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Synthesis of Tetrahydrodibenzofuran and Tetrahydrophenanthridinone Skeletons by Intramolecular Nucleopalladation/Oxidative Heck Cascades

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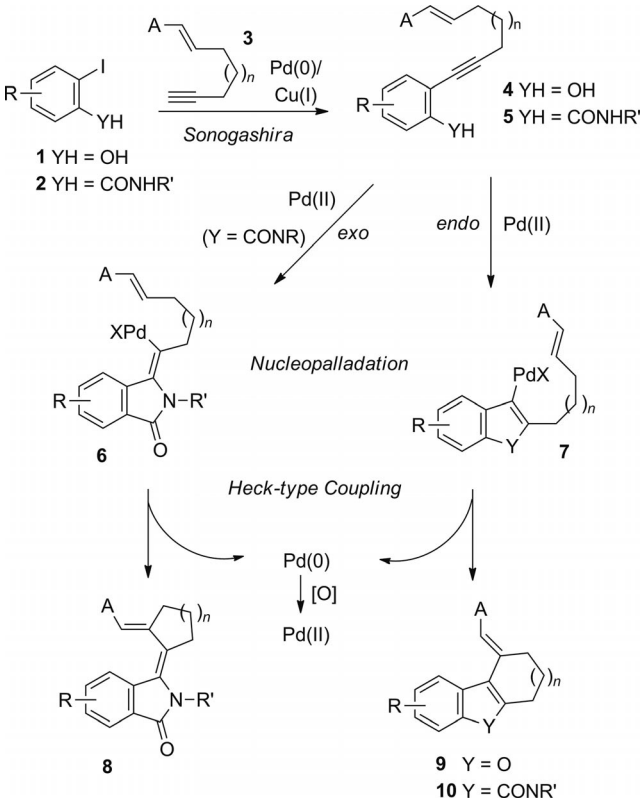
Functionalized alkylidene-1,2,3,4-tetrahydrodibenzo[*b*,*d*]-furans and -phenanthridin-6(5*H*)-ones have been synthesized regio- and stereoselectively from either *o*-iodophenols or -benzamides and alkynes by consecutive Pd-catalyzed Sonogashira coupling and nucleophilic addition/oxidative Heck-type coupling cascade reactions. In the case of iodobenzamide substrates, the whole sequence can be conveniently carried out without the isolation of intermediates. Maleic anhydride has been found to be useful as an additive in the Heck coupling step.

Introduction

Within the realm of rapidly expanding palladium-catalyzed oxidative coupling reactions,[1] a particular set of applications, those in which a heterocyclization step precedes a Heck-type coupling[2] in a cascade process, has attracted increasing attention because it offers the possibility of a rapid access to structurally diverse functionalized heterocyclic motifs.[3–14] An even higher level of complexity could be reached if the coupling step was an intramolecular reaction, yielding functionalized polycyclic structures. However, so far the application of this kind of strategy has been rare and examples are limited to 5-*exo*-amidopalladations of 2-allyl-[9,12,13] or 2-alkynylanilides[4] followed by a Heck-type reaction with a tethered alkene partner.[15] The extension of this strategy to a wider range of alkynes as electrophilic partners in combination with both N- and O-nucleophiles, as well as its application to the formation of six-membered heterocyclic structures, would be a valuable addition to the current synthetic repertoire. We have previously reported a Pd-catalyzed heterocyclization/oxidative Heck cascade process that leads to alkenyl-substituted benzofurans, indoles, and isoquinolones.[14,16] In this contribution we report the application of this methodology to cases in which the oxidative Heck coupling is performed intramolecularly, thus providing an additional fused ring in each instance. The reaction products contain substructures that have recently attracted attention because they are structurally related to natural products and other biologically interesting molecules.[17–19]

The underlying general synthetic idea is outlined in Scheme 1. After Sonogashira coupling between nucleo-



Scheme 1. General outline of the consecutive Sonogashira and oxidative intramolecular nucleopalladation/Heck coupling cascade.

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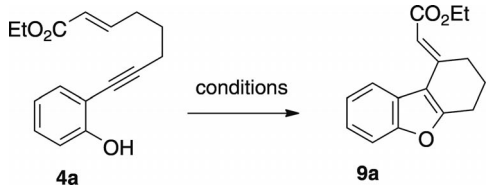
phile-containing aryl halides **1** or **2** and enynes **3**, the resulting 2-alkynylphenols **4** or -benzamides **5** (depending on the identity of the nucleophilic center Y = O or CONR, respectively) would be expected to undergo a palladium-catalyzed nucleopalladation/Heck-type coupling cascade to afford polycyclic products **8**–**10** stereoselectively. The oxidation of the Pd^0 released in the last step is needed to regenerate the catalytic PdX_2 species. Regiochemical variants are possible in the case of benzamides, for which the two possible modes of nucleopalladation, *exo* and *endo*, would lead to the corresponding isoindolone- (**8**) or phenanthridinone-type (**10**) structures, respectively. Similarly, depending on the size of the tether (*n*), *exo* and *endo* pathways could also compete in the Heck coupling reaction (only the *exo* product is shown).

Results and Discussion

The reaction conditions were briefly surveyed by using phenol **4a** derived from 2-iodophenol **1a** (R = H) and alkyne **3a** (*n* = 1; A = CO_2Et), and the results are collected in Table 1. The application of conditions analogous to those previously used in the corresponding intermolecular couplings[14] afforded a reasonable yield of the desired coupling product **9a** (entry 1). Interestingly, the use of maleic anhydride (MA) as additive in stoichiometric amounts produced a considerable improvement in yield (entry 2). However, the change from $PdCl_2$ to a phosphane-containing catalyst resulted in a diminished yield of **9a** (entry 3). A control experiment at 80 °C (entry 4) showed that higher temperatures were indeed needed. Accordingly, the conditions of entry 2 were taken as standard for subsequent reactions.

Table 1. Optimization of the reaction conditions for phenol **4a**.



4a **9a**

Entry	Conditions[a]	Yield[b] [%]
1	$PdCl_2$, KI, DMF, 100 °C, air	55
2	$PdCl_2$, KI, MA, DMF, 100 °C, air	91
3	$[PdCl_2(PPh_3)_2]$, KI, MA, DMF, 100 °C, air	45
4	$PdCl_2$, KI, MA, DMF, 80 °C, air	–[c]

[a] Relative amounts of reagents: Pd catalyst (5 mol-%), KI (0.5 mol-equiv.), MA (1 mol-equiv.), DMF (4×10^{-2} M), 20 h. MA = maleic anhydride. [b] Yield of the isolated product. [c] Starting material was recovered.

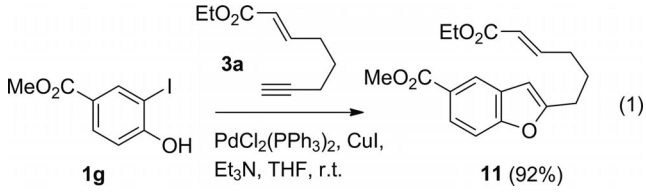
The optimized conditions were then applied to various alkynylphenols (Table 2). In this manner, tetrahydrodibenzo[*b*,*d*]furans **9** were formed efficiently from alkynylphenols **4** containing a tethered α,β-unsaturated ester or ketone. Electron-donating groups on the phenol moiety were well tolerated and this enabled the preparation of methoxy-substituted tetrahydrodibenzo[*b*,*d*]furans **9d** and **9e** (entries 4 and 5, respectively), which contain a substructure present in the tricyclic core of JBIR-23 and JBIR-24, two natural products with cytotoxic activity.[20] However, the use of an electron-withdrawing group (R^1 = CO_2Me), effective in analogous intermolecular reactions,[14] was hampered in this case by the apparent high tendency of substrate **4** (R^1 = CO_2Me; R^2 = R^3 = H; R^4 = CO_2Et) to cycloisomerize under the Sonogashira conditions that presumably had led to its formation [Equation (1)]. On the other hand, other tether lengths did not prove useful. For example, starting from Sonogashira adduct **4** with a homologated tether (*n* = 2; R = H; A = CO_2Et, in Scheme 1), a mixture of *endo*/*exo* Heck regioisomers was formed. Attempts to form other fused ring sizes led to either the recovery of the starting phenol (*n* = 0) or decomposition products (*n* = 3).

Table 2. Preparation of alkylidenetetrahydrodibenzo[*b*,*d*]furans.[a]

4a–f **9a–f**

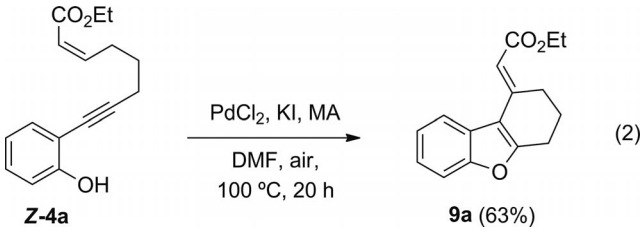
Entry	**4**	R^1, R^2, R^3, R^4	**9**, Yield [%]
1	**4a**	H, H, H, CO_2Et	**9a**, 91
2	**4b**	*t*Bu, H, *t*Bu, CO_2Et	**9b**, 62
3	**4c**	H, H, H, COMe	**9c**, 72
4	**4d**	OMe, H, H, CO_2Et	**9d**, 62[c]
5[b]	**4e**	OMe, H, H, COMe	**9e**, 60[c]
6	**4f**	H, OMe, H, CO_2Et	**9f**, 53[c]

[a] Unless otherwise indicated, the conditions of entry 2 in Table 1 were employed. [b] Reaction performed at 140 °C with 10 mol-% $PdCl_2$.



1g **11** (92%) (1)

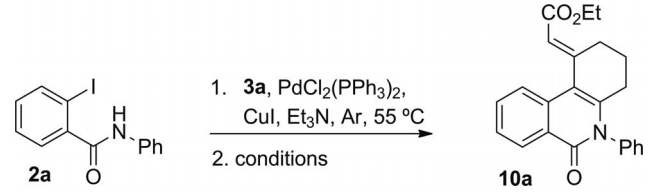
Alkene (*Z*)-**4a** with a *Z* double bond was also incorporated into the study to determine the effect of double-bond geometry on reactivity. As shown in Equation (2), **9a** was formed in 63% yield under the standard conditions. Therefore the same product is obtained irrespective of the geometry (*E* or *Z*) of the double bond. Presumably, hydropalladation/dehydropalladation equilibria intervene to isomerize the expected initial *Z* double bond geometry to the final more stable *E* configuration of the observed product **9a**.[21,22]



This methodology was also applied to benzamides. It was noted that in analogous intermolecular reactions of these substrates, $[PdCl_2(PPh_3)_2]$ was the universally employed catalyst and was also used in the Sonogashira couplings leading to the required starting materials. Therefore the possibility of performing the sequential Sonogashira/heterocyclization/intramolecular Heck transformation without isolation of the intermediates was considered. We explored this idea with representative 2-iodobenzamide **2a** and alkyne **3a** (Table 3). Initially we attempted to perform the Sonogashira reaction in DMF as this was the solvent used in the subsequent Heck coupling. However, this led to a sluggish reaction at 55 °C and degradation at 80 °C. Thus, as an alternative, we used the standard conditions for the Sonogashira coupling reactions of benzamides in an amine solvent.[14] When complete consumption of the starting iodobenzamide **2a** and formation of the Sonogashira coupling product **5a** (Scheme 1; R = H; R′ = Ph; *n* = 1; A = CO_2-Et)[23] were observed by TLC, maleic anhydride and air were introduced into the system and the mixture was heated at 80 °C. The expected tetrahydrophenanthridinone **10a** was obtained, albeit in moderate yield (47%, entry 1, Table 3). Small amounts of what appeared to be other regioisomers were also observed in the crude ^{1}H NMR spectrum. Replacement of Et_3N by DMF in the second stage of the reaction led to a significant improvement in the yield of **10a** (60%) and a reduction in the amounts of byproducts (entry 2). To check the effect of Et_3N on the Heck coupling reaction, we performed an experiment in which 5 equiv. of Et_3N were added at the same stage (entry 3). This confirmed the negative impact of the presence of Et_3N on the aminopalladation/Heck cascade as **10a** was obtained in only 22% yield. In line with the results obtained in the benzofuran series, omitting the use of maleic anhydride under otherwise identical conditions again resulted in inferior results (entry 4). However, use of the analogous ethyl acrylate was not successful either (entry 5), yielding a very similar result to that obtained in the absence of additives (entry 4), which suggests that this alkene has no effect on the coupling reaction. Recent reports on copper-catalyzed coupling reactions involving benzamide nucleophiles and alkynes,[24] as well as other nucleophiles and coupling agents,[25,26] prompted us to consider the possibility that the presence of Cu salts (left over from the Sonogashira reaction) could be partially responsible for the formation of the byproducts in these reactions. Accordingly, catechol was introduced as a possible Cu trap[27] (entry 6). In fact, this led to a cleaner reaction and a more efficient formation of **10a**, which was isolated in a very respectable 70% yield. As a result, the conditions of entry 6 were used as standard in subsequent applications.

The results of the application of the reaction conditions of entry 6 to different 2-iodobenzamides **2a**–**f** and enyne **3a** are collected in Table 4. In common with phenol substrates, substitution on the benzamide ring is also well tolerated (entry 2). In addition, the benzamides offer the possibility of substitution at the nitrogen as a means of structure diversification. This is highlighted by entries 3–6, in which substrates derived from anilines with substituents of different electronic character all participate effectively (entries 3–5) and alkyl substitution at the N atom is seen to be equally effective (entry 6). As pointed out earlier, the issue of regiochemical control is always a concern with benzamide substrates as the two possible cyclization modes, 5-*exo* and 6-*endo*, have previously been reported for 2-alkynylbenzamides under Pd-catalyzed conditions.[28–30] However, in line with observations made in the corresponding intermolecular cases, these benzamides display a remarkable prefer-

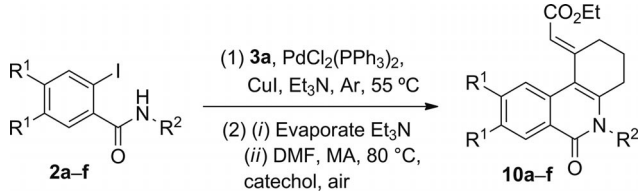
Table 3. Survey of reaction conditions for consecutive Sonogashira/aminocyclization/intramolecular Heck coupling cascade of benzamide **2a**.[a]



Entry	Conditions for step 2	Yield [%]
1[b]	MA, air, 80 °C	47
2	(i) Evaporate Et_3N; (ii) MA, DMF, air, 80 °C	60
3	(i) Evaporate Et_3N; (ii) Et_3N,[c] MA, DMF, air, 80 °C	22
4[b]	(i) Evaporate Et_3N; (ii) DMF, air, 80 °C	37
5[b]	(i) Evaporate Et_3N; (ii) ethyl acrylate,[d] DMF, air, 80 °C	37
6	(i) Evaporate Et_3N; (ii) MA, DMF, catechol, air, 80 °C	70

[a] Relative amounts of reagents: $[PdCl_2(PPh_3)_2]$ (5 mol-%), CuI (1 mol-%), Et_3N, 55 °C, MA (1 mol-equiv.), catechol (2 mol-%). [b] Yield in the crude as determined by ^{1}H NMR using (3,4-dimethoxyphenyl)acetonitrile as internal standard. [c] 5 mol-equiv. of Et_3N were used. [d] 1 mol-equiv. of ethyl acrylate was used.

Table 4. Preparation of 1,2,3,4-tetrahydrophenanthridin-6(5*H*)-ones.

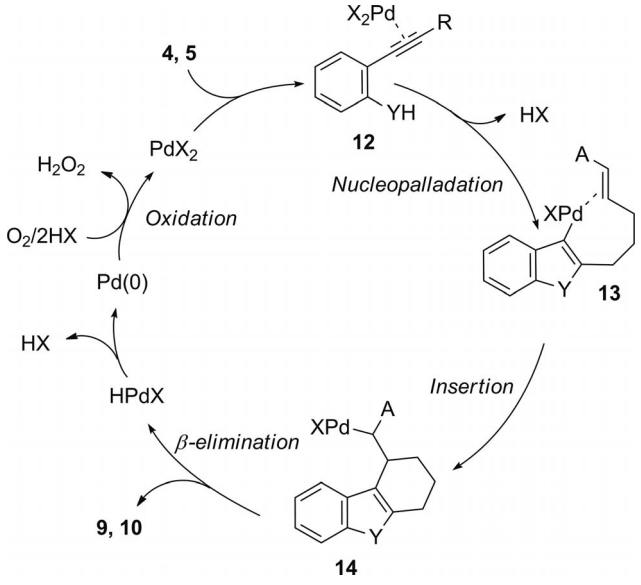


Entry	**2**	R^1	R^2	**10**, Yield [%]
1	**2a**	H	Ph	**10a**, 70
2	**2b**	OMe	Ph	**10b**, 56
3	**2c**	H	pMeOC_6H_4	**10c**, 49
4	**2d**	H	pMeC_6H_4	**10d**, 76
5	**2e**	H	pClC_6H_4	**10e**, 66
6	**2f**	H	*n*Bu	**10f**, 67

ence for the 6-*endo* mode in the initial intramolecular addition of the amide N onto the triple bond, and this leads to the predominant formation of tetrahydrophenanthridin-6(5*H*)-ones **10a**–**f** rather than the alternative regioisomeric isoindolones **8** (Scheme 1). As a result, a convenient two-step sequential protocol becomes available for the regioselective preparation of phenanthridinones, directly from iodobenzamides, without isolation of intermediates.

Inspection of Table 2 and Table 4 reveals that for the heterocyclization/Heck cascade process (either with or without isolation of the Sonogashira product) very similar reaction conditions, with minor adjustments in catalyst and temperature, are suitable for phenol and benzamide nucleophiles, despite significant differences in acidity.[31] One apparent difference between the two sets of conditions is the absence of KI when the oxidative coupling reaction is performed without isolation of the Sonogashira adduct. However, in this case, the Et_3NHI byproduct formed upon Sonogashira coupling probably plays the same role, which could be related to the participation of iodide anions in the reoxidation of Pd^0 (Scheme 1), as previously noted.[14]

A reasonable mechanism for the cascade oxidative process involving nucleopalladation, insertion, and β-elimination steps is given in Scheme 2. Oxidation of the Pd^0 eventually released upon formation of products **9** or **10** would then regenerate the catalytic PdX_2 species.



Scheme 2. Mechanism proposed for the formation of products **9** and **10**.

A beneficial effect of maleic anhydride on the coupling reaction was observed with both types of substrates, phenol and benzamide. This effect could be related to the stabilization of palladium species at different stages of the reaction, as previously documented for the related dba ligand.[32] In addition, as a π-acidic ligand, it could provide a more efficient Pd^{II} promoter for nucleophilic attack on the intermediate alkyne–Pd complex **12**, thereby accelerating the initial intramolecular nucleopalladation (Scheme 2). This type of role has previously been suggested for the same ligand in oxidative indole–alkene coupling reactions.[33] Alternatively, as has been observed for benzoquinone ligands, maleic anhydride could conceivably stabilize Pd^0, eventually formed upon β-elimination, as well as facilitate its reoxidation to Pd^{II}, thus preventing precipitation of "Pd black" and the subsequent interruption of the catalytic cycle.[34] Whatever the origin of the effect, these and related[33] results suggest the possibility of a more general use of maleic anhydride as a useful additive in oxidative coupling reactions.

Conclusions

We have developed a straightforward approach to tetrahydrodibenzofurans and -phenanthridinones that is based on consecutive Pd-catalyzed Sonogashira/nucleopalladation/oxidative intramolecular Heck sequences, the last two reactions in tandem, starting from *o*-iodophenols and -benzamides (without isolation of the intermediate alkynes in the latter case). An intriguing beneficial role of maleic anhydride in the Heck reaction has been discovered that merits further investigation. Given that structural diversification is feasible by the appropriate selection of the starting components, the rapid construction of these heterocyclic scaffolds will also be of interest in Medicinal Chemistry.

Experimental Section

General: See refs.[10,11] for general details. In addition, COSY, NOE, HSQC, and HMBC data were recorded to enable interpretation of the NOE data and to establish the structure of phenanthridinones **10**. Iodoamides **2a**–**f** were prepared from the corresponding acids according to a literature procedure,[35] but by using toluene in place of benzene. Compounds **2a**,[36] **2c**,[36] **2d**,[29] **2e**,[37] and **2f**[38] were characterized by comparison with literature data.

2-Iodo-4,5-dimethoxy-*N*-phenylbenzamide (2b): Yield: 99%; m.p. 164–166 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.66–7.63 (m, 3 H), 7.38 (t, J = 7.8 Hz, 2 H), 7.25 (s, 1 H), 7.17 (t, J = 7.4 Hz, 1 H), 7.11 (s, 1 H), 3.87 and 3.83 (2 s, 6 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 166.8 (s), 150.6 (s), 149.1 (s), 137.6 (s), 134.2 (s), 129.0 (d), 124.7 (d), 121.9 (d), 119.9 (d), 111.9 (d), 81.0 (s), 56.2 (q), 56.0 (q) ppm. IR (film): $\tilde{\nu}$ = 3277 (m, NH), 1655 (s, C=O) cm^{-1}. MS (EI): m/z (%) = 383 (8) $[M]^+$. HRMS: calcd. for $C_{15}H_{14}INO_3$ 383.0018; found 383.0017.

Ethyl (*E*)-Oct-2-en-7-ynoate (3a):[39] A solution of 5-hexyn-1-ol (4.06 g, 41.4 mmol) in CH_2Cl_2 (2.0 mL) was added dropwise to a suspension of pyridinium chlorochromate (PCC; 13.4 g, 62.1 mmol) and Celite® (13.5 g) in CH_2Cl_2 (83 mL), and the mixture was stirred at room temp. for 24 h. Ethyl (triphenylphosphoranylidene)acetate (24.5 g, 70.3 mmol) was then added and the reaction mixture was stirred at room temperature for 24 h. After the addition of Et_2O (150 mL), the reaction mixture was filtered through Celite® and the solids were washed with hexanes/EtOAc (9:1, 500 mL). The filtrate and washings were combined, the solvent was removed, and the residue was purified by flash chromatography (silica gel, 98:2 hexanes/EtOAc) to afford **3a** (4.65 g, 68%) as a colorless liquid, the spectral properties of which were in good agreement with those reported in the literature for the same compound.[39]

(*E*)-Non-3-en-8-yn-2-one (3b): Hex-4-yn-1-ol (0.360 g, 3.67 mmol) was added to a mixture of PCC (1.19 g, 5.50 mmol) and Celite® (3.60 g) in CH_2Cl_2 (31 mL). After stirring for 24 h at 25 °C, the resulting mixture was filtered through Celite®, the solids were washed with CH_2Cl_2, and the solvent (filtrate and washings) was evaporated. The residue was dissolved in CH_2Cl_2 (10 mL), 1-triphenylphosphoranylidene-2-propanone (1.98 g, 6.24 mmol) was added, and the mixture was stirred for 5 h at 37 °C. The solvent was evaporated and the residue was purified by column chromatography (silica gel, 80:20 hexane/EtOAc) to afford 0.254 g (50% for two steps) of **3b** as a colorless oil. ^{1}H NMR (400.16 MHz, $CDCl_3$): δ = 6.76 (dt, J = 15.9, 6.9 Hz, 1 H), 6.08 (dt, J = 15.9, 1.5 Hz, 1 H), 2.4–2.3 (m, 2 H), 2.3–2.2 (m, 2 H), 2.21 (s, 3 H), 1.95 (t, J = 2.6 Hz, 1 H), 1.68 (q, J = 7.1 Hz, 2 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 198.8 (s), 147.2 (d), 141.4 (d), 83.6 (s), 68.3 (d), 31.6 (t), 27.2 (q), 26.9 (t), 18.1 (t) ppm. IR (NaCl): $\tilde{\nu}$ = 3294 (w, C≡H), 2215 (w, C≡C), 1674 (s, C=O) cm^{-1}. MS (EI): *m*/*z* (%) = 135 (18) [M – 1]$^+$. HRMS (EI): calcd. for $C_9H_{11}O$ [M – 1]$^+$ 135.0816; found 135.0810.

Sonogashira Coupling Reactions with Iodophenols 1

Procedure A: A solution of **1**, $[PdCl_2(PPh_3)_2]$ (5 mol-%), CuI (4 mol-%), **3** (2 mol equiv.), and Et_3N (2 mol equiv.) in DMF (5 mL/mmol) was stirred at 25 °C for 19 h under Ar. A saturated NH_4Cl solution was added and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography (silica gel, hexane/EtOAc) to afford **4**.

Procedure B: The same as for procedure A using $[PdCl_2(PPh_3)_2]$ (4 mol-%), CuI (13 mol-%), **3** (1.2 mol-equiv.), and Et_3N (2 mol-equiv.) in THF (3 mL/mmol).

Procedure C: A solution of **1**, Et_3N (2 mol-equiv.), $[PdCl_2(PPh_3)_2]$ (3.5 mol-%), and CuI (4 mol-%) in DMF (8 mL/mmol) was stirred for 20 min at 25 °C under Ar before the addition of **3** (1.2 mol-equiv.). The reaction mixture was stirred for 24 h at 25 °C, and then it was poured into H_2O and extracted with EtOAc. Subsequently, procedure A was followed.

Ethyl (*E*)-8-(2-Hydroxyphenyl)oct-2-en-7-ynoate (4a): Procedure A was followed starting with 2-iodophenol and **3a** to afford **4a** (97%). Yellowish oil. ^{1}H NMR (400.16 MHz, $CDCl_3$): δ = 7.29 (dd, J = 7.7, 1.3 Hz, 1 H), 7.19 (t, J = 8.2 Hz, 1 H), 6.96 (dt, J = 15.6, 6.9 Hz, 1 H), 6.91 (dd, J = 8.2, 0.8 Hz, 1 H), 6.85 (td, J = 8.2, 0.8 Hz, 1 H), 5.89 (d, J = 15.6 Hz, 1 H), 5.91 (s, 1 H), 4.20 (q, J = 7.1 Hz, 2 H), 2.52 (t, J = 7.0 Hz, 2 H), 2.39 (dd, J = 14.5, 7.2 Hz, 2 H), 1.9–1.7 (m, 2 H), 1.29 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 166.5 (s), 156.5 (s), 147.7 (d), 131.7 (d), 129.7 (d), 122.2 (d), 120.2 (d), 114.5 (d), 109.9 (s), 96.5 (s), 75.5 (s), 60.3 (t), 31.2 (t), 26.9 (t), 19.1 (t), 14.2 (q) ppm. IR (NaCl): $\tilde{\nu}$ = 3600–3100 (br, O–H), 2224 (w, C≡C), 1716 (s, C=O), 1653 (m, C=C) cm^{-1}. MS (EI): *m*/*z* (%) = 258 (17) [M]$^+$. HRMS (EI): calcd. for $C_{16}H_{18}O_3$, 258.1256; found 258.1268.

Ethyl (*E*)-8-(3,5-Di-*tert*-butyl-2-hydroxyphenyl)oct-2-en-7-ynoate (4b): Procedure B was followed starting with 2,4-di-*tert*-butyl-6-iodophenol[40] and **3a** to afford **4b** (98%). Colorless oil. ^{1}H NMR (400.16 MHz, $CDCl_3$): δ = 7.25 (d, J = 2.4 Hz, 1 H), 7.17 (d, J = 2.3 Hz, 1 H), 6.98 (dt, J = 15.7, 6.9 Hz, 1 H), 6.00 (s, 1 H), 5.89 (dt, J = 15.7, 1.5 Hz, 1 H), 4.13 (q, J = 7.1 Hz, 2 H), 2.53 (t, J = 7.0 Hz, 2 H), 2.4–2.3 (m, 2 H), 1.8–1.7 (m, 2 H), 1.40 (s, 9 H), 1.29 (t, J = 7.1 Hz, 3 H), 1.28 (s, 9 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 166.3 (s), 153.0 (s), 147.7 (d), 141.8 (s), 134.6 (s), 125.8 (d), 124.5 (d), 122.3 (d), 109.8 (s), 96.0 (s), 76.5 (s), 60.2 (t), 34.9 (s), 34.2 (s), 31.6 (q, 3×), 31.2 (t), 29.5 (q, 3×), 27.2 (t), 19.1 (t), 14.3 (q) ppm. IR (NaCl): $\tilde{\nu}$ = 3600–3100 (br, O–H), 1719 (s, C=O) cm^{-1}. MS (EI): *m*/*z* (%) = 370 (26) [M]$^+$. HRMS (EI): calcd. for $C_{24}H_{34}O_3$ 370.2508; found 370.2511.

(*E*)-9-(2-Hydroxyphenyl)non-3-en-8-yn-2-one (4c): Procedure B was followed starting with 2-iodophenol and **3b** to afford **4c** (80%). Brown oil. ^{1}H NMR (400.16 MHz, $CDCl_3$): δ = 7.29 (dd, J = 7.7, 1.6 Hz, 1 H), 7.2–7.1 (m, 1 H), 6.93 (dd, J = 8.2, 0.8 Hz, 1 H), 6.9–6.7 (m, 2 H), 6.14 (dt, J = 15.9, 1.5 Hz, 1 H), 5.77 (br., 1 H), 2.54 (t, J = 7.0 Hz, 2 H), 2.5–2.4 (m, 2 H), 2.25 (s, 3 H), 1.9–1.8 (m, 2 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 198.6 (s), 156.6 (s), 146.9 (d), 131.7 (d, 2×), 129.7 (d), 119.9 (d), 114.5 (d), 109.9 (s), 95.9 (s), 75.7 (s), 31.3 (t), 26.9 (t), 26.8 (q), 19.0 (t) ppm. IR (NaCl): $\tilde{\nu}$ = 3600–3100 (br, O–H), 1672 (s, C=O) cm^{-1}. MS (EI): *m*/*z* (%) = 228 (33) [M]$^+$. HRMS (EI): calcd. for $C_{15}H_{16}O_2$ 228.1150; found 228.1153.

Ethyl (*E*)-8-(2-Hydroxy-5-methoxyphenyl)oct-2-en-7-ynoate (4d): Procedure C was followed starting with 2-iodo-4-methoxyphenol[41] and **3a** to afford **4d** (96%). Yellow oil. ^{1}H NMR (400.16 MHz, $CDCl_3$): δ = 6.96 (dt, J = 15.5, 7.0 Hz, 1 H), 6.9–6.7 (m, 3 H), 5.87 (d, J = 15.6 Hz, 1 H), 5.56 (br., 1 H), 4.18 (q, J = 7.1 Hz, 2 H), 3.73 (s, 3 H), 2.50 (t, J = 7.0 Hz, 2 H), 2.37 (q, J = 7.2 Hz, 2 H), 1.79 (q, J = 7.2 Hz, 2 H), 1.27 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 166.6 (s), 152.9 (s), 150.9 (s), 148.2 (d), 122.2 (d), 116.6 (d), 115.6 (d), 115.3 (d), 110.1 (s), 96.3 (s), 75.7 (s), 60.3 (t), 55.8 (q), 31.2 (t), 27.0 (t), 19.1 (t), 14.3 (q) ppm. IR (NaCl): $\tilde{\nu}$ = 3600–3100 (br, OH), 1715 (s, C=O) cm^{-1}. MS (EI): *m*/*z* (%) = 288 (40) [M]$^+$. HRMS (EI): calcd. for $C_{17}H_{20}O_4$ 288.1372; found 288.1362.

(*E*)-9-(2-Hydroxy-5-methoxyphenyl)non-3-en-8-yn-2-one (4e): Procedure C was followed starting with 2-iodo-4-methoxyphenol[41] and **3b** to afford **4e** (81%). Yellow oil. ^{1}H NMR (400.16 MHz, $CDCl_3$): δ = 6.8–6.7 (m, 4 H), 6.14 (d, J = 16.0 Hz, 1 H), 5.43 (br., 1 H), 3.74 (s, 3 H), 2.53 (t, J = 7.0 Hz, 2 H), 2.41 (q, J = 7.4 Hz, 2 H), 2.25 (s, 3 H), 1.82 (quint., J = 7.2 Hz, 2 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 198.7 (s), 152.9 (s), 151.0 (s), 147.1 (d), 147.0 (d), 131.8 (d), 116.5 (d), 115.8 (d), 110.1 (s), 95.9 (s), 66.1 (s), 55.8 (q), 31.5 (t), 27.0 (t), 26.9 (q), 19.1 (t) ppm. IR (NaCl): $\tilde{\nu}$ = 3600–3100 (br, OH), 1671 (s, C=O) cm^{-1}. MS (EI): *m*/*z* (%) = 258 (34) [M]$^+$. HRMS (EI): calcd. for $C_{16}H_{18}O_3$ 258.1256; found 258.1262.

Ethyl (*E*)-8-(2-Hydroxy-4-methoxyphenyl)oct-2-en-7-ynoate (4f): Procedure B was followed starting with 2-iodo-5-methoxyphenyl acetate[42] (50 mg, 0.17 mmol) and **3a** (57 mg, 0.34 mmol) in DMF and by heating at 50 °C for 17 h. The purified product (54 mg) was treated with K_2CO_3 (40 mg, 0.28 mmol) in EtOH (12 mL) to afford **4f** (37 mg, 75% for two steps). ^{1}H NMR (400.16 MHz, $CDCl_3$): δ = 7.18 (d, J = 8.6 Hz, 1 H), 6.96 (dt, J = 15.6, 7.0 Hz, 1 H), 6.48 (d, J = 2.5 Hz, 1 H), 6.41 (dd, J = 8.6, 2.5 Hz, 1 H), 5.85 (dt, J = 15.6, 1.5 Hz, 1 H), 5.76 (s, 1 H, OH), 4.18 (q, J = 7.1 Hz, 2 H), 3.76 (s, 3 H), 2.49 (t, J = 7.0 Hz, 2 H), 2.36 (qd, J = 7.5, 1.4 Hz, 2 H), 1.77 (quint., J = 7.2 Hz, 2 H), 1.28 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 166.6 (s), 161.0 (s), 157.9 (s), 147.9 (d), 132.3 (d), 122.2 (d), 107.0 (d), 102.4 (s), 100.0 (d), 95.1 (s), 75.3 (s), 60.3 (t), 55.4 (q), 31.2 (t), 27.1 (t), 19.1 (t), 14.3 (q) ppm. IR (NaCl): $\tilde{\nu}$ = 1716 (s, C=O) cm^{-1}. MS (EI): *m*/*z* (%) = 288 (31) [M]$^+$. HRMS (EI): calcd. for $C_{17}H_{20}O_4$ 288.1362; found 288.1360.

Ethyl (*Z*)-8-(2-Hydroxyphenyl)oct-2-en-7-ynoate (*Z*-4a): Procedure B was followed starting with 2-iodophenol and ethyl (*Z*)-oct-2-en-7-ynoate[43] to afford (*Z*)-**4a** (80%). Colorless oil. ^{1}H NMR (400.16 MHz, $CDCl_3$): δ = 7.29 (dd, J = 7.7, 1.5 Hz, 1 H), 7.19 (t, J = 7.1 Hz, 1 H), 6.92 (d, J = 8.2 Hz, 1 H), 6.83 (t, J = 7.5 Hz, 1

H), 6.82 (dt, J = 11.6, 7.7 Hz, 1 H), 5.84 (d, J = 11.6 Hz, 1 H), 4.18 (q, J = 7.1 Hz, 2 H), 2.86 (q, J = 7.7 Hz, 2 H), 2.51 (t, J = 6.9 Hz, 2 H), 1.79 (quint., J = 7.1 Hz, 2 H), 1.28 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 166.4 (s), 156.8 (s), 148.9 (d), 131.7 (d), 129.5 (d), 120.8 (d), 119.9 (d), 114.7 (d), 110.1 (s), 98.7 (s), 75.2 (s), 60.0 (t), 27.8 (t), 27.7 (t), 19.0 (t), 14.1 (q) ppm. IR (NaCl): $\tilde{\nu}$ = 3600–3100 (br, O–H), 1714 (s, C=O) cm^{-1}. MS (EI): m/z (%) = 258 (8) [M]$^+$. HRMS (EI): calcd. for $C_{16}H_{17}O_3$ [M – 1]$^+$ 257.1178; found 257.1179.

Methyl (*E*)-2-[5-(Ethoxycarbonyl)pent-4-en-1-yl]benzofuran-5-carboxylate (11): Procedure B was followed starting with methyl 4-hydroxy-3-iodobenzoate and **3a** using DMF instead of THF to afford **11** (92%). Yellow oil. ^{1}H NMR (400.16 MHz, $CDCl_3$): δ = 8.22 (d, J = 1.7 Hz, 1 H), 7.95 (dd, J = 8.6, 1.7 Hz, 1 H), 7.42 (d, J = 8.6 Hz, 1 H), 6.97 (td, J = 15.6, 6.9 Hz, 1 H), 6.46 (s, 1 H), 5.86 (d, J = 15.6 Hz, 1 H), 4.18 (q, J = 7.1 Hz, 2 H), 3.93 (s, 3 H), 2.82 (t, J = 7.5 Hz, 2 H), 2.3–2.2 (m, 2 H), 1.94 (q, J = 7.5 Hz, 2 H), 1.29 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 167.4 (s), 166.5 (s), 159.9 (s), 157.2 (s), 147.7 (d), 128.7 (s), 125.1 (d), 124.7 (s), 122.6 (d), 122.0 (d), 110.5 (d), 102.6 (d), 60.1 (t), 51.9 (q), 31.3 (t), 27.6 (t), 25.7 (t), 14.2 (q) ppm. IR (NaCl): $\tilde{\nu}$ = 1719 (s, C=O), 1654 (s, C=O) cm^{-1}. MS (EI): m/z (%) = 285 (17). HRMS (EI): calcd. for $C_{18}H_{20}O_5$ 316.1312; found 316.1311.

Representative Procedure for Pd-Catalyzed Oxidative Cyclization Cascades: $PdCl_2$ (0.001 g, 0.004 mmol), KI (0.006 g, 0.040 mmol), and maleic anhydride (0.007 g, 0.080 mmol) was added to a solution of phenol **4** (0.080 mmol) in DMF (2 mL) and the mixture was stirred at 100 °C for 20 h. After allowing the mixture to cool to 25 °C, water was added. The mixture was extracted with EtOAc, the combined organic layers were dried (Na_2SO_4), and the solvent was removed. The product **9** was purified by column chromatography (silica gel, hexane/EtOAc).

Ethyl (*E*)-2-[3,4-Dihydrodibenzo[*b*,*d*]furan-1(2*H*)-ylidene]acetate (9a): White solid; m.p. 65 °C (hexane/EtOAc). ^{1}H NMR (400.16 MHz, $CDCl_3$): δ = 7.9–7.8 (m, 1 H), 7.47 (dd, J = 6.1, 3.1 Hz, 1 H), 7.4–7.2 (m, 2 H), 6.37 (s, 1 H), 4.24 (q, J = 7.1 Hz, 2 H), 3.3–3.2 (m, 2 H), 2.91 (t, J = 6.3 Hz, 2 H), 2.1–2.0 (m, 2 H), 1.35 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 167.3 (s), 161.7 (s), 154.7 (s), 150.6 (s), 124.9 (s), 124.2 (d), 123.5 (d), 120.6 (d), 114.3 (s), 111.4 (d), 110.7 (d), 59.7 (t), 26.6 (t), 24.0 (t), 22.7 (t), 14.4 (q) ppm. IR (NaCl): $\tilde{\nu}$ = 1707 (s, C=O), 1615 (s, C=C) cm^{-1}. MS (EI): m/z (%) = 256 (88) [M]$^+$. HRMS (EI): calcd. for $C_{16}H_{16}O_3$ 256.1099; found 256.1104.

Ethyl (*E*)-2-[6,8-Di-*tert*-butyl-3,4-dihydrodibenzo[*b*,*d*]furan-1(2*H*)-ylidene]acetate (9b): Yellow solid; m.p. 90 °C (hexane/EtOAc). ^{1}H NMR (400.16 MHz, $CDCl_3$): δ = 7.64 (d, J = 1.7 Hz, 1 H), 7.27 (d, J = 1.7 Hz, 1 H), 6.35 (s, 1 H), 4.25 (q, J = 7.1 Hz, 2 H), 3.3–3.2 (m, 2 H), 2.92 (t, J = 6.2 Hz, 2 H), 2.1–2.0 (m, 2 H), 1.51 (s, 9 H), 1.42 (s, 9 H), 1.40 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 167.5 (s), 160.9 (s), 151.2 (s), 151.0 (s), 146.3 (s), 133.7 (s), 125.0 (s), 118.9 (d), 114.7 (d), 113.9 (s), 110.3 (d), 59.6 (t), 35.0 (s), 34.5 (s), 31.9 (q, 3×), 29.9 (q, 3×), 26.9 (t), 24.2 (t), 22.9 (t), 14.5 (q) ppm. IR (NaCl): $\tilde{\nu}$ = 1712 (s, C=O), 1620 (s, C=C) cm^{-1}. MS (EI): m/z (%) = 368 (46) [M]$^+$. HRMS (EI): calcd. for $C_{24}H_{32}O_3$ 368.2351; found 368.2345.

(*E*)-1-[3,4-Dihydrodibenzo[*b*,*d*]furan-1(2*H*)-ylidene]propan-2-one (9c): White solid; m.p. 75 °C (hexane/EtOAc). ^{1}H NMR (400.16 MHz, $CDCl_3$): δ = 7.9–7.8 (m, 1 H), 7.6–7.5 (m, 1 H), 7.4–7.3 (m, 2 H), 6.77 (s, 1 H), 3.2–3.1 (m, 2 H), 2.90 (t, J = 6.3 Hz, 2 H), 2.34 (s, 3 H), 2.1–2.0 (m, 2 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 198.7 (s), 163.1 (s), 154.8 (s), 149.4 (s), 124.8 (s), 124.3 (d), 123.6 (d), 120.6 (d), 118.4 (d), 114.2 (s), 111.5 (d), 32.4 (q), 26.9 (t), 24.1 (t), 22.8 (t) ppm. IR (NaCl): $\tilde{\nu}$ = 1674 (s, C=O), 1590 (s) cm^{-1}. MS (EI): m/z (%) = 226 (70) [M]$^+$. HRMS (EI): calcd. for $C_{15}H_{14}O_2$ 226.0994; found 226.0994.

Ethyl (*E*)-2-[8-Methoxy-3,4-dihydrodibenzo[*b*,*d*]furan-1(2*H*)-ylidene]acetate (9d): White solid; m.p. 102 °C (hexane/EtOAc). ^{1}H NMR (400.16 MHz, $CDCl_3$): δ = 7.35 (d, J = 8.9 Hz, 1 H), 7.27 (d, J = 2.4 Hz, 1 H), 6.88 (dd, J = 8.9, 2.5 Hz, 1 H), 6.26 (s, 1 H), 4.22 (q, J = 7.1 Hz, 2 H), 3.89 (s, 3 H), 3.21 (dd, J = 8.9, 3.6 Hz, 2 H), 2.87 (t, J = 6.3 Hz, 2 H), 2.1–1.9 (m, 2 H), 1.34 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 167.3 (s), 162.6 (s), 156.5 (s), 150.6 (s), 149.7 (s), 125.5 (s), 114.4 (s), 111.6 (d), 111.4 (d), 110.5 (d), 104.9 (d), 59.7 (q), 56.2 (t), 26.7 (t), 24.2 (t), 22.7 (t), 14.5 (q) ppm. IR (NaCl): $\tilde{\nu}$ = 1708 (s, C=O), 1615 (s, C=C) cm^{-1}. MS (EI): m/z (%) = 286 (100) [M]$^+$. HRMS (EI): calcd. for $C_{17}H_{18}O_4$ 286.1205; found 286.1204.

(*E*)-1-[8-Methoxy-3,4-dihydrodibenzo[*b*,*d*]furan-1(2*H*)-ylidene]-propan-2-one (9e): Reaction temperature was 140 °C. Colorless solid; m.p. 119 °C (hexane/EtOAc). ^{1}H NMR (400.16 MHz, $CDCl_3$): δ = 7.35 (d, J = 8.9 Hz, 1 H), 7.25 (d, J = 2.5 Hz, 1 H), 6.87 (dd, J = 8.9, 2.5 Hz, 1 H), 6.65 (s, 1 H), 3.87 (s, 3 H), 3.2–3.1 (m, 2 H), 2.85 (t, J = 6.3 Hz, 2 H), 2.31 (s, 3 H), 2.04–1.95 (m, 2 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 198.8 (s), 164.2 (s), 156.6 (s), 149.9 (s), 149.7 (s), 125.7 (s), 118.3 (d), 114.4 (s), 111.8 (d), 111.1 (d), 105.5 (d), 56.4 (q), 32.6 (q), 27.2 (t), 24.4 (t), 22.9 (t) ppm. IR (NaCl): $\tilde{\nu}$ = 1672 (s, C=O), 1580 (s, C=C) cm^{-1}. MS (EI): m/z (%) = 256 (62) [M]$^+$. HRMS (EI): calcd. for $C_{16}H_{16}O_3$ 256.1100; found 256.1099.

Ethyl (*E*)-2-[7-Methoxy-3,4-dihydrodibenzo[*b*,*d*]furan-1(2*H*)-ylidene]-acetate (9f): White solid; m.p. 100–101 °C (Et_2O). ^{1}H NMR (400.16 MHz, $CDCl_3$): δ = 7.67 (d, J = 8.6 Hz, 1 H), 7.00 (d, J = 2.3 Hz, 1 H), 6.91 (dd, J = 8.6, 2.3 Hz, 1 H), 6.29 (s, 1 H), 4.22 (q, J = 7.1 Hz, 2 H), 3.85 (s, 3 H), 3.20 (t, J = 5.6 Hz, 2 H), 2.86 (t, J = 6.3 Hz, 2 H), 2.1–2.0 (quint., J = 6.3 Hz, 2 H), 1.33 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 167.3 (s), 160.9 (s), 157.6 (s), 155.8 (s), 150.7 (s), 120.8 (d), 118.2 (s), 114.2 (s), 111.6 (d), 110.4 (d), 96.5 (d), 59.7 (t), 55.7 (q), 26.6 (t), 24.0 (t), 22.8 (t), 14.5 (q) ppm. IR (NaCl): $\tilde{\nu}$ = 1706 (m, C=O), 1672 (s), 1580 (s, C=C) cm^{-1}. MS (EI): m/z (%) = 283 (64) [M]$^+$. HRMS (EI): calcd. for $C_{17}H_{18}O_4$ 286.1205; found 286.1205.

Representative Procedure for Consecutive Sonogashira/Oxidative Cascade Cyclization Reactions: $[PdCl_2(PPh_3)_2]$ (0.011 g, 0.015 mmol) and CuI (0.6 mg, 0.003 mmol) were added to a solution of amide **2** (0.310 mmol) and **3a** (0.062 g, 0.371 mmol) in Et_3N (2.6 mL). The resulting mixture was heated under Ar at 55 °C for 2.5 h and then Et_3N was removed in vacuo. Maleic anhydride (0.030 g, 0.309 mmol), 1,2-dihydroxybenzene (0.7 mg, 0.006 mmol), and DMF (2.6 mL) were added and the mixture was stirred at 80 °C for 3–6 h in air. After cooling to 25 °C, saturated $NaHCO_3$ was added and the mixture was extracted with EtOAc. The combined organic extracts were washed with water and dried with Na_2SO_4. The solvent was evaporated and the product **10** was purified by flash chromatography (silica gel saturated with Et_3N, hexanes/EtOAc/Et_3N).

Ethyl (*E*)-[6-Oxo-5-phenyl-3,4,5,6-tetrahydrophenanthridin-1(2*H*)-ylidene]acetate (10a): Yellowish solid; m.p. 100–101 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.40 (d, J = 8.0 Hz, 1 H), 7.80 (d, J = 7.9 Hz, 1 H), 7.6–7.5 (m, 1 H), 7.5–7.4 (m, 1 H), 7.4–7.3 (m, 2 H), 7.18 (d, J = 8.2 Hz, 2 H), 7.10 (t, J = 7.3 Hz, 1 H), 6.19 (s, 1 H), 4.21 (q, J = 7.1 Hz, 2 H), 3.15 (t, J = 6.4 Hz, 2 H), 2.50 (t, J = 6.5 Hz, 2 H), 2.0–1.9 (m, 2 H), 1.32 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 166.9 (s), 155.6 (s), 150.9 (s), 148.3 (s), 146.1 (s), 132.0 (d), 131.1 (s), 128.7 (d), 128.2 (d), 127.6 (d),

124.6 (s), 123.8 (d), 123.6 (d), 122.7 (d), 115.6 (d), 112.2 (s), 59.9 (t), 27.4 (t), 27.3 (t), 21.6 (t), 14.3 (q) ppm. IR (KBr): $\tilde{\nu}$ = 1709 (s, OC=O), 1654 (s, NC=O), 1590 (s, C=C) cm^{-1}. MS (EI): *m*/*z* (%) = 359 (63) $[M]^+$. HRMS: calcd. for $C_{23}H_{21}NO_3$ 359.1521; found 359.1525.

Ethyl (*E*)-[8,9-Dimethoxy-6-oxo-5-phenyl-3,4,5,6-tetrahydrophenanthridin-1(2*H*)-ylidene]acetate (10b): A mixture of Et_3N/THF (4:1.5; 10.5 mL/mmol) was used instead of Et_3N. Yellow solid; m.p. 171–173 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.84 (s, 1 H), 7.4–7.3 (m, 2 H), 7.25 (s, 1 H), 7.18 (d, *J* = 8.1 Hz, 2 H), 7.08 (t, *J* = 7.3 Hz, 1 H), 6.22 (s, 1 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 4.01 (s, 3 H), 3.95 (s, 3 H), 3.15 (t, *J* = 6.4 Hz, 2 H), 2.49 (t, *J* = 6.5 Hz, 2 H), 2.0–1.9 (m, 2 H), 1.30 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 166.9 (s), 154.7 (s), 152.4 (s), 151.6 (s), 148.8 (s), 148.4 (s), 146.4 (s), 128.6 (d, 2×), 125.6 (s), 123.4 (d), 122.7 (d, 2×), 117.6 (s), 115.1 (d), 111.9 (s), 109.0 (d), 105.6 (d), 59.8 (t), 56.2 (q), 56.0 (q), 27.3 (t), 27.1 (t), 21.6 (t), 14.3 (q) ppm. IR (KBr): $\tilde{\nu}$ = 1710 (s, OC=O), 1652 (s, NC=O), 1591 (s, C=C) cm^{-1}. MS (EI): *m*/*z* = 419 (base) $[M]^+$. HRMS: calcd. for $C_{25}H_{25}NO_5$ 419.1733; found 419.1731.

Ethyl (*E*)-[5-(4-Methoxyphenyl)-6-oxo-3,4,5,6-tetrahydrophenanthridin-1(2*H*)-ylidene]acetate (10c): Yellow solid; m.p. 129–131 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.39 (d, *J* = 8.0 Hz, 1 H), 7.78 (d, *J* = 8.1 Hz, 1 H), 7.6–7.5 (m, 1 H), 7.40 (t, *J* = 7.7 Hz, 1 H), 7.3–7.2 (m, 2 H), 6.9–6.8 (m, 2 H), 6.19 (s, 1 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 3.83 (s, 3 H), 3.17 (t, *J* = 6.5 Hz, 2 H), 2.55 (t, *J* = 6.5 Hz, 2 H), 2.0–1.9 (m, 2 H), 1.32 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 166.9 (s), 156.3 (s), 155.6 (s), 150.9 (s), 147.5 (s), 138.7 (s), 131.6 (d), 130.9 (s), 128.0 (d), 127.5 (d), 124.9 (s), 124.6 (d, 2×), 123.5 (d), 115.4 (d), 113.8 (d, 2×), 112.1 (s), 59.9 (t), 55.4 (q), 27.4 (t), 27.3 (t), 21.6 (t), 14.3 (q) ppm. IR (KBr): $\tilde{\nu}$ = 1710 (s, OC=O), 1653 (s, NC=O), 1506 (s, C=C) cm^{-1}. MS (EI): *m*/*z* = 389 (base) $[M]^+$. HRMS: calcd. for $C_{24}H_{23}NO_4$ 389.1627; found 389.1625.

Ethyl (*E*)-[6-Oxo-5-(*p*-tolyl)-3,4,5,6-tetrahydrophenanthridin-1(2*H*)-ylidene]acetate (10d): Yellow viscous oil. ^1H NMR [300 MHz, $(CD_3)_2CO$]: δ = 8.34 (d, *J* = 7.8 Hz, 1 H), 7.79 (d, *J* = 8.0 Hz, 1 H), 7.7–7.6 (m, 1 H), 7.44 (t, *J* = 7.5 Hz, 1 H), 7.14 (s, 4 H), 6.13 (s, 1 H), 4.16 (q, *J* = 7.1 Hz, 2 H), 3.14 (t, *J* = 6.4 Hz, 2 H), 2.52 (t, *J* = 6.5 Hz, 2 H), 2.30 (s, 3 H), 1.9–1.8 (m, 2 H), 1.26 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR [75.5 MHz, $(CD_3)_2CO$]: δ = 166.9 (s), 156.8 (s), 151.6 (s), 148.2 (s), 144.2 (s), 133.9 (s), 132.8 (d), 131.8 (s), 129.9 (d, 2×), 128.7 (d), 128.4 (d), 125.5 (s), 124.3 (d), 123.9 (d, 2×), 116.2 (d), 112.5 (s), 60.2 (t), 27.8 (t), 27.7 (t), 22.4 (t), 21.00 (q), 14.7 (q) ppm. IR (KBr): $\tilde{\nu}$ = 1711 (s, OC=O), 1655 (s, NC=O), 1602 (m, C=C) cm^{-1}. MS (EI): *m*/*z* (%) = 373 (90) $[M]^+$. HRMS: calcd. for $C_{24}H_{23}NO_3$ 373.1678; found 373.1683.

Ethyl (*E*)-[5-(4-Chlorophenyl)-6-oxo-3,4,5,6-tetrahydrophenanthridin-1(2*H*)-ylidene]acetate (10e): Yellow solid; m.p. 103–105 °C. ^1H NMR [300 MHz, $(CD_3)_2CO$]: δ = 8.35 (d, *J* = 7.8 Hz, 1 H), 7.84 (d, *J* = 8.2 Hz, 1 H), 7.7–7.6 (m, 1 H), 7.5–7.4 (m, 1 H), 7.34 (d, *J* = 8.7 Hz, 2 H), 7.24 (d, *J* = 8.7 Hz, 2 H), 6.15 (s, 1 H), 4.17 (q, *J* = 7.1 Hz, 2 H), 3.2–3.1 (m, 2 H), 2.55 (t, *J* = 6.5 Hz, 2 H), 2.0–1.9 (m, 2 H), 1.26 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR [75.5 MHz, $(CD_3)_2CO$]: δ = 166.9 (s), 156.6 (s), 151.4 (s), 149.5 (s), 146.0 (s), 133.3 (d), 132.0 (s), 129.4 (d, 2×), 129.2 (s), 128.9 (d), 128.6 (d), 125.5 (d, 2×), 125.1 (s), 124.4 (d), 116.5 (d), 112.8 (s), 60.3 (t), 27.8 (t), 27.7 (t), 22.4 (t), 14.7 (q) ppm. IR (KBr): $\tilde{\nu}$ = 1711 (s, OC=O), 1654 (s, NC=O), 1610 (m, C=C) cm^{-1}. MS (EI): *m*/*z* (%) = 395 (27) $[M]^+$. HRMS: calcd. for $C_{23}H_{20}{}^{35}ClNO_3$ 393.1132; found 393.1129; calcd. for $C_{23}H_{20}{}^{37}ClNO_3$ 395.1102; found 395.1108.

Ethyl (*E*)-[5-Butyl-6-oxo-3,4,5,6-tetrahydrophenanthridin-1(2*H*)-ylidene]acetate (10f): Yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.18 (dd, *J* = 7.9, 1.1 Hz, 1 H), 7.71 (d, *J* = 8.0 Hz, 1 H), 7.5–7.4 (m, 1 H), 7.3–7.2 (m, 1 H), 6.16 (s, 1 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 3.49 (t, *J* = 7.0 Hz, 2 H), 3.2–3.1 (m, 2 H), 2.56 (t, *J* = 6.5 Hz, 2 H), 2.0–1.9 (m, 2 H), 1.7–1.6 (m, 2 H), 1.5–1.4 (m, 2 H), 1.30 (t, *J* = 7.1 Hz, 3 H), 0.96 (t, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 167.1 (s), 155.9 (s), 151.3 (s), 148.6 (s), 131.0 (d), 130.3 (s), 127.3 (d, 2×), 125.1 (s), 123.5 (d), 114.9 (d), 111.5 (s), 59.8 (t), 46.0 (t), 32.9 (t), 27.5 (t, 2×), 21.6 (t), 20.7 (t), 14.3 (q), 14.0 (q) ppm. IR (KBr): $\tilde{\nu}$ = 1713 (s), 1668 (s), 1627 (m) cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{26}NO_3$ $[M + H]^+$ 340.1907; found 340.1902.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra for all new compounds.

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[1] For recent reviews, see: a) C. Liu, L. Q. Jin, A. W. Lei, *Synlett* **2010**, 2527–2536; b) J. Le Bras, J. Muzart, *Chem. Rev.* **2011**, *111*, 1170–1214; c) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215–1292; d) W. Shi, C. Liu, A. W. Lei, *Chem. Soc. Rev.* **2011**, *40*, 2761–2776.

[2] For reviews of the Heck reaction, see: a) S. Braese, A. de Meijere in *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: A. de Meijere, F. Diederich), 2nd ed., Wiley-VCH, Weinheim, Germany, **2004**, vol. 1, pp. 217–315; b) M. M. Heravi, A. Fazeli, *Heterocycles* **2010**, *81*, 1979–2026.

[3] M. F. Semmelhack, W. R. Epa, *Tetrahedron Lett.* **1993**, *34*, 7205–7208.

[4] A. Yasuhara, Y. Takeda, N. Suzuki, T. Sakamoto, *Chem. Pharm. Bull.* **2002**, *50*, 235–238.

[5] Q. H. Huang, R. C. Larock, *Tetrahedron Lett.* **2002**, *43*, 3557–3560.

[6] Q. Huang, R. C. Larock, *J. Org. Chem.* **2003**, *68*, 980–988.

[7] B. Alcaide, P. Almendros, R. Rodriguez-Acebes, *Chem. Eur. J.* **2005**, *11*, 5708–5712.

[8] L. F. Tietze, F. Stecker, J. Zinngrebe, K. M. Sommer, *Chem. Eur. J.* **2006**, *12*, 8770–8776.

[9] K.-T. Yip, M. Yang, K.-L. Law, N.-Y. Zhu, D. Yang, *J. Am. Chem. Soc.* **2006**, *128*, 3130–3131.

[10] J. M. Aurrecoechea, A. Durana, E. Pérez, *J. Org. Chem.* **2008**, *73*, 3650–3653.

[11] C. Martínez, R. Álvarez, J. M. Aurrecoechea, *Org. Lett.* **2009**, *11*, 1083–1086.

[12] K.-T. Yip, N.-Y. Zhu, D. Yang, *Org. Lett.* **2009**, *11*, 1911–1914.

[13] W. He, K.-T. Yip, N.-Y. Zhu, D. Yang, *Org. Lett.* **2009**, *11*, 5626–5628.

[14] R. Álvarez, C. Martínez, Y. Madich, J. G. Denis, J. M. Aurrecoechea, Á. R. de Lera, *Chem. Eur. J.* **2010**, *16*, 12746–12753.

[15] For a related cascade ending with reductive elimination in the absence of oxidants, see: D. M. Schultz, J. P. Wolfe, *Org. Lett.* **2010**, *12*, 1028–1031.

[16] For reviews dealing with palladium-catalyzed cascade reactions, see: a) ref.[11d]; b) E. A. Anderson, *Org. Biomol. Chem.* **2011**, *9*, 3997–4006; c) T. Vlaar, E. Ruijter, R. V. A. Orru, *Adv. Synth. Catal.* **2011**, *353*, 809–841.

[17] For a recent review on Pd-catalyzed synthesis of oxygen heterocycles, see: K. C. Majumdar, B. Chattopadhyay, P. K. Maji,

S. K. Chattopadhyay, S. Samanta, *Heterocycles* **2010**, *81*, 517–584.
[18] For recent reviews on the synthesis and biological activity of benzofurans, see: K.-S. Yeung, Z. Yang, X.-S. Peng, X.-L. Hou, in: *Progress in Heterocyclic Chemistry* (Eds.: G. W. Gribble, J. A. Joule), Elsevier, **2011**, vol. 22, pp. 181–216, and previous issues in the series.
[19] For recent synthetic efforts towards fused isoquinolone systems, see: a) G.-W. Wang, T.-T. Yuan, D.-D. Li, *Angew. Chem. Int. Ed.* **2011**, *50*, 1380–1383; b) B. Haffemayer, M. Gulias, M. J. Gaunt, *Chem. Sci.* **2011**, *2*, 312–315.
[20] K. Motohashi, J. H. Hwang, Y. Sekido, M. Takagi, K. Shinya, *Org. Lett.* **2009**, *11*, 285–288.
[21] Similar observations have previously been noted in related cases: see ref.[14], and references cited therein. See also: a) D. Gauthier, A. T. Lindhardt, E. P. K. Olsen, J. Overgaard, T. Skrydstrup, *J. Am. Chem. Soc.* **2010**, *132*, 7998–8009; b) E. W. Werner, K. B. Urkalan, M. S. Sigman, *Org. Lett.* **2010**, *12*, 2848–2851.
[22] B3LYP/6-31G* calculations (Spartan 04, v. 1.0.3, Wavefunction, Inc., **2005**) afford a difference in the gas phase of 7.4 kcal/mol in favor of **9a** relative to the alternative *Z* isomer.
[23] The formation of **5a** was confirmed by independent synthesis.
[24] M. Jithunsa, M. Ueda, O. Miyata, *Org. Lett.* **2011**, *13*, 518–521.
[25] J. Y. Lu, X. Y. Gong, H. J. Yang, H. Fu, *Chem. Commun.* **2010**, *46*, 4172–4174.
[26] S. Cacchi, G. Fabrizi, A. Goggiamani, *Org. Biomol. Chem.* **2011**, *9*, 641–652.
[27] Y. Kawamura, Y. Kawano, T. Matsuda, Y. Ishitobi, T. Hosokawa, *J. Org. Chem.* **2009**, *74*, 3048–3053.
[28] H. Sashida, A. Kawamukai, *Synthesis* **1999**, 1145–1148.
[29] N. G. Kundu, M. W. Khan, *Tetrahedron* **2000**, *56*, 4777–4792.
[30] H. Cao, L. McNamee, H. Alper, *Org. Lett.* **2008**, *10*, 5281–5284.
[31] For pK_a values in DMSO, see: http://www.chem.wisc.edu/areas/reich/pkatable/index.htm.
[32] I. J. S. Fairlamb, *Org. Biomol. Chem.* **2008**, *6*, 3645–3656.
[33] X. L. Han, X. Y. Lu, *Org. Lett.* **2009**, *11*, 2381–2384.
[34] N. Decharin, S. S. Stahl, *J. Am. Chem. Soc.* **2011**, *133*, 5732–5735.
[35] A. Beaume, C. Courillon, E. Derat, M. Malacria, *Chem. Eur. J.* **2008**, *14*, 1238–1252.
[36] S. Goswami, A. K. Adak, R. Mukherjee, S. Jana, S. Dey, J. F. Gallagher, *Tetrahedron* **2005**, *61*, 4289–4295.
[37] M. W. Khan, A. F. G. M. Reza, *Tetrahedron* **2005**, *61*, 11204–11210.
[38] K. Cherry, A. Duchene, J. Thibonnet, J.-L. Parrain, M. Abarbri, *Synthesis* **2005**, 2349–2356.
[39] M. Rodríguez-Rivero, J. C. Carretero, *J. Org. Chem.* **2003**, *68*, 2975–2978.
[40] E. Pérez-Santín, H. Khanwalkar, J. Voegel, C. Collette, P. Mauvais, H. Gronemeyer, A. R. de Lera, *ChemMedChem* **2009**, *4*, 780–791.
[41] M. Inoue, M. W. Carson, A. J. Frontier, S. J. Danishefsky, *J. Am. Chem. Soc.* **2001**, *123*, 1878–1889.
[42] H. Miao, Z. Yang, *Org. Lett.* **2000**, *2*, 1765–1768.
[43] R. J. Spandl, H. Rudyk, D. R. Spring, *Chem. Commun.* **2008**, 3001–3003.

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