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A Novel Palladium-Catalyzed Dicarbonylation Process Leading to Coumarins

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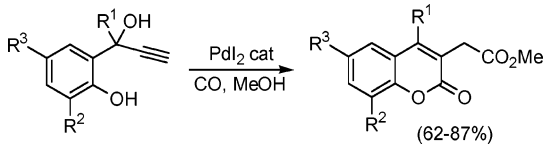
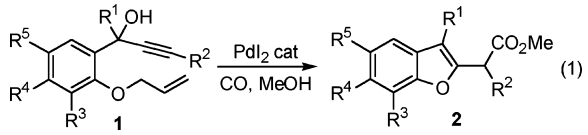


A novel approach to coumarin derivatives has been developed starting from readily available 2-(1-hydroxyprop-2-ynyl)phenols, based on an unprecedented palladium-catalyzed dicarbonylation process. Reactions were carried out in the presence of catalytic amounts of PdI_2 in conjunction with an excess of KI in MeOH as the solvent at room temperature and under 90 atm of CO to give 3-[(methoxycarbonyl)-methyl]coumarins in good to high isolated yields (62−87%).

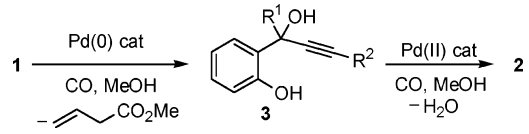
We have recently reported a new and convenient approach to 2-benzofuran-2-ylacetic esters **2** starting from readily available (2-allyloxyaryl)-2-yn-1-ols **1** according to eq 1.[1]



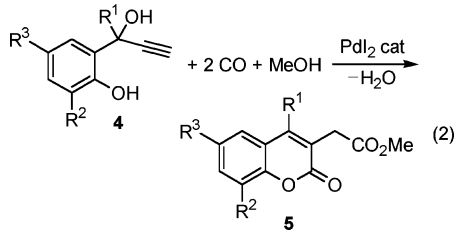
Formation of **2** occurred through the concatenation of two catalytic cycles: the first one, corresponding to deallylation of **1** with formation of free phenols **3**, catalyzed by Pd(0), and the second one, corresponding to a heterocyclization-alkoxycarbonylation sequence, catalyzed by Pd(II) (*sequential homobimetallic catalysis*, Scheme 1).[2]

We have now found that, under appropriate conditions, 2-(1-hydroxyprop-2-ynyl)phenols **4**, bearing a terminal triple bond,[3] can selectively undergo a dicarbonylation process with formation

SCHEME 1



of 3-[(methoxycarbonyl)methyl]coumarins **5** in good to high yields, according to eq 2.



The possibility to obtain particularly important functionalized coumarins in one step by carbonylation of readily available substrates[4] appears to be of particular synthetic interest,[5−9] also in view of the considerable importance of this class of heterocyclic compounds.[10] In fact, coumarin derivatives are known to possess a wide range of biological activities, including anticancer, anti-HIV, antiacetylcholinesterase, antifungal, antioxidant, antihelmintic, anticoagulant, antibacterial, antiviral, and anticlotting activity, and find extensive application in pharmaceuticals, fragrances, agrochemicals, additives in food and

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(2) Free phenols **3** with R^2 = alkyl could not be used directly as substrates for the heterocyclization−alkoxycarbonylation process, owing to their instability. On the other hand, unprotected phenols with R^2 = Ar were sufficiently stable to be used as substrates, but better results were still obtained by forming them in situ starting from their allylated precursors.

(3) 2-(1-Hydroxyprop-2-ynyl)phenols **4**, bearing a terminal triple bond, are sufficiently stable to be isolated at the pure state and to be used as substrates.

(4) Substrates **4** were easily prepared by the Grignard reaction between 2-hydroxybenzaldehydes or 2-hydroxyaryl ketones and ethynylmagnesium bromide. See the Supporting Information for details.

(5) Coumarins (2*H*-1-benzopyran-2-ones, 2*H*-chromen-2-ones) have been classically synthesized by several routes, such as the reaction of 2-hydroxybenzaldehydes or 2-hydroxyaryl alkyl ketones with carboxylic anhydrides [Kostanecki−Robinson reaction: (a) Kostanechi, S. v.; Rózycki, A. *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 102−112. (b) Baker, W.; Eastwood, F. M. *J. Chem. Soc.* **1929**, *51*, 2897−2907. (c) Heilbron, I. M.; Hey, D. H.; Lythgoe, B. *J. Chem. Soc.* **1936**, *58*, 295−300. (d) Shah, D. N.; Shah, N. M. *J. Am. Chem. Soc.* **1955**, *77*, 1699−1700] and the reaction of β-keto esters with phenols [von Pechmann reaction: (e) von Pechmann, H.; *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 929−979. (f) Sethna, S. M.; Phadke, R. *Org. React.* **1953**, *7*, 1−58. (g) Horning, E. C. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, pp 281−285]. Other classical coumarins syntheses include the Perkin [(h) Johnson, J. R. *Org. React.* **1942**, *1*, 210−265], Knoevenagel [(i) Jones, G. *Org. React.* **1967**, *15*, 204−599. (j) Brufola, G.; Fringuelli, F.; Piermatti, O.; Pizzo, F. *Heterocycles* **1996**, *43*, 1257−1266], Reformatsky [(k) Shriner, R. L. *Org. React.* **1942**, *1*, 15−46. (l) Rathke, M. W. *Org. React.* **1975**, *22*, 423−460. (m) Fürstner, A. *Synthesis* **1989**, 571−590], and Wittig [(n) Maerker, A. *Org. Synth.* **1934**, *14*, 270−291. (o) Narasimhan, N. S.; Mali, R. S.; Barve, M. V. *Synthesis* **1979**, 906−909. (p) Yavari, I.; Hekmet-Shoar, R.; Zonouzi, A. *Tetrahedron Lett.* **1998**, *39*, 2391−2392] reactions.

(6) For some examples of classical syntheses of 3-[(alkoxycarbonyl)-methyl]coumarins, see: (a) Ferroud, D.; Collard, J.; Klich, M.; Dupuis-Hamelin, C.; Mauvais, P.; Lassaigne, P.; Bonnefoy, A.; Musicki, B. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2881−2886. (b) Sun, W.-C.; Gee, K. R.; Haugland, R. P. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3107−3110. (c) Feng, Y.; Burgess, K.; Pledger, D.; Cairns, N.; Linthicum, D. S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 881−884. (d) Parmar, V. S.; Singh, S.; Rathore, J. S. *J. Indian Chem. Soc.* **1987**, *64*, 254−257. (e) Chodankar, N. K.; Joshi, S. D.; Sequeria, S.; Seshadri, S. *Indian J. Chem. Sect. B* **1987**, *26*, 427−430. (f) Goya, S.; Takadate, A.; Fujino, H.; Otagiri, M.; Uekama, K. *Chem. Pharm. Bull.* **1982**, *30*, 1363−1369.

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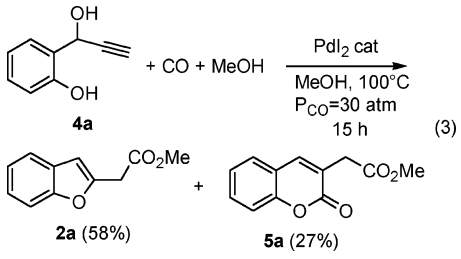
cosmetics, and insecticides.[10a−i,11,12] Moreover, coumarins find application as dyes in laser technology, fluorescent indicators, optical brighteners, and photosensitizers.[10a,13]

The first experiments were carried out with 2-(hydroxyprop-2-ynyl)phenol **4a**, which was initially allowed to react under conditions similar to those previously used for the conversion of (2-allyloxyphenyl)-2-yn-1-ols **1** into 2-benzofuran-2-ylacetic esters **2** (PdI_2 as the catalyst in conjunction with an excess of KI, **4a**/KI/PdI_2 molar ratio = 100:100:1, in MeOH as the solvent at 100 °C and under 30 atm of CO). After 15 h, a mixture of carbonylated products, that is, the benzofuran-2-acetic methyl ester **2a** (58% isolated yield) together with 3-[(methoxycarbonyl)methyl]coumarin **5a** (27% isolated yield), was obtained at total substrate conversion (eq 3 and Table 1, entry 1).

TABLE 1. Reactions of 2-(Hydroxyprop-2-ynyl)phenol 4a with CO and MeOH in the Presence of the PdI_2−KI Catalytic System in MeOH as the Solvent

entry	**4a**/KI/PdI_2 molar ratio	*T* (°C)	P_{CO} (atm)	*t* (h)	convn of **4a**[a] (%)	yield of **2a**[b] (%)	yield of **5a**[b] (%)
1[c]	100:100:1	100	30	15	100	(58)	(27)
2[c]	100:100:1	100	60	15	100	(35)	(48)
3[c]	100:100:1	60	60	1	90	20	53
4[c]	100:100:1	25	60	2	81	10	58
5[c]	200:100:1	25	60	2	65	8	46
6[d]	200:100:1	25	60	2	63	5	49
7[d]	200:100:1	40	60	2	90	20	65
8[d]	200:100:1	60	60	2	100	28	60
9[d]	200:10:1	25	60	2	35	9	19
10[d]	200:200:1	25	60	2	20	5	13
11[d]	200:100:1	25	90	2	75	6	62

[a] Determined by GLC. [b] GLC yield (isolated yield) based on **4a**. [c] Substrate concentration was 0.22 mmol/mL of MeOH. [d] Substrate concentration was 0.50 mmol/mL of MeOH.



Formation of the coumarin derivative was not observed in the case of (2-allyloxyaryl)-2-yn-1-ols **1**, bearing an internal triple bond.[1] Evidently, in the case of substrate **4a**, bearing a terminal triple bond, a second reaction route, corresponding to dicarbonylation to give coumarin **5a**, becomes competitive with the heterocyclization−alkoxycarbonylation route leading to benzofurans. This is in agreement with what we have already observed in other PdI_2-catalyzed carbonylation reactions of alkynes, namely, that usually only terminal triple bonds undergo PdI_2-catalyzed dicarbonylation.[14] Formation of the coumarin derivative may occur through two different pathways (Scheme 2, anionic iodide ligands are omitted for clarity).[15] The first possibility (path a) corresponds to triple-bond insertion into the Pd−C bond of a phenoxycarbonylpalladium intermediate followed by alkoxycarbonylation. Alternatively, triple-bond insertion into the Pd−C bond of a methoxycarbonylpalladium species may occur, followed by CO insertion and intramolecular nucleophilic displacement (path b). In either case, intermediate **6** and an H−Pd−I complex are formed, which, according to a known reactivity,[1,16] react to afford an allylpalladium intermediate with elimination of water. Protonolysis of the allylpalladium

(7) For some very recent developments in the synthesis of coumarins, see: (a) Henry, C. E.; Kwon, O. *Org. Lett.* **2007**, *9*, 3069−3072. (b) Valizadeh, H.; Shockravi, A.; Gholipur, H. *J. Heterocycl. Chem.* **2007**, *44*, 867−870. (c) Shi, Y. L.; Shi, M. *Org. Biomol. Chem.* **2007**, *5*, 1499−1504. (d) Kumar, S.; Saini, A.; Sandhu, J. S. *Arkivok* **2007**, 18−23. (e) Selvakumar, S.; Chidambaram, M.; Singh, A. P. *Catal. Commun.* **2007**, *8*, 777−783. (f) Reddy, B. M.; Patil, M. K.; Lakshmanan, P. *J. Mol. Catal. A:Chem.* **2006**, *256*, 290−294. (g) Maheswara, M.; Siddaiah, V.; Damu, G. L. V.; Rao, Y. K.; Rao, C. V. *J. Mol. Catal. A:Chem.* **2006**, *255*, 49−52. (h) Baldoumi, V.; Gautam, D. R.; Litinas, K. E.; Nicolaides, D. N. *Tetrahedron* **2006**, *62*, 8016−8020. (i) Oyamada, J.; Kitamura, T. *Tetrahedron* **2006**, *62*, 6918−6925. (j) Manhas, M. S.; Ganguly, S. N.; Mukherjee, A. K. J.; Bose, A. K. *Tetrahedron Lett.* **2006**, *47*, 2423−2425. (k) Liu, Y.; Mills, A. D.; Kurth, M. J. *Tetrahedron Lett.* **2006**, *47*, 1985−1988. (l) Santana, L.; Uriarte, E.; Gonzalez-Diaz, H.; Zagotto, G.; Soto-Otero, R.; Mendez-Alvarez. E *J. Med. Chem.* **2006**, *49*, 1149−1156.

(8) Only a few transition metal-catalyzed approaches to the synthesis of coumarins have been reported. For representative examples, see ref 9 and: (a) Trost, B. M.; Toste, F. D.; Greenman, K. *J. Am. Chem. Soc.* **2003**, *125*, 4518−4526. (b) Rayabarapu, D. K.; Sambaiah, T.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1286−1288. (c) Jia, C.; Piao, D.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992−1995. (d) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1996**, *118*, 6305−6306. (e) Catellani, M.; Chiusoli, G. P.; Fagnola, M. C.; Solari, G. *Tetrahedron Lett.* **1994**, *35*, 5919−5922.

(9) To our knowledge, only very few reports on coumarin synthesis by a direct carbonylation approach have appeared in the literature so far: (a) Cao, H.; Xiao, W. J. *Can. J. Chem.* **2005**, *83*, 826−831. (b) Kadnikov, D. V.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 9423−9432. (c) Yoneda, E.; Sugioka, T.; Hirao, K.; Zhang, S. W.; Takahashi, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 477−483. (d) Catellani, M.; Chiusoli, G. P.; Fagnola, M. C.; Solari, G. *Tetrahedron Lett.* **1994**, *35*, 5923−5926. None of these methods, however, led to 3-[(alkoxycarbonyl)methyl]coumarins by direct dicarbonylation of acyclic substrates.

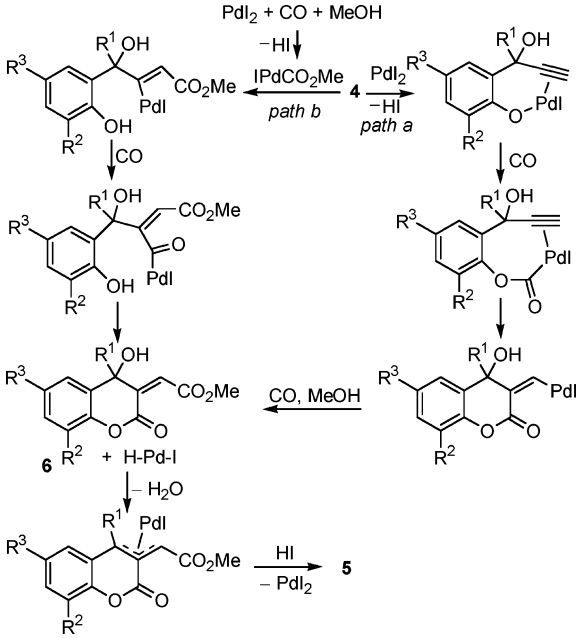
(10) (a) Murray, R. D. H.; Méndez, J.; Brown, S. A. *The Natural Coumarins: Occurrence, Chemistry, and Biochemistry*; Wiley: New York, 1982. (b) *Coumarins: Biology, Applications, and Mode of Action*; O'Kennedy, R., Thornes, R. D., Eds.; John Wiley & Sons: New York, 1997. (c) Murray, R. D. H. *Prog. Chem. Org. Nat. Prod.* **2002**, *83*, 1−673. (d) Kulkarni, M. V.; Kulkarni, G. M.; Lin, C. H.; Sun, C. M. *Curr. Med. Chem.* **2006**, *13*, 2795−2818. (e) Kostova, I. *Curr. HIV Res.* **2006**, *4*, 347−363. (f) Kostova, I. *Mini-Rev. Med. Chem.* **2006**, *6*, 365−374. (g) Borges, F.; Roleira, F.; Milhazes, N.; Santana, L.; Uriarte, E. *Curr. Med. Chem.* **2005**, *12*, 887−916. (h) Lacy, A.; O', Kennedy, R. *Curr. Pharm. Design* **2004**, *10*, 3797−3811. (i) Yu, D.; Suzuki, M.; Xie, L.; Morris-Natscke, S. L.; Lee, K.-H. *Med. Res. Rev.* **2003**, *23*, 322−345. (j) Trenor, S. R.; Shultz, A. R.; Love, B. J.; Long, T. E. *Chem. Rev.* **2004**, *104*, 3059−3077.

(11) For very recent examples on the pharmacological activity of coumarins, see: (a) Jacquot, Y.; Laios, L.; Cleeren, A.; Nonclercq, D.; Bermont, L.; Refouvelet, B.; Boubekeur, K;, Xicluna, A.; Leclercq, G.; Laurent, G. *Bioorg. Med. Chem. Lett.* **2007**, *15*, 2269−2282. (b) Hadjipavlou-Litina, D.; Kontogiorgis, C.; Pontiki, E.; Dakanali, M.; Akoumianaki, A.; Katerinopoulos, H. E. *J. Enzym. Inhib. Med. Ch.* **2007**, *22*, 287−292. (c) Ruiz-Marcial, C.; Chilpa, R. R.; Estrada, E.; Reyes-Esparza, J.; Farina, G. G.; Rodriguez-Fragoso, L. *J. Pharm. Pharmacol.* **2007**, *59*, 719−725. (d) Garazd, M. M.; Muzychka, O. V.; Vovk, A. I.; Nagorichna, I. V.; Ogorodniichuk, A. S. *Chem. Nat. Compd.* **2007**, *43*, 19−23. (e) Zhang, Q. Y.; Qin, L. P.; He, W. D.; Van Puyvelde, L.; Maes, D.; Adams, A.; Zheng, H. C.; De Kimpe, N. *Planta Med.* **2007**, *73*, 13−19.

(12) For recent examples on the pharmacological activity of [(3-alkoxycarbonyl)methyl]coumarins, see: (a) Patterson, A. W.; Wood, W. J. L.; Hornsby, M.; Lesley, S.; Spraggon, G.; Ellman, J. A. *J. Med. Chem.* **2006**, *49*, 6298−6307. (b) Wood, J. L.; Patterson, A. W.; Tsuruoka, H.; Jain, R. K.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 15521−15527. (c) Raj, H. G.; Parmar, V. S.; Jain, S. C.; Goel, S.; Himanshu, P.; Malhotra, S.; Singh, A.; Olsen, C. E.; Wengel, J. *Bioorg. Med. Chem.* **1998**, *6*, 833−839. (d) Raj, H. G.; Gupta, S.; Biswas, G.; Singh, S.; Singh, A.; Jha, A.; Bisht, K. S.; Sharma, S. K.; Jain, S. C.; Parmar, V. S. *Bioorg. Med. Chem.* **1996**, *4*, 2225−2228.

(13) See, for example: (a) Zabradnik, M. *The Production and Application of Fluorescent Brightening Agents*; John Wiley & Sons: New York, 1992. (b) Sekar, N. *Colourage* **2003**, *50*, 55−56. (c) Maeda, M. *Laser Dyes*; Academic Press: New York, 1984. (d) Brun, M.-P.; Bischoff, L.; Garbay, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3432−3436.

SCHEME 2



complex by HI eventually leads to the coumarin derivative with regeneration of PdI_2.

Based on this initial result, we tried to selectively activate the catalytic process toward the formation of the coumarin derivative by suitably changing the reaction parameters (Table 1, entries 2−11). As can be seen, the selectivity toward **5a** could be significantly improved by raising the CO pressure, decreasing the reaction temperature, and increasing the substrate concentration.

Under the final optimized conditions (**4a**/KI/PdI_2 molar ratio = 200:100:1, concentration of **4a** = 0.50 mmol/mL of MeOH, T = 25 °C, P_{CO} = 90 atm, t = 8 h), coumarin **5a** was obtained in an isolated yield as high as 83%, benzofuran **2a** being also obtained in only 8% isolated yield (Table 2, entry 12). Under these conditions, other 2-(1-hydroxyprop-2-ynyl)phenols **4b**−**d**, bearing a π-donor or an electron-withdrawing group on the aromatic ring, afforded, after 8−15 h, the corresponding coumarins in good yields (70−81%) and high selectivity (Table 2, entries 13, 15, and 17).

TABLE 2. Synthesis of 3-[(Methoxycarbonyl)methyl]coumarins 5a−d by PdI_2/KI-Catalyzed Dicarbonylation of 2-(1-Hydroxyprop-2-ynyl)phenols 4a−d[a]

entry	4	R^1	R^2	R^3	t (h)	conv of 4[b] (%)	5	yield of 5[c] (%)
12	**4a**	H	H	H	8	100	**5a**	87 (83)[d]
13	**4b**	H	OMe	H	8	100	**5b**	(81)[e]
14	**4c**	H	H	OMe	8	71	**5c**	42[f]
15	**4c**	H	H	OMe	15	100	**5c**	(70)[g]
16	**4d**	H	H	Cl	8	68	**5d**	47[h]
17	**4d**	H	H	Cl	15	100	**5d**	(74)[i]

[a] All reactions were carried out at room temperature in MeOH (0.5 mmol of **4**/mL of MeOH, 5 mmol scale based on **4**) under 90 atm of CO in the presence of PdI_2 in conjunction with KI (**4**/KI/PdI_2 molar ratio = 200/100/1). [b] Determined by GLC. [c] GLC yield (isolated yield) based on **4**. [d] Benzofuran-2-ylacetic acid methyl ester **2a** was also formed in 10% isolated yield (8% isolated). [e] (7-Methoxybenzofuran-2-yl)acetic acid methyl ester **2b** was also formed in 9% isolated yield. [f] (5-Methoxybenzofuran-2-yl)acetic acid methyl ester **2c** was also formed in 8% GLC yield. [g] Benzofuran **2c** was also formed in 10% isolated yield. [h] (5-Chlorobenzofuran-2-yl)acetic acid methyl ester **2d** was also formed in 5% GLC yield. [i] Benzofuran **2d** was also formed in 6% isolated yield.

TABLE 3. Reactions of 2-(Hydroxy-1-methylprop-2-ynyl)phenol 4e with CO and MeOH in the Presence of the PdI_2−KI Catalytic System in MeOH as the Solvent (0.50 mmol of 4e/mL of MeOH)

entry	**4e**/KI/PdI_2 molar ratio	T (°C)	P_{CO} (atm)	t (h)	convn of **4e**[a] (%)	yield of **2e**[b] (%)	yield of **5e**[b] (%)
18	200:100:1	25	90	8	67	45	20
19	100:100:1	40	60	2	31	5	17
20	100:50:1	40	60	2	51	9	28
21	100:10:1	40	60	2	80	19	57
22	100:10:1	40	90	2	79	15	61
23	100:10:1	40	90	15	95	18	71

[a] Determined by GCL. [b] GLC yield based on **4e**.

As expected in view of the higher steric hindrance on the triple bond, substrates bearing an additional benzylic substituent (R^1 = alkyl, phenyl) were slightly less reactive than the analogous ones with R^1 = H. Thus, the reaction of 2-(1-hydroxy-1-methylprop-2-ynyl)phenol **4e** (R^1 = Me, R^2 = R^3 = H), carried out under the same conditions as entry 12, led to the corresponding coumarin and benzofuran derivatives (**5e** and **2e**, respectively) in 45% and 20% GLC yields at 67% substrate conversion (Table 3, entry 18). In order to find the optimal reaction conditions also for this substrate, we next tested its reactivity at 40 °C under various conditions (Table 3, entries 19−23). Working under 60 atm of CO with a **4e**/KI/PdI_2 molar ratio of 100/100/1, substrate conversion after 2 h was 31%, while the GLC yields of the benzofuran and coumarin derivatives (**2e** and **5e**, respectively) were 17 and 5%, respectively. Interestingly, the substrate conversion and products yields were higher by working with lower KI/PdI_2 ratios (entries 20 and 21). This is conceivable, since, in the presence of a less coordinating triple bond, iodide anions may compete more effectively for coordination to the metal center. As already observed for **4a**, an increase of the carbon monoxide pressure from 60 to 90 atm caused an increase of the selectivity toward the coumarin derivative (entry 22). Under these latter conditions, substrate conversion reached 95% after 15 h, with GLC yields of **2e** and **5e** of 18 and 71%, respectively (entry 23). As expected, the same reaction, carried out at 25 °C rather than 40 °C, was slower but more selective toward coumarin **5e**: substrate conversion was 100% after 24 h, with GLC yields of **2e** and **5e** of 90% and 10%, respectively (87% and 9% isolated, Table 4, entry 24). Similar results were obtained with 4-chloro-2-(1-hydroxy-1-methylprop-2-ynyl)phe-

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TABLE 4. Synthesis of 3-[(Methoxycarbonyl)methyl]coumarins 5e−g by PdI_2/KI-Catalyzed Dicarbonylation of 2-(1-Hydroxyprop-2-ynyl)phenols 4e−g[a]

entry	4	R^1	R^2	R^3	*t* (h)	convn of 4[b] (%)	5	yield of 5[c] (%)
24	**4e**	Me	H	H	24	100	**5e**	90 (87)[d]
25	**4f**	Me	H	Cl	24	100	**5f**	(76)
26	**4g**	Ph	H	H	24	100	**5g**	66 (63)[e]

[a] All reactions were carried out at room temperature in MeOH (0.5 mmol of **4**/mL of MeOH, 5 mmol scale based on **4**) under 90 atm of CO in the presence of PdI_2 in conjunction with KI (**4**/KI/PdI_2 molar ratio = 100/10/1). [b] Determined by GLC. [c] GLC yield (isolated yield) based on **4**. [d] (3-Methylbenzofuran-2-yl)acetic acid methyl ester **2e** was also formed in 9% isolated yield. [e] (3-Phenylbenzofuran-2-yl)acetic acid methyl ester **2g** was also formed in 30% GLC yield (27% isolated).

nol **4f**, bearing a chloro substituent on the aromatic ring (R^3 = Cl) (entry 25, Table 4), while the reaction was slightly less selective in the case of 2-(1-hydroxy-1-phenylprop-2-ynyl)-phenol **4g**, bearing a phenyl rather than a methyl group at the benzylic position (R^1 = Ph), as shown by entry 26 (Table 4).

In conclusion, we have reported a novel synthesis of 3-[(alkoxycarbonyl)methyl]coumarins **5** in good to high yields starting from readily available 2-(1-hydroxyprop-2-ynyl)phenols **4**, based on an unprecedented palladium-catalyzed dicarbonylation process.[9] The selectivity of the process toward the formation of the coumarin derivatives rather than toward benzofuran derivatives **2** (deriving from a competitive heterocyclization−alkoxycarbonylation process) turned out to be highly dependent on both carbon monoxide pressure and reaction temperature. Very good selectivities toward coumarins **5** could in fact be obtained working at room temperature and under 90 atm of CO.

Experimental Section

Preparation of Substrates. Substrates were prepared and characterized as described in the Supporting Information.

General Procedure for the Carbonylation of 2-(1-Hydroxyprop-2-ynyl)phenols 4a-d To Give Coumarins 5a−d (Table 2, Entries 12, 13, 15, and 17). In a typical experiment, a 250 mL stainless steel autoclave was charged with PdI_2 (9.0 mg, $2.5 \cdot 10^{-2}$ mmol), KI (415.0 mg, 2.5 mmol), and a solution of **4** (5.0 mmol) in anhydrous MeOH (10.0 mL). The autoclave was sealed, purged at room temperature several times with CO with stirring (10 atm), and eventually pressurized at 90 atm. After being stirred at room temperature for 8 h (**4a**, **4b**) or 15 h (**4c**, **4d**), the autoclave was degassed. The solvent was evaporated, and products were purified by column chromatography on silica gel using 8:2 hexane−AcOEt (reaction crude deriving from **4a**) or 7:3 hexane−AcOEt (reaction crude deriving from the reactions of **4b**, **4c**, and **4d**) as eluent. The benzofuran derivatives **2a−d** were eluted first in all cases: **2a** was a yellow oil (77.5 mg, 8% based on **4a**, Table 2, entry 12); **5a** was a yellow solid, mp 77−78 °C (0.91 g, 83% based on **4a**, Table 2, entry 12); **2b** was a yellow oil (100.3 mg, 9% based on **4b**, Table 2, entry 13); **5b** was a yellow solid, mp 108−110 °C (1.01 g, 81% based on **4b**, Table 2, entry 13); **2c** was a yellow solid, mp 78−80 °C (109.8 mg, 10% based on **4c**, Table 2, entry 15); **5c** was a yellow solid, mp 128−130 °C (0.87 g, 70% based on **4c**, Table 2, entry 15); **2d** was a yellow solid, mp 58−59 °C (65.8 mg, 6% based on **4d**, Table 2, entry 17); **5d** was a yellow solid, mp 128−129 °C (0.93 g, 74% based on **4d**, Table 2, entry 17).

2-Benzofuran-2-ylacetic acid methyl ester **2a** was characterized by comparison with literature data.[1] Complete characterization data for all the other products are given in the Supporting Information.

General Procedure for the Carbonylation of 2-(1-Hydroxyprop-2-ynyl)phenols 4e−g To Give Coumarins 5e−g (Table 4, Entries 24−26). In a typical experiment, a 250 mL stainless steel autoclave was charged with PdI_2 (18.0 mg, 5.0×10^{-2} mmol), KI (83.0 mg, 2.5 mmol), and a solution of **4** (5.0 mmol) in anhydrous MeOH (10.0 mL). The autoclave was sealed, purged at room temperature several times with CO with stirring (10 atm), and eventually pressurized at 90 atm. After being stirred at room temperature for 24 h, the autoclave was degassed. The solvent was evaporated, and products were purified by column chromatography on silica gel using 7:3 hexane−AcOEt (reaction crude deriving from the reactions of **4e**, **4f**) or 9:1 hexane−acetone (reaction crude deriving from the reaction of **4g**) as eluent. The benzofuran derivatives **2e** and **2g** were eluted first: **2e** was a yellow oil (90.5 mg, 9% based on **4e**, Table 4, entry 24); **5e** was a yellow solid, mp 130−131 °C (1.01 g, 87% based on **4e**, Table 4, entry 24); **5f** was a yellow solid, mp 55−56 °C (1.01 g, 76% based on **4f**, Table 4, entry 25); **2g** was a yellow oil (360.3 mg, 27% based on **4g**, Table 4, entry 26); **5g** was a yellow solid, mp 120−121 °C (0.92 g, 63% based on **4g**, Table 4, entry 29). Complete characterization data for all products are given in the Supporting Information.

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Supporting Information Available: General experimental methods, preparation and characterization of substrates, characterization data, and copies of ^1H and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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