideneacetic acid esters by indirect carbonylation of 2-aminophenols or benzene-1,2-diol with 4-chlorobut-2-ynoic acid methyl ester has been reported: (a) Cabiddu, S.; Floris, C.; Melis, S.; Sotgiu, F.; Cerioni, G. *J. Heterocycl. Chem.* **1986**, *23*, 1815−1820. The indirect carbonylation of 2-aminophenol with 4-chloro-3-oxobutyric acid ethyl ester to give (4*H*-benzo[1,4]oxazin-3-ylidene)acetic acid ethyl ester has also been reported: (b) Puebla, P.; Honores, Z.; Medarde, M.; Caballero, E.; Feliciano, A. S.; Moran, L. *J. Heterocycl. Chem.* **1999**, *36*, 1097−1100. For other syntheses of (4*H*-benzo[1,4]oxazin-3-ylidene)acetic esters, not involving cyclization reactions, see: (c) Sabitha, G.; Reddy, M. M.; Srinivas, D.; Yadov, J. S. *Tetrahedron Lett.* **1999**, *40*, 165−166. (d) Pippich, S.; Bartsch, H.; Holzer, W. *Tetrahedron* **1997**, *53*, 8439−8446.

(7) For representative recent examples of synthesis of 2,3-dihydrobenzo-[1,4]dioxines by cyclization of acyclic substrates, see: (a) Krois, S.; Steglich, W. *Tetrahedron* **2004**, *60*, 4921−4930. (b) Labrosse, J.-R.; Lhoste, P.; Delbecq, F.; Sinou, D. *Eur. J. Org. Chem.* **2003**, 2813−2822. (c) Labrosse, J.-R.; Lhoste, P.; Sinou, D. *Eur. J. Org. Chem.* **2002**, 1966−1971. (d) Kuwabe, S.-I.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 12202−12206. (e) Wells, G. J.; Tao, M.; Josef, K. A.; Bihovsky, R. *J. Med. Chem.* **2001**, *44*, 3488−3503. (f) Kitaori, K.; Furukawa, Y.; Yoshimoto, H.; Otera, J. *Adv. Synth. Catal.* **2001**, *343*, 95−101. (g) Fukuda, Y.; Seto, S.; Furuta, H.; Ebisu, H.; Oomori, Y.; Terashima, S. *J. Med. Chem.* **2001**, *44*, 1396−1406. (h) Valoti, E.; Pallavicini, M.; Villa, L.; Pezzetta, D. *J. Org. Chem.* **2001**, *66*, 1018−1025. (i) Labrosse, J.-R.; Lhoste, P.; Sinou, D. *J. Org. Chem.* **2001**, *66*, 6634−6642. (j) Fang, Q. K.; Grover, P.; Han, Z.; McConville, F. X.; Rossi, R. F.; Olsson, D. J.; Kessler, D. W.; Wald, S. A.; Senanayake, C. H. *Tetrahedron: Asymmetry.* **2001**, *12*, 2169−2174.

(8) For representative recent examples of the synthesis of 3,4-dihydro-2*H*-benzo[1,4]oxazines by cyclization of acyclic substrates, see: (a) Omar-Amrani, R.; Schneider, R.; Fort, Y. *Synthesis* **2004**, 2527−2534. (b) Yang, S.-C.; Lai, H.-C.; Tsai, Y.-C. *Tetrahedron Lett.* **2004**, *45*, 2693−2698. (c) Banik, B. K.; Banik, I.; Samajdar, S.; Wilson, M. *Heterocycles* **2004**, *63*; 283−296. (d) Bunce, R. A.; Herron, D. M.; Hale, L. Y. *J. Heterocycl. Chem.* **2003**, *40*, 1031−1040. (e) Touzeau, F.; Arrault, A.; Guillaumet, G.; Scalbert, E.; Pfeiffer, B.; Rettori, M.-C.; Renard, P.; Merour, J.-Y. *J. Med. Chem.* **2003**, *46*, 1962−1979. (f) Largeron, M.; Neudorffer, A.; Vuilhorgne, M.; Blattes, E.; Fleury, M.-B. *Angew. Chem., Int. Ed.* **2002**, *41*, 824−827. (g) Romeo, G.; Materia, L.; Manetti, F.; Cagnotto, A.; Mennini, T.; Nicoletti, F.; Botta, M.; Russo, F.; Minneman, K. P. *J. Med. Chem.* **2003**, *46*, 2877−2894. (h) Stefanic, P.; Turnsek, K.; Kikelj, D. *Tetrahedron* **2003**, *59*, 7123−7130.

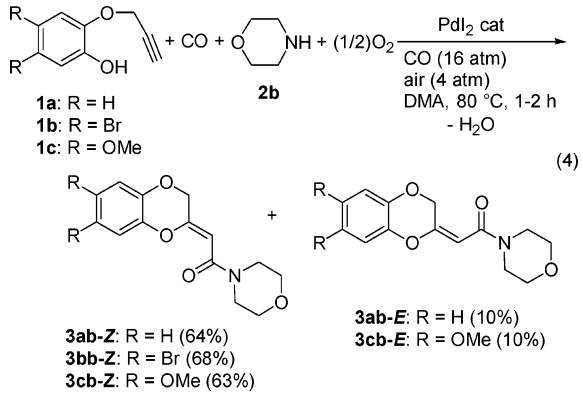
(9) For some very recent examples of pharmacologically active 2,3-dihydrobenzo[1,4]dioxine derivatives, see: (a) Clark, R. D.; Jahangir, A.; Alam, M.; Rocha, C.; Lin, L.; Bjorner, B.; Nguyen, K.; Grady, C.; Williams, T. J.; Stepan, G.; Tang, H. M.; Ford, A. P. D. W. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1697−1700. (b) Whitehead, J. W. F.; Lee, G. P.; Gharagozloo, P.; Hofer, P.; Gehrig, A.; Wintergerst, P.; Smyth, D.; McCoull, W.; Hachicha, M.; Patel, A.; Kyle, D. J. *J. Med. Chem.* **2005**, *48*, 1237−1243. (c) Evrard, D. A.; Zhou, P.; Yi, S. Y.; Zhou, D.; Smith, D. L.; Sullivan, K. M.; Hornby, G. A.; Schechter, L. E.; Andree, T. H.; Mewshaw, R. E. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 911−914. (d) Berger, Y.; Dehmlow, H.; Blum-Kaelin, D.; Kitas, E. A.; Loeffler, B.-M.; Aebi, J. D.; Juillerat-Jeanneret, L. *J. Med. Chem.* **2005**, *48*, 483−498. (e) Wang, G. T.; Wang, S.; Gentles, R.; Sowin, T.; Leitza, S.; Reilly, E. B.; Von Geldern, T. W. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 195−201. (f) Mader, M. M.; Shih, C.; Considine, E.; De Dios, A.; Grossman, C. S.; Hipskind, P. A.; Lin, H.-S.; Lobb, K. L.; Lopez, B.; Lopez, J. E.; Martin Cabrejas, L. M.; Richett, M. E.; White, W. T.; Cheung, Y.-Y.; Huang, Z.; Reilly, J. E.; Dinn, S. R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 617−620. (g) Tumey, L. N.; Bom, D.; Huck, B.; Gleason, E.; Wang, J.; Silver, D.; Brunden, K.; Boozer, S.; Rundlett, S.; Sherf, B.; Murphy, S.; Dent, T.; Leventhal, C.; Bailey, A.; Harrington, J.; Bennani, Y. L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 277−282. (h) Doherty, E. M.; Fotsch, C.; Bo, Y.; Chakrabarti, P. P.; Chen, N.; Gavva, N.; Han, N.; Kelly, M. G.; Kincaid, J.; Klionsky, L.; Liu, Q.; Ognyanov, V. I.; Tamir, R.; Wang, X.; Zhu, J.; Norman, M. H.; Treanor, J. J. S. *J. Med. Chem.* **2005**, *48*, 71−90.

a **2a**/**1a** molar ratio of 5 led to a 46% yield of **3aa** at 86% substrate conversion (entry 3). The selectivity toward **3aa** in this reaction (yield of **3aa**/conversion of **1a**) was, however, lower (53%) compared to that obtained in the initial experiment carried out with a **2a**/**1a** molar ratio of 2 (68%, entry 1). The use of a KI/PdI_2 molar ratio of 100 rather than 10 led to a faster reaction rate and to a higher yield of **3aa** (entry 4). A similar effect was observed by increasing the concentration of **1a** (from 0.5 to 1.0 mmol of product per milliliter of solvent, entry 5) or by raising the reaction temperature (from 80 to 100 °C, entry 6). We finally screened the reaction medium (entries 7−9). Of the solvents tested, *N*,*N*-dimethylacetamide (DMA) led to the most satisfactory results, both in terms of product yield and stereoselectivity (entry 9). On the basis of these results, the next experiment was carried out at 100 °C in DMA as the solvent with a **2a**/**1a**/KI/PdI_2 molar ratio of 400:200:100:1 and a **1a** concentration of 1 mmol per milliliter of DMA. Under these optimized conditions, the substrate conversion was quantitative after 2 h, with a 75% GLC yield of **3aa** (67% isolated) and a *Z*/*E* ratio of ca. 3:1 (eq 3) (Table 2, entry 10, see the Supporting Information).



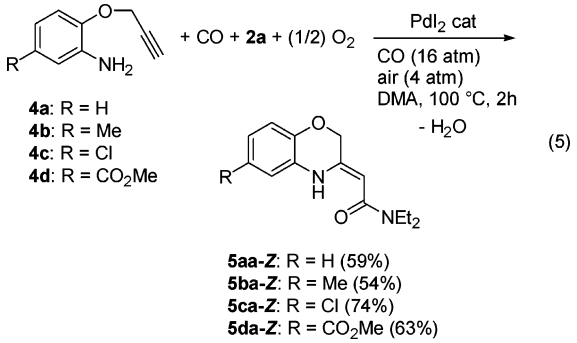
The reaction was successfully extended to other substrates, bearing either electron-withdrawing or π-donating groups, as shown in eq 3 and Table 2, entries 11 and 12.

Interestingly, the use of morpholine **2b** instead of diethylamine **2a** led to the corresponding 2,3-dihydrobenzo[1,4]dioxine **3ab** in only 23% GLC yield ($Z/E \cong 6.7$, entry 13) at total substrate conversion. The formation of unidentified chromatographically immobile materials accounted for the remaining part of the converted substrate. This low yield was due to the instability of the product under the reaction conditions, as shown by blank experiments.[12] However, a good yield of **3ab** (81% by GLC, 74% isolated, $Z/E = 6.4$, at 83% substrate conversion) could be obtained by simply decreasing the reaction temperature from 100 to 80 °C (entry 14 and eq 4). It should be noted that the same reaction, carried out for 3 h rather than 2 h, led to a 20% yield of **3ab** at total substrate conversion (entry 15). Substituted substrates **1b**,**c** also led to satisfactory yields in the corresponding dihydrobenzodioxines **3bb-*Z*** and **3cb** (as a 6.3:1 *Z*:*E* mixture), after 1−2 h reaction time (entries 16−17 and eq 4).



As we have already observed in the PdI_2-catalyzed oxidative aminocarbonylation of simple terminal alkynes,[1] a secondary nucleophilic amine, such as **2a** or **2b**, was required for the reaction to occur. In fact, hindered secondary amines (such as diisopropylamine) or secondary amines of low basicity (such as *N*-ethylaniline) turned out to be unreactive. On the other hand, primary amines underwent oxidative carbonylation with formation of ureas and oxamides, according to a reactivity that we have already described.[13]

The optimized conditions found for 2-prop-2-ynyloxyphenols **1** were then applied to 2-prop-2-ynyloxyanilines **4**. The reaction of 2-prop-2-ynyloxyphenylamine **4a** with diethylamine **2a** afforded (*Z*)-2-(4*H*-benzo[1,4]oxazin-3-ylidene)-*N*,*N*-diethylacetamide **5aa-*Z*** in 59% isolated yield (eq 5) (Table 3, entry 18, see the Supporting Information), whose structure was confirmed by single-crystal X-ray analysis (see the Supporting Information for details).



No formation of the corresponding *E* isomer was observed, while the formation of unidentified chromatographically immobile materials accounted for the substrate conversion (100%).

(10) For representative recent examples of pharmacologically active 3,4-dihydro-2*H*-benzo[1,4]oxazine derivatives, see refs 9h and: (a) Blattes, E.; Lockhart, B.; Lestage, P.; Schwendimann, L.; Gressens, P.; Fleury, M.-B.; Largeron, M. *J. Med. Chem.* **2005**, *48*, 1282−1286. (b) Wu, Y.-J.; Boissard, C. G.; Chen, J.; Fitzpatrick, W.; Gao, Q.; Gribkoff, V. K.; Harden, D. G.; He, H.; Knox, R. J.; Natale, J.; Pieschl, R. L.; Starrett, J. E., Jr.; Sun, L.-Q.; Thompson, M.; Weaver, D.; Wu, D.; Sworetzky, S. I. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1991−1996. (c) Torisu, K.; Kobayashi, K.; Iwahashi, M.; Nakai, Y.; Onoda, T.; Nagase, T.; Sugimoto, I.; Okada, Y.; Matsumoto, R.; Nanbu, F.; Ohuchida, S.; Nakai, H.; Toda, M. *Bioorg. Med. Chem.* **2004**, *12*, 5361−5378. (d) Chen, X.; Kempf, D. J.; Li, L.; Sham, H. L.; Vasavanonda, S.; Wideburg, N. E.; Saldivar, A.; Marsh, K. C.; MacDonald, E.; Norbeck, D. W. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3657−3660.

(11) When pure **3aa-*Z*** or **3aa-*E*** was allowed to react in DME (0.5 mmol per milliliter of DME) at 80 °C for 3 h in the presence of Et_2NH (2 equiv), formation of a *Z*/*E* mixture (*Z*/*E* ratio = 2.6) was observed, ensuing from equilibration of the two diastereomers under these conditions.

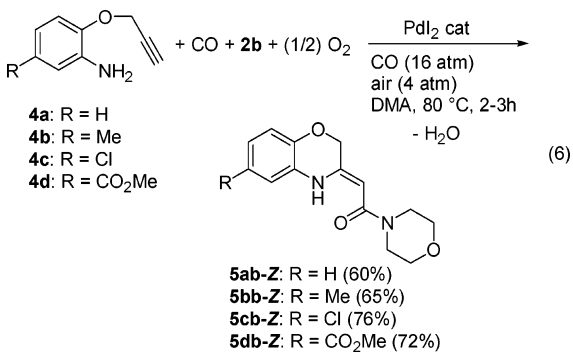
(12) When pure **3ab-*Z*** or **3ab-*E*** was allowed to react under the same reaction conditions of entry 13, extensive decomposition occurred, with formation of chromatographically immobile materials. Only 20−30% of the starting material remained in the reaction mixture, as shown by GLC analysis.

(13) (a) Gabriele, B.; Salerno G.; Mancuso, R.; Costa, M. *J. Org. Chem.* **2004**, *69*, 4741−4750. (b) Gabriele, B.; Mancuso, R.; Salerno, G.; Costa, M. *Chem. Commun.* **2003**, 486−487.

The reason for the exclusive formation of the *Z* isomer lies in its much higher stability with respect to the *E* isomer, owing to the possibility of an intramolecular hydrogen bond between the hydrogen of the amino group and the oxygen of the carbonyl. This was confirmed by the X-ray structure of **5aa-*Z*** at the solid state, which clearly showed this interaction (see the Supporting Information).

Other 2-prop-2-ynyloxyphenylamines **4b**−**d**, bearing electron-donating or electron-withdrawing groups on the aromatic ring, behaved similarly and afforded the corresponding (*Z*)-benzoxazine derivatives in satisfactory isolated yields (54−74%, eq 5 and Table 3, entries 19−21). As expected in view of the higher nucleophilicity of a secondary cyclic amine compared to that of an acyclic dialkylamine,[14] the aminocarbonylation of **4a**−**d** was faster using morpholine **2b** as the nucleophile rather than diethylamine **2a** and could be successfully carried out at 80 °C rather than 100 °C for 2−3 h. Also in this case, the reaction was completely stereoselective, affording the corresponding (*Z*)-2,3-dihydrobenzo[1,4]oxazines in good isolated yields (60−76%, eq 6 and Table 3, entries 22−25).

In conclusion, we have described the one-step synthesis of 2-[(dialkylcarbamoyl)methylene]-2,3-dihydrobenzo[1,4]-dioxines **3** and (*Z*)-3-[(dialkylcarbamoyl)methylene]-3,4-dihydro-2*H*-benzo[1,4]oxazines **5** by tandem PdI_2-catalyzed oxidative aminocarbonylation of the triple bond−intramolecular conjugate addition, starting from readily available 2-prop-2-ynyloxyphenols and 2-prop-2-ynyloxyanilines. The products



(6)

have been obtained in acceptable isolated yields, and the reaction has showed a high degree of stereoselectivity toward the formation of the *Z* isomer, which in several cases has been obtained exclusively. The structure of some representative products was confirmed by X-ray diffraction analysis.

Acknowledgment. We thank the Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR) for financial support and for a grant to Z.L. (Progetto di Ricerca di Interesse Nazionale PRIN 2003039774).

Supporting Information Available: Tables 1−3, Experimental Section, X-ray crystallographic data for compounds **3aa-*Z*** and **5aa-*Z***, and spectroscopic and elemental analysis data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO061229L

(14) Katritzky, A. R.; Pozharskii, A. F. *Handbook of Heterocyclic Chemistry*, 2nd ed.; Pergamon: Kidlington, Oxford, 2000; p 248.