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Palladium-catalyzed carbonylative cyclization of Baylis–Hillman adducts. An efficient approach for the stereoselective synthesis of 3-alkenyl phthalides

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Abstract—A palladium-mediated carbonylative cyclization reaction of Baylis–Hillman adducts is disclosed. This simple, efficient and straightforward sequence leads to the formation of an array of 3-alkenylphthalides with different substitution patterns on the aromatic ring, with good chemical yields and selectivities.

1. Introduction

Natural products play a pivotal role in modern drug discovery. Among the class of oxygen heterocycles, benzoannulated lactones (phthalides or 3*H*-isobenzofuran-1-one) are commonly found in many naturally occurring substances,[1–6] as well as some of their synthetically related compounds and show a broad spectrum of biological effects.[7]

Particularly, the 3-alkylated phthalides are present in some natural products such as vermistatin (**1**),[8] (−)-hidrastine (**2**) and fuscinarin (**3**),[9,10] alcyopterosin E (**4**),[11] isoochracinic (**5**) and herbaric (**6**) acids (Fig. 1).[7,12] Phthalides, such as the

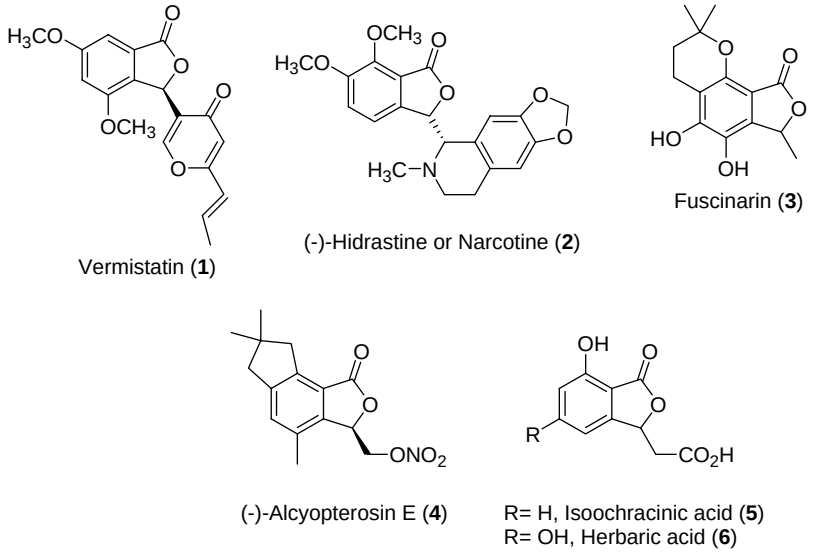

Figure 1. Some naturally occuring 3-substituted phthalides, which exhibited relevant biological activity.

Keywords: Baylis–Hillman adducts; Phthalides; Cyclization; Palladium.
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aforementioned, possess a wide range of biological activity. (−)-Hidrastine (**2**) is active at the human opioid receptor known as CCR5, while fuscinarin (**3**) interferes with HIV entry into cells. Vermistatin (**1**) and alcyopterosin E (**4**) are both cytotoxic.

Besides its biological activities, phthalides are versatile starting materials for the synthesis of a variety of structures, including key intermediates in the synthesis of functionalized naphtalenes and anthracenes, which in turn are used as synthons for tricyclic and tetracyclic linear aromatic natural products.[13–18]

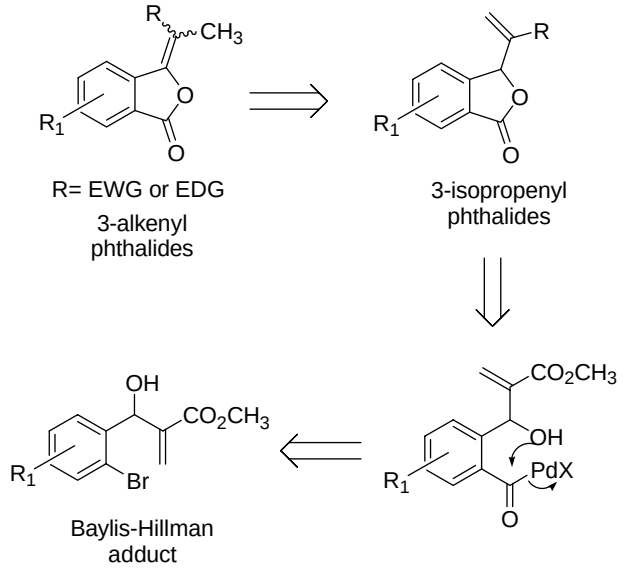
Due to its biological and synthetic importance, several methods have been developed for the synthesis of phthalides.[19–22] Classical methods for their preparation are based on the chloromethylation of benzoic acids, which unfortunately often result in low yields and are not suitable for the regioselective preparation of substituted phthalides.[23–25] To circumvent these difficulties, useful approaches based on the reduction of phthalic anhydrides or the oxidation of diols have been developed, however, the regioselectivity of the products obtained from these methods are frequently problematic.[26–28] Strategies based on the solid phase-synthesis have already been used as alternative for the preparation of this important class of compounds.[29]

More recently, palladium-catalyzed carbonylation reactions[30] of several halogenated substrates have been reported as a convenient route for the synthesis of phthalides using either CO gas[31] or $Mo(CO)_6$[32] as carbonylation source. The use of supercritical CO_2 as solvent has also been successfully combined with palladium-mediated carbonylations to prepare phthalides.[33]

The Baylis–Hillman (BH) reaction is a useful and general σ C–C bond-forming reaction, providing a straightforward single-step synthetic method to form densely functionalized precursors (α-methylene-β-hydroxy derivatives).[34,35] The versatility of these multifunctionalized compounds have made these adducts valuable synthetic intermediates[36] and has also stimulated their utilization as substrates for chemical transformations mediated by palladium, especially for Heck reactions.[37,38]

Owing to its highly synthetic versatility, Baylis–Hillman adducts are also employed as substrates for the preparation of phthalides. Kim et al.[39] described the utilization of Baylis–Hillman adducts generated from 2-carboxyaldehyde as substrates for the synthesis of phthalides. Despite its elegance, the method has some drawbacks with respect to the preparation of phthalides having different substituents on the aromatic ring. The scope of the method was demonstrated only by varying the acrylates used in the Baylis–Hillman reaction.

In an ongoing research program based on the biological evaluation of 3-alkenylphthalides as antiproliferative agents, we needed to prepare some particular derivatives of this class of compounds. In a preliminary approach, we were interested in exploring a palladium-catalyzed carbonylative cyclization of Baylis–Hillman adducts as an alternative to prepare the required phthalides. An oxidative addition of a Pd catalyst to the C–Br bond followed by a CO insertion would give an acyl–palladium intermediate (Scheme 1). The secondary hydroxyl group of the Baylis–Hillman adduct could then effect a nucleophilic addition on the acyl–palladium complex to give a free lactone (phthalide), as depicted in Scheme 1.



Scheme 1. Retrosynthetic proposition for the synthesis of phthalides from Baylis–Hillman adducts mediated by palladium.

From our point of view, the impressive list of biological effects associated with phthalides (also for 3-alkenylphthalides)[40] promptly justify the development of alternative strategies for the preparation of these compounds.

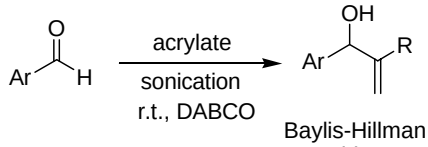
A palladium-mediated carbonylation of an *o*-brominated Baylis–Hillman adduct could tolerate different substituents on the aromatic ring as well as different types of acrylates. Besides, *o*-brominated substituted aldehydes could be prepared using directed ortho metallation reactions, through the trapping of the aryl–lithium intermediates with bromine.[41] As far as we know, Baylis–Hillman adducts has never been used before as substrates for a palladium-catalyzed carbonylation reaction[42] having as aim the preparation of 3-alkenyl phthalides.

In this communication, we describe an efficient and direct approach for the preparation of phthalides based on a palladium-mediated cyclocarbonylation reaction of Baylis–Hillman adducts.

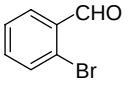
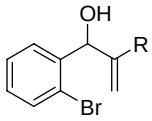
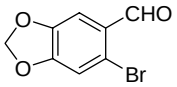
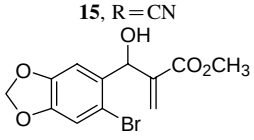
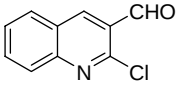
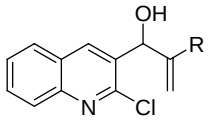
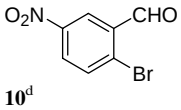
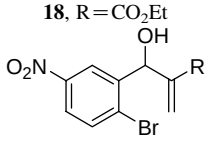
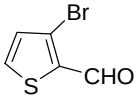
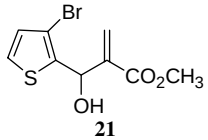
2. Results and discussions

We started our work by preparing the Baylis–Hillman adducts, using a method we recently developed.[43] The results are summarized in Table 1. Most aldehydes we used are commercially available, although aldehyde **10** had to be prepared from the corresponding carboxylic acid, according to a method described by Brown et al.[44]

Table 1. Results for the preparation of Baylis–Hillman adducts



Ar= *o*-brominated aromatic substituent

Aldehyde	Product[a]	Time (h)[b]	Yield (%)[c]
 **7**	 **12**, R=CO_2Me	18	89
	13, R=CO_2Et	17	92
	14, R=CO_2n-Bu	96	85
	15, R=CN	7	93
 **8**	 **16**	96	76
 **9**	 **17**, R=CO_2Me	1	≤99
	18, R=CO_2Et	15	97
 **10**[d]	 **19**, R=CO_2Me	2	92
	20, R=CO_2Et	3	91
 **11**	 **21**	18	98

[a] All reactions were carried out using an excess of acrylate (methyl, ethyl, *n*-butyl and acrylonitrile) in the presence of DABCO (0.65 equiv). For the preparation of Baylis–Hillman adducts **12**, **13**, **16** and **17**, *N*-butyl-2-methyl-imidazolium hexafluorate [(bmim)PF_6] (7 mol%) was used as co-catalyst.

[b] For total conversion.

[c] Yields refer to isolated and purified products.

[d] 5-Nitro-2-bromobenzaldehyde was prepared from the corresponding carboxylic acid by reduction with borane, followed by treatment of the intermediate trialkoxyboroxine with PCC in dichloromethane to afford the required aldehyde in 61% overall yield.[44]

After that, our work aimed at finding or developing a set of reaction conditions that would use the Baylis–Hillman adducts to produce the required 3-alkenylphthalides. Recently, Littke and Fu[45] described mild conditions for the Heck reaction of aryl chlorides and bromides. Since the initial step of the palladium-catalyzed carbonylative cyclization process, as well as in the Heck reaction, is an oxidative addition of the C–halogen bond to a Pd catalyst, we started our work testing the experimental conditions proposed by Littke and Fu.[45]

Solutions of Baylis–Hillman adducts (**12**–**21**) in anhydrous dioxane were treated with $Pd_2(dba)_3$/P(*t*Bu)$_3$ in the presence of dicyclohexylmethylamine (Cy_2NMe), at 70–90 °C under CO (2 atm) pressure. To our delight, the reactions worked quite nicely to provide the expected 3-alkenylphthalides (**22**–**32**) as the sole detectable products in few hours. The results are summarized in Table 2.

Analysis of the data shown in Table 2 revealed that the carbonylation cyclization procedure works well with different Baylis–Hillman adducts. In most cases, the phthalides were obtained with good to excellent yields. The presence of electron-withdrawing (see entries 8 and 9) or electron-donating groups (see entry 5) has no influence on the rate and efficiency of the procedure. Baylis–Hillman adducts prepared from heteroaromatic aldehydes work equally well as substrates for this palladium-mediated carbonylative process (entries 6 and 7), although the yield is lower when a sulfur-containing Baylis–Hillman adduct was used (see entry 10). Moreover, we observed some restrictions with respect to the acrylates. Cyanide derivatives might deactivate palladium(0) in the catalytic cycle,[46] which perhaps could explain the moderate yield achieved in the preparation of the corresponding phthalide (entry 4).

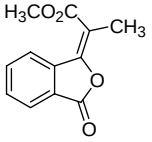
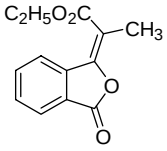
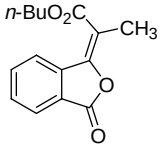
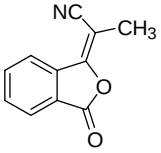
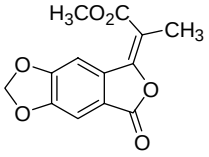
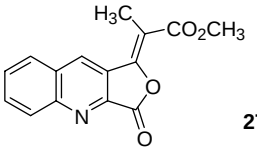
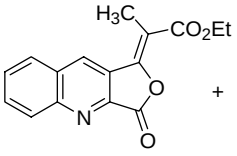
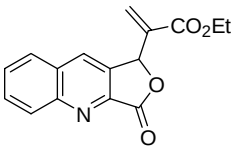
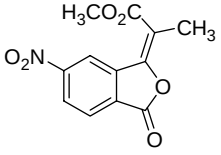
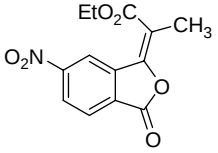
In most cases, the only afforded product was that in which the double bond was totally conjugated (tetrasubstituted alkene). Probably a palladium–hydride intermediate is responsible for double bond isomerization, leading to the formation of the most stable alkene. The only exception was observed when Baylis–Hillman adduct **18**, prepared from the reaction between ethyl acrylate and 2-chloro-3-quinolinecarboxyaldehyde, was employed as substrate. In this particular case, we observed the formation of 3-isopropenyl phthalide (**29**), which could be considered as a Baylis–Hillman adduct in which the conformation was partially restricted, in 60% yield.

The formation of this unusual product is particularly interesting, because it constitutes evidence that the formation of the 3-alkenylphthalides (with a tetrasubstituted double bond) may go through this intermediate, with an in situ palladium-catalyzed double bond isomerization step being responsible for the formation of the enol–lactones, as expected (see Scheme 2). The presence of large substituents would hamper re-coordination of the palladium species, preventing the isomerization step and thus favoring the formation of phthalide **29**.

The configuration of the double bond was deduced from NOE experiments. The aromatic proton adjacent to the double bond of the phthalide was irradiated and an increment was observed in the spectra. For the *Z* configuration an increment in the absorption of the vinylic methyl group was observed (increments ranged from 0.3 to 0.45%).[39] Otherwise, for the *E* configurations increments in the absorption of the alkyl residue of the ester group were observed (increments ranged form 0.3–0.4%) (Fig. 2).

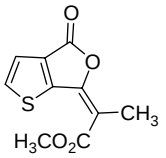
In most cases, the *E* isomer was exclusively or almost exclusively formed. The degree of stereoselectivity might vary depending on the Baylis–Hillman adduct employed, and an inversion in the stereoselectivity *Z*/*E* could also be

Table 2. Palladium-catalyzed carbonylative cyclization of Baylis–Hillman adducts

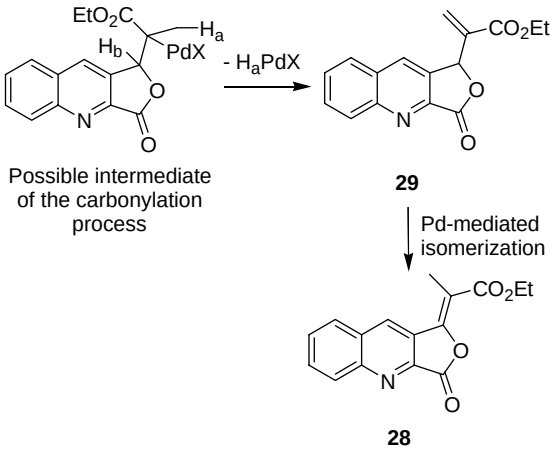
Entry	BH adducts	Phthalides[a]	Time (h)	%[b,c]
1	**12**	 **22** (*E*/*Z* ≥ 95:5)	15	94
2	**13**	 **23** (*E*/*Z* 88:12)	5[b]	96
3	**14**	 **24** (*E*/*Z* ≥ 95:5)	78	68[d]
4	**15**	 **25** (*E*/*Z* ≥ 95:5)	15	59
5	**16**	 **26** (*E*/*Z* ≥ 95:5)	15	96
6	**17**	 **27** (*E*/*Z* 5:95)	15	98
7	**18**	 +  **28** (*E*/*Z* ≥ 5:95) **29**	18	82;[e] 22 (**28**); 60 (**29**)
8	**19**	 **30** (*E*/*Z* ≥ 95:5)	16	76
9	**20**	 **31** (*E*/*Z* 95:5)	25	71

(*continued on next page*)

Table 2 (*continued*)

Entry	BH adducts	Phthalides[a]	Time (h)	%[b,c]
10	**21**	 **32** (*E*/*Z* 85:15)[f]	72	29[d]

[a] The double bond configurations were determined using NOE experiments, in which the aromatic proton adjacent to the phthalide double bond was irradiated.[39] In some cases the isomer distribution could also be observed by ^{1}H NMR.
[b] All reactions were carried out in the presence of $Pd_2(dba)_3$ (1 or 2 mol%)/P(^{t}Bu$_3$), Cy_2NCH_3 and CO (2 atm) at 70–90 °C.
[c] Yields refer to isolated and purified products.
[d] Yield based on the recovered starting material.
[e] Global yield (mixture of products).
[f] We assume the stereochemistry of the majoritary product as being *E* or *Z* based on NOE experiments. We observed an increment of only 0.1% on proton adjacent to the sulfur atom when the methylic ester was irradiated. No increment was observed when vinylic methyl was irradiated.



Scheme 2. Palladium–hydride elimination and double bond isomerization of **29**.

observed (see entry 7, Table 2). Apparently, the stereoselectivity observed has no direct relationship with the size of the ester residue exhibited by the acrylate.

In summary, we disclosed herein a stereoselective, straightforward and high yielding method to prepare phthalides, in only one step, from Baylis–Hillman adducts. The method tolerates different types of substituents in the aromatic ring, as expected for a palladium-mediated procedure. The method can be easily scaled up, since experiments in a scale of 1 g were carried out without any significant alterations in either chemical yield or product quality. In this particular aspect, we believe that the disclosed approach could be used for the stereoselective preparation of several phthalides.

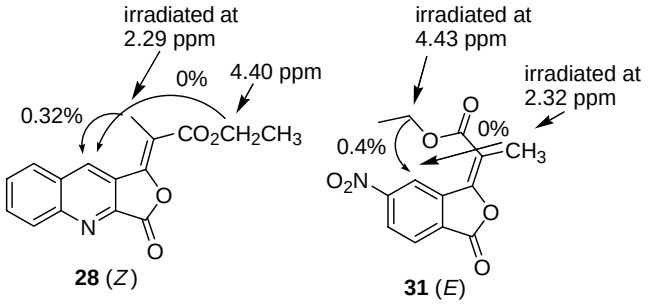


Figure 2. Exemplifying the procedure for determination of the configuration of the tetrasubstituted double bond of phthalides.

Due to its operational simplicity this approach could be considered as a valuable, broadly applicable alternative for the preparation of this class of compounds, since *o*-brominated Baylis–Hillman adducts are readily accessible from the corresponding *o*-brominated aromatic aldehydes. This simplicity could be seen as an advantage of our approach, since some palladium-mediated methods reported for the synthesis of phthalides require the preparation of elaborated starting materials.

Additional work describing the biological profile of these phthalides and their synthetic utility are underway in our laboratory and the results will be disclosed in due course. Although palladium-mediated carbonylative methodology for the preparation of phthalides have already been reported,[31] as far as we know, this is the first report describing a successful palladium-mediated carbonylative cyclization from Baylis–Hillman adducts.

3. Experimental

3.1. General

The following procedures are representative for all the Baylis–Hillman adducts and phthalides prepared in this work. All the reagents were purchased from specialized suppliers with analytical purity and were utilized without previous purification, unless noted. The dioxane was refluxed over CaH_2 under an argon atmosphere for 48 h and distilled at ambient pressure prior to use. After, this solvent was degasified through external ultrasound irradiation in a water bath cleaner (81 W, 40 kHz), over activated molecular sieves 4 Å and under continuous positive pressure of argon during about 5 h. The ^{1}H and ^{13}C spectra were recorded on a Varian GEMINI BB-300 at 300 and 75.4 MHz, respectively, or on an Inova instrument at 500 and 125 MHz, respectively. The mass spectra were recorded using a HP model 5988A GC/MS with a High-Resolution Autospec-Micromass/EBE. IR were obtained with a Nicolet model Impact 410. Melting points were

measured in open capillary tubes using an Electrothermal apparatus model 9100, and are uncorrected. Only the spectral data of the unknown Baylis–Hillman adducts are enclosed.

3.1.1. General procedure for the preparation of the Baylis–Hillman adducts. A mixture of the aromatic aldehyde (1–2 mmol), an excess of acrylate (methyl, ethyl, butyl or acrylonitrile −20 equiv, used as reagent and solvent) and DABCO (0.65 equiv) was sonicated (1000 W, 25 kHz) for a certain period of time (for details, see Table 1 in text). The ultrasound bath temperature was constantly monitored and kept at 30–40 °C during the reaction, through ice addition or by using a refrigerated circulator. After the reaction time, the mixture was evaporated under reduced pressure in order to remove the excess of acrylate. The residue was diluted with ethyl acetate (30 mL). The organic solution was washed with 10% aqueous HCl (2×10 mL), saturated $NaHCO_3$ (20 mL), brine (20 mL), and dried over Na_2SO_4 or $MgSO_4$. After filtration and solvent removal, the residue was filtered through a pad of gel of silica.

3.1.1.1. Ethyl 2-[(2-bromophenyl)(hydroxy)methyl]-acrylate (13). Yield: 92%; for chromatographic purification: ethyl acetate–hexane (20/80); colorless viscous oil; IR (Film, υ_{max}): 3473, 2987, 1720, 1630, 1466, 1430, 1266, 1135, 1025, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (m, 2H), 7.35 (m, 1H), 7.17 (m, 1H), 6.37 (s, 1H), 5.95 (s, 1H), 5.58 (s, 1H), 4.23 (q, J=7.0 Hz, 2H), 3.13 (broad s, 1H, exchangeable with D_2O), 1.28 (t, J=7.0 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.3, 141.2, 140.3, 133.0, 129.6, 128.7, 128.0, 127.1, 123.5, 71.9, 61.5, 14.6; HRMS (70 eV, *m/z*) Calcd for $C_{12}H_{13}BrO_3$ 285.13382; Found 285.13375.

3.1.1.2. Butyl 2-[(2-bromophenyl)(hydroxy)methyl]-acrylate (14). Yield: 85%; for chromatographic purification: ethyl acetate–hexane (20/80); tinged yellow viscous oil; IR (Film, υ_{max}): 3444, 2958, 1719, 1634 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (m, 2H), 7.32 (m, 1H), 7.15 (m, 1H), 6.35 (broad s, 1H), 5.93 (broad s, 1H), 5.61 (s, 1H), 4.14 (m, 2H), 3.37 (broad s, 1H, exchangeable with D_2O), 1.61 (quintet, J=7.5 Hz, 2H), 1.31 (sextet, J=7.5 Hz, 2H), 0.90 (t, J=7.5 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.2, 140.8, 139.8, 132.5, 129.0, 128.1, 127.4, 126.4, 123.0, 71.2, 64.8, 30.4, 19.0, 13.6; HRMS (ESI, *m/z*) Calcd for $C_{14}H_{17}BrNaO_3$ $[M+Na]^+$335.0253; Found 335.0323.

3.1.1.3. 2-[(2-Bromophenyl)(hydroxy)methyl]acrylo-nitrile (15). Yield: 93%; eluent for chromatographic purification: ethyl acetate–hexane (30/70); white solid, mp 48–50 °C; IR (neat, υ_{max}): 3444, 3064, 2950, 2234, 1466, 1437 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58 (m, 2H), 7.41 (m, 1H), 7.23 (m, 1H), 6.07 (broad s, 2H), 5.74 (m, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 138.4, 133.5, 131.9, 130.8, 128.7, 128.6, 125.0, 123.1, 117.0, 73.1; HRMS (70 eV, *m/z*) Calcd for $C_{10}H_8NBrO$ 236.97892; Found 236.97314.

3.1.1.4. Methyl 2-[(2-chloroquinolin-3-yl)(hydroxy)-methyl]acrylate (17). Yield: >99%; eluent for chromatographic purification: ethyl acetate–hexane (30/70); white solid, mp 69–71 °C; IR (neat, υ_{max}) 3209, 1715, 1491, 1331, 1298, 1147, 1060, 764 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.22 (d, J=8.4 Hz, 1H), 8.03 (d, J=8.4 Hz, 1H), 7.94 (ddd, J=1.5, 8.4 Hz, 1H), 7.76 (ddd, J=1.5, 8.4 Hz, 1H), 6.60 (s, 1H), 6.25 (s, 1H), 5.84 (s, 1H), 4.0 (s, 3H), 1.89 (broad s, exchangeable with D_2O); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.8, 149.2, 147.1, 140.1, 137.0, 132.6, 130.6, 128.1, 127.8, 127.7, 127.2, 127.1, 69.2, 52.2; HRMS (70 eV, *m/z*) Calcd for $C_{14}H_{12}ClNO_3$ 277.0506; Found 277.0497.

3.1.1.5. Ethyl 2-[(2-chloroquinolin-3-yl)(hydroxy)-methyl]acrylate (18). Yield: 97%; eluent for chromatographic purification: ethyl acetate–hexane (30/70); yellow solid, mp 75–77 °C; IR (neat, υ_{max}): 3378, 3064, 2978, 1711, 1621, 1589, 1143 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.02 (d, J=8.5 Hz, 1H), 7.85 (d, J=8.2 Hz, 1H), 7.73 (m, 1H), 7.57 (m, 1H), 6.40 (s, 1H), 6.05 (s, 1H), 5.63 (s, 1H), 4.24 (q, J=7.2 Hz, 2H), 3.60 (broad s, exchangeable with D_2O, 1H), 1.29 (t, J=7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 149.2, 147.0, 140.3, 137.0, 132.6, 130.5, 128.1, 127.8, 127.4, 127.2, 127.1, 69.3, 61.3, 14.0; HRMS (70 eV, *m/z*) Calcd for $C_{15}H_{14}ClNO_3$ 291.06622; Found 291.05665.

3.1.1.6. Methyl 2-[(2-bromo-5-nitrophenyl)(hydroxy)-methyl]acrylate (19). Yield: 92%; white solid, mp 81–84 °C; eluent for chromatographic purification: ethyl acetate–hexane (30/70); IR (Film, υ_{max}): 3452, 3105, 1723, 1629, 1523, 1343 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, J=2.9 Hz, 1H), 8.03 (dd, J=2.9, 8.8 Hz, 2H), 7.73 (d, J=8.8 Hz, 1H), 6.39 (s, 1H), 5.94 (s, 1H), 5.56 (s, 1H), 3.81 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.4, 147.3, 142.0, 139.5, 133.6, 129.8, 127.7, 123.7, 123.5, 71.1, 52.4; HRMS (70 eV, *m/z*) Calcd for $C_{11}H_9NO_5Br$ 314.97423; Found 314.97939.

3.1.1.7. Ethyl 2-[(2-bromo-5-nitrophenyl)(hydroxy)-methyl]acrylate (20). Yield: 91%; tinged yellow viscous oil; eluent for chromatographic purification: ethyl acetate–hexane (30/70); IR (Film, υ_{max}): 3444, 3109, 1711, 1634, 1527, 1339 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, J=2.7 Hz, 1H), 8.03 (dd, J=2.7, 8.8 Hz, 1H), 7.72 (d, J=8.8 Hz, 1H), 6.39 (s, 1H), 5.94 (s, 1H), 5.57 (s, 1H), 4.25 (q, J=7.5 Hz, 2H), 3.22 (broad s, exchangeable with D_2O, 1H), 1.29 (t, J=7.5 Hz, 3H); ^{13}C NMR (125.4 MHz, $CDCl_3$) δ 166.4, 147.6, 142.3, 139.8, 133.7, 130.0, 127.5, 123.7, 123.6, 71.1, 61.4, 14.0; HRMS (70 eV, *m/z*) Calcd for $C_{12}H_{12}BrNO_5$ 328.9899; Found 328.9880.

3.1.1.8. Methyl 2-[(3-bromo-2-thienyl)(hydroxy)-methyl]acrylate (21). Yield: 98%; eluent for chromatographic purification: ethyl acetate–hexane (30/70); pale yellow viscous oil; IR (Film, υ_{max}): 3436, 3113, 2949, 1711, 1629, 1442, 1266, 1147, 1029, 874, 714 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J=5.5 Hz, 1H), 6.93 (d, J=5.5 Hz, 1H), 6.36 (s, 1H), 5.85 (s, 1H), 5.82 (s, 1H), 3.77 (s, 3H), 3.24 (broad s, exchangeable with D_2O, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.3, 139.7, 139.2, 129.9, 126.8, 125.4, 109.0, 68.4, 52.1; HRMS (ESI, *m/z*) Calcd for $C_9H_9BrNaO_3S$ $[M+Na]^+$298.9348; Found 298.9445.

3.1.2. General procedure for the cyclocarbonylation reactions—synthesis of phthalides. In a dry Fisher-Porter flask equipped with a magnetic stirrer was deposited

1.0 mol% (2.0 mol% for Baylis–Hillman adducts **14** and **21**) of $Pd_2(dba)_3$. The reactor was then closed and the internal atmosphere exchanged by argon. Then, there was injected into the flask, sequentially, under magnetic stirring and an argon atmosphere, 1.0 mL of anhydrous and degasified 1,4-dioxane, 1.1 equiv of Cy_2NMe and 4.0 mol% (8.0 mol% when Baylis–Hillman adducts **14** and **21**) of a 0.1 mol L^{-1} solution of P(*t*Bu)$_3$ in 1,4-dioxane, previously and freshly prepared in a dry box. This catalytic mixture was stirred for 5 min at room temperature (rt) under argon, until the purple color changed to red-brown. In other dry flask a solution of the Baylis–Hillman adduct (1.12 mmol) in 2.0 mL of anhydrous and degasified 1,4-dioxane, under argon, was prepared. This solution was then injected into the Fisher-Porter reactor, and the reaction mixture was stirred at rt under argon for 15 min. At this point, the color changed to a pale yellow. Finally, the reactor was pressurized with carbon monoxide (CO, 2 atm). The temperature was raised to 70–90 °C with a silicon oil bath, and the mixture stirred under these conditions for the required time. Initially, the color of the system changed from pale yellow to orange-brown. In the final hours of the reaction, a gray precipitate forms, indicating the deactivation of the catalyst (Pd black along with the salt $Cy_2NMeH^+Br^-$). After, the mixture was cooled to rt and the reactor carefully opened. The mixture was then filtered and the residue was washed with ethyl acetate (10 mL). The combined solutions were washed with a 10% solution of HCl (10 mL) and with water (10 mL) and brine (10 mL). The organic phase was separated, dried over a pad of Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residue obtained was then purified by silica gel column chromatography (elution with ethyl acetate/hexane–10:90) to provide the corresponding phthalide.

3.1.2.1. Methyl (2*E*)-2-(3-oxo-2-benzofuran-1(3*H*)-ylidene)propanoate (22). White solid, mp 133–135 °C (lit.[39] 133–136 °C); IR (neat, υ_{max}): 2958, 2917, 2851, 1781, 1708, 1634, 1246, 1062, 764 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.58 (d, J=8.1 Hz, 1H), 7.95 (d, J=8.1 Hz, 1H), 7.75 (m, 1H), 7.62 (m, 1H), 3.91 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 167.6, 151.9, 136.8, 134.9, 131.0, 126.5, 125.4, 112.6, 70.1, 52.3, 29.7, 14.8; HRMS (70 eV, *m*/*z*) Calcd for $C_{12}H_{10}O_4$ 218.05791; Found 218.05437.

3.1.2.2. Ethyl (2*E*)-2-(3-oxo-2-benzofuran-1(3*H*)-ylidene)propanoate (23). Diastereoisomeric mixture (*E*)+(*Z*); tinged yellow solid, mp 70–72 °C (lit.[39] 69–70 °C); IR (neat, υ_{max}): 2958, 2925, 2847, 1793, 1711, 1621, 1470, 1237, 1045 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.56 (d, J=8.2 Hz, 1H), 8.02 (d, J=7.6 Hz, 1H, minoritary diastereoisomer), 7.95 (d, J=7.6 Hz, 1H, majoritary diastereoisomer), 7.91 (d, J=7.9 Hz, 1H, minoritary diastereoisomer), 7.78–7.72 (m, 2H), 7.67–7.59 (m, 2H), 7.44–7.42 (m, 2H), 4.37 (q, J=7.0 Hz, 2H), 2.39 (s, 3H, minoritary diastereoisomer), 2.28 (s, 3H, majoritary diastereoisomer), 1.44 (t, J=7.0 Hz, 3H, minoritary diastereoisomer), 1.39 (t, J=7.0 Hz, 3H, majoritary diastereoisomer); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 143.8, 137.3, 135.3, 131.4, 130.9, 129.4, 128.8, 126.9, 126.6, 126.5, 125.9, 125.7, 125.1, 113.4, 62.0, 61.8, 30.1, 15.3, 14.6; HRMS (70 eV, *m*/*z*) Calcd for $C_{13}H_{12}O_4$ 232.07356; Found 232.07346.

3.1.2.3. Butyl (2*E*)-2-(3-oxo-2-benzofuran-1(3*H*)-ylidene)propanoate (24). Yield: 68% (based on recovered starting material—see Table 2); tinged yellow viscous oil; IR (neat, υ_{max}) 2949, 2933, 2868, 1789, 1719, 1634, 1466, 1237, 1045 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, J=8.4 Hz, 1H), 7.92 (d, J=7.6 Hz, 1H), 7.69 (ddd, J=1.1, 7.5 Hz, 1H), 7.59 (m, 1H), 4.29 (t, J=7.0 Hz, 2H), 2.26 (s, 3H), 1.71 (quintet, J=7.0 Hz, 2H), 1.45 (sextet, J=7.0 Hz, 2H), 0.97 (t, J=7.0 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 167.2, 165.8, 151.6, 136.8, 134.8, 130.9, 126.4, 126.1, 125.2, 112.9, 65.2, 30.5, 19.1, 14.8, 13.6; HRMS (ESI, *m*/*z*) Calcd for $C_{15}H_{16}NaO_4$ $[M+Na]^+$283.0941; Found 283.1046.

3.1.2.4. (2*E*)-2-(3-Oxo-2-benzofuran-1(3*H*)-ylidene)-propanenitrile (25). Yield: 63% (based on recovered starting material—see Table 2); white solid, mp 142–144 °C (lit.[19] 143–144 °C); IR (neat, υ_{max}) 2953, 2917, 2847, 2214, 1805, 1646, 1466, 1207, 1127, 1041, 980, 767, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.42 (d, J=8.0 Hz, 1H), 7.99 (d, J=7.0 Hz, 1H), 7.84 (m, 1H), 7.7 (m, 1H), 2.32 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 164.0, 155.3, 136.0, 135.4, 131.9, 125.9, 125.0, 123.6, 118.0, 88.7, 14.8; HRMS (70 eV, *m*/*z*) Calcd for $C_{11}H_7NO_2$ 185.0477; Found 185.0440.

3.1.2.5. Methyl (2*E*)-2-(7-oxofuro[3,4-*f*][1,3]benzodioxol-5(7*H*)-ylidene)propanoate (26). Yield: 96%; white solid, mp 109–110 °C; IR (neat, υ_{max}): 2987, 2920, 1769, 1712, 1479, 1307, 1283, 1277, 1091, 1033 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.12 (s, 1H), 7.20 (s, 1H), 6.18 (s, 2H), 3.98 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 167.4, 164.9, 153.8, 150.4, 133.1, 127.3, 121.3, 111.3, 106.4, 103.7, 102.9, 52.3, 14.8; HRMS (70 eV, *m*/*z*) Calcd for $C_{13}H_{10}O_6$ 262.04774; Found 262.04352.

3.1.2.6. Methyl (2*Z*)-2-(3-oxofuro[3,4-*b*]quinolin-1(3*H*)-ylidene)propanoate (27). IR (neat, υ_{max}): 2933, 2855, 1785, 1719, 1617, 1454, 1372, 1241, 1196, 1119, 1057 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.59 (s, 1H), 8.31 (d, J=8.8 Hz, 1H), 8.03 (d, J=8.1 Hz, 1H), 7.88 (m, 1H), 7.72 (m, 1H), 3.93 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 166.8, 162.7, 150.4, 149.2, 143.8, 142.7, 136.3, 132.8, 131.8, 129.3, 129.0, 113.1, 52.0, 14.0; HRMS (70 eV, *m*/*z*) Calcd for $C_{15}H_{11}NO_4$ 269.06881; Found 269.06656.

3.1.2.7. Ethyl (2*Z*)-2-(3-oxofuro[3,4-*b*]quinolin-1(3*H*)-ylidene)propanoate (28). Yield: 22%; tinged yellow solid, mp 196–198 °C; IR (neat, υ_{max}): 2962, 2917, 1805, 1711, 1634, 1609, 1372, 1294, 1233 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.66 (s, 1H), 8.36 (d, J=9.0 Hz, 1H), 8.08 (d, J=9.0 Hz, 1H), 7.89 (m, 1H), 7.74 (m, 1H), 4.40 (q, J=7.0 Hz, 2H), 2.32 (s, 3H), 1.43 (t, J=7.0 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.8, 163.2, 150.6, 149.7, 144.2, 136.7, 132.1, 130.7, 129.6, 129.5, 129.4, 126.2, 114.0, 61.5, 14.4, 14.3; HRMS (ESI, *m*/*z*) Calcd for $C_{16}H_{13}NNaO_4$ $[M+Na]^+$306.0737; Found 306.0828.

3.1.2.8. Ethyl 2-(3-oxo-1,3-dihydrofuro[3,4-*b*]-quinolin-1-yl)acrylate (29). Yield: 60%; white solid, mp

162–164 °C; IR (neat, υ_{max}): 2982, 2921, 2847, 1772, 1711, 1629, 1376, 1335, 1286, 1123 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.38 (s, 1H), 8.34 (d, $J=8.5$ Hz, 1H), 7.93 (d, $J=8.0$ Hz, 1H), 7.83 (m, 1H), 7.69 (m, 1H), 6.47 (broad s, 2H), 6.08 (broad s, 1H), 4.21 (m, 2H), 2.32 (s, 3H), 1.24 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 167.4, 164.3, 149.7, 144.2, 136.7, 136.1, 136.0, 131.3, 130.9, 130.8, 129.2, 129.0, 128.1, 128.0, 76.5, 61.5, 14.0; HRMS (ESI, *m/z*) Calcd for $C_{16}H_{13}NNaO_4$ $[M+Na]^+$306.0737; Found 306.0808.

3.1.2.9. Methyl (2*E*)-2-(6-nitro-3-oxo-2-benzofuran-1(3*H*)-ylidene)propanoate (30). Yield: 76%; tinged yellow solid, mp 155–157 °C; IR (neat, υ_{max}): 3133, 3096, 2966, 1809, 1707, 1644, 1618, 1544, 1441 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.51 (d, $J=1.8$ Hz, 1H), 8.44 (dd, $J=1.8$, 8.4 Hz, 1H), 8.09 (d, $J=8.4$ Hz, 1H), 3.95 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.8, 163.6, 152.3, 150.3, 137.7, 130.4, 126.3, 125.9, 122.6, 115.7, 52.7, 15.0; HRMS (70 eV, *m/z*) Calcd for $C_{12}H_9NO_6$ 263.04298; Found 263.04145.

3.1.2.10. Ethyl (2*E*)-2-(6-nitro-3-oxo-2-benzofuran-1(3*H*)-ylidene)-propanoate (31). Yield: 71%; pale yellow solid, mp 141–144 °C; IR (neat, υ_{max}): 3133, 3101, 2962, 2921, 2843, 1809, 1711, 1642, 1540, 1343 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.50 (d, $J=1.8$ Hz, 1H), 8.45 (dd, $J=1.8$, 8.4 Hz, 1H), 8.11 (d, $J=8.4$ Hz, 1H), 4.43 (q, $J=6.9$ Hz, 2H), 2.32, (s, 3H), 1.43 (t, $J=6.9$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.4, 163.6, 152.2, 149.9, 137.7, 130.4, 126.3, 125.8, 122.4, 116.1, 62.0, 15.1, 14.1; HRMS (70 eV, *m/z*) Calcd for $C_{13}H_{11}NO_6$ 277.05864; Found 277.04955.

3.1.2.11. Methyl (2*E*)-2-(4-oxothieno[2,3-*c*]furan-6(4*H*)-ylidene)-propanoate (32). Yield: 29% (based on recovered starting material—see Table 2); light yellow viscous oil; IR (neat, υ_{max}): 3105, 2953, 2917, 2855, 1777, 1695, 1638, 1433, 1323, 1266, 1053 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, $J=5.19$ Hz, 1H), 7.32 (d, $J=5.19$ Hz, 1H), 3.89 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 160.6, 150.6, 149.0, 137.0, 120.8, 108.3, 52.3, 12.6; HRMS (ESI, *m/z*) Calcd for $C_{10}H_8NaO_4S$ $[M+Na]^+$247.0035; Found 247.0094.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2006.02.045. Spectra (^1H and ^{13}C NMR, and HRMS) of almost all compounds (unknown Baylis–Hillman adducts and phthalides) are available. For some compounds IR spectra is also available.

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