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An unprecedented Pd-catalyzed carbonylative route to fused furo[3,4-*b*]indol-1-ones

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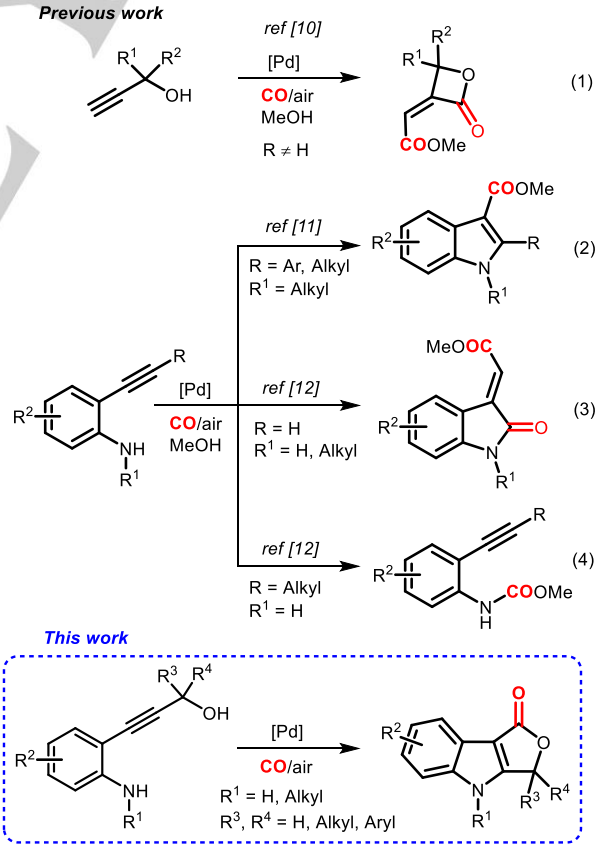
Abstract: A novel and efficient catalytic approach to functionalized furo[3,4-*b*]indol-1-ones is reported. It is based on a palladium-catalyzed sequential process involving an initial cyclization of 2-(hydroxypropyn-1-yl)anilines to form the indole moiety, followed by insertion of carbon monoxide and a second annulation step to build the lactone ring. In a single transformation, two fused heterocycles and three new bonds (C-N, C-C and C-O) are generated. The present methodology gives direct access to structurally complex molecules starting from readily available reagents.

Introduction

Over the years, the interest for indole chemistry has increased enormously due to its omnipresent motif in natural compounds, pharmaceuticals, agrochemicals and functional materials.[1] A plethora of variegated syntheses of the indolyl core have been consequently discovered and, among these, palladium-based methodologies play a leading role in this context.[2] Indole skeleton fused with an heterocycle ring originates a series of new interesting classes of polycyclic compounds displaying a wide range of improved properties.[3] In particular, indoles condensed with a 5-membered lactone ring, are also valuable synthetic intermediates for natural products, such as murrayaquinone A or clausevatine D.[4] Unfortunately, the sporadic protocols for the synthesis of furo[3,4-*b*]indol-1-ones feature a really limited generality and applicability.[5] Matsuo et al. reported a two-step procedure based on the amination of tetronic acid with 2-iodoaniline and the subsequent copper-mediated ring closure by C-H bond activation.[5a] Only two members of this class, however, were prepared in this way. An alternative protocol consists in an acid-catalyzed rearrangement of a 2,5-diazido-1,4-benzoquinone to the 5-methylenefuran-2(5H)-one derivative and its thermal decomposition that provides an indole-fused furanone molecule with a very low yield.[5b] In another report, the treatment of indole-2,3-dicarboxylic anhydrides with Wittig reagents led to 3-methylene-3,4-dihydro-1H-furo[3,4-*b*]indol-1-one derivatives with big regioselectivity issues.[5c] Consequently, there is a need for new and powerful methods that offer greater generality, flexibility and higher functional group tolerance in the synthesis of these polycyclic compounds.

Palladium-catalyzed carbonylation reactions represent one of the most useful tool to conveniently transform low-cost starting materials such as alkenes and alkynes into high-value added compounds such as acids, esters, amides and ketones.[6] Suitably pre-functionalized reagents can lead to an high degree of molecular complexity in a single synthetic step, which is hardly accessible by a conventional approach.



Scheme 1. PdI_2/KI-catalyzed carbonylation of propargyl alcohols and alkynylanilines: previous and present works.

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Generally, tedious isolation and purification steps are also removed allowing to save time and materials. In this context, oxidative carbonylation reactions feature a powerful carbonylative methodology for the preparation of pharmaceuticals, agrochemicals and advanced materials both on laboratory and industrial scale.[7] These reactions are generally promoted by a palladium(II) complex and the presence of an external oxidant is essential to restore the catalytic species. The entire process becomes even more economically advantageous if the oxidant is a cheap, abundant and safe agent such as molecular oxygen. In this framework, the organic ligand-free PdI_2/KI catalytic system disclosed several years ago by our research group,[8] is one of the most simple and robust catalysts used to synthesize a large number of complex carbonylated structures in a short and efficient manner.[9] Re-oxidation of palladium(0) is guarantee by molecular oxygen, which is able to restore the catalytically active palladium(II) species in the presence of an excess of iodide anions.[8]

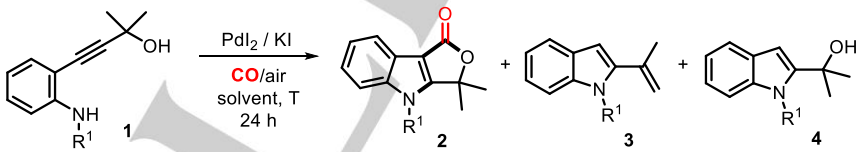
We have previously reported that tertiary *α*-hydroxyalkynes undergo oxidative carbonylation in methanol in the presence of PdI_2/KI to give *β*-lactones arising from alkoxycarbonylation at the terminal carbon of the alkyne and *syn*-carbonylation at the internal carbon, followed by C-O coupling to the 4-membered lactone ring (Scheme 1, eq 1).[10] More recently, our research group has disclosed the PdI_2/KI – catalyzed synthesis of indole-3-carboxylic esters from ethynylanilines, CO and methanol.[11] In a single operation, the construction of the indole skeleton and the further functionalization with an ester group in 3 position was accomplished (Scheme 1, eq 2). The preferred reaction pathway was totally different when substrates with terminal triple bonds (R = H) were employed, dihydroindol-2-one derivatives being the main products in this case (Scheme 1, eq 3).[12] However, ethynylanilines with a primary amino group and a substituted triple bond selectively led to acyclic carbamates (Scheme 1, eq 4).[12]

In this work, we have studied the reactivity of substrates containing both the NHR^1 and the propargylic alcohol moiety in *ortho* position[13] under PdI_2/KI-catalyzed oxidative carbonylation conditions. Based on our previous finding on carbonylation of propargyl alcohols and 2-alkynylanilines, as shown in Scheme 1, different reaction pathway could have been in principle followed. We have, however, found that, under suitable conditions, a selective process, consisting of a 5-*endo-dig* cyclization followed by cyclocarbonylation, takes place, with selective formation of furo[3,4-*b*]indol-1-one derivative. Notably, the formation of indole core with subsequent exocyclic carbonylation is the preferred way with either a primary or a secondary amino group (Scheme 1, *this work*). Despite the tendence of propargyl alcohols to give *β*-lactones under various carbonylative conditions,[10,14] here, a regioselective 5-*endo-dig* cyclization to γ-lactones took place exclusively. To the best of our knowledge, this is the first general and direct route to indole-fused furanones.

Results and Discussion

We first investigated the behavior of alkynykaniline **1a** bearing the tertiary OH function in β position with respect to the triple bond and a primary amino group (R^1 = H).[15] Based on our previous experience,[9] carbonylation of **1a** was initially carried out in MeCN at 80 °C and under 30 bar (at 25 °C) of a 1:4 mixture of CO/air, in the presence of 2 mol% of PdI_2 and 20 mol% of KI, with a substrate concentration of 0.2 mmol per mL of solvent. In the absence of an alcohol (MeOH) that could act as a competitive reagent, the solvent of choice was MeCN which gave excellent results in other palladium-catalyzed oxidative carbonylation reactions.[9a]

Table 1. Condition Screening for the Synthesis of **2**.[a]



Entry	1	R^1	Solvent	P CO/air (bar)	Pd (mol%)	T (°C)	Conv[b] (%) **1**	Yield[c] (%) **2**	Yield[c] (%) **3**	Yield[c] (%) **4**
1	**1a**	H	MeCN	6/24	2	80	45	26	6	-
2	**1a**	H	MeCN	6/24	2	100	100	49 (45)[d]	13	-
3	**1a**	H	MeCN	12/48	2	100	100	39	11	-
4	**1a**	H	MeCN	24/6	2	100	100	5	-	-
5	**1b**	Bn	MeCN	6/24	2	100	100	76	14	-
6	**1b**	Bn	NMP	6/24	2	100	100	21	9	-
7	**1b**	Bn	DME	6/24	2	100	82	23	11	15
8	**1b**	Bn	Toluene	6/24	2	100	100	7	27	52
9	**1b**	Bn	MeCN	12/48	2	100	100	77	6	-
10	**1b**	Bn	MeCN	24/6	2	100	100	7	-	-
11	**1b**	Bn	MeCN	12/48	5	100	100	68	21	-
12	**1b**	Bn	MeCN	12/48	1	120	100	85 (82)[d]	6	-

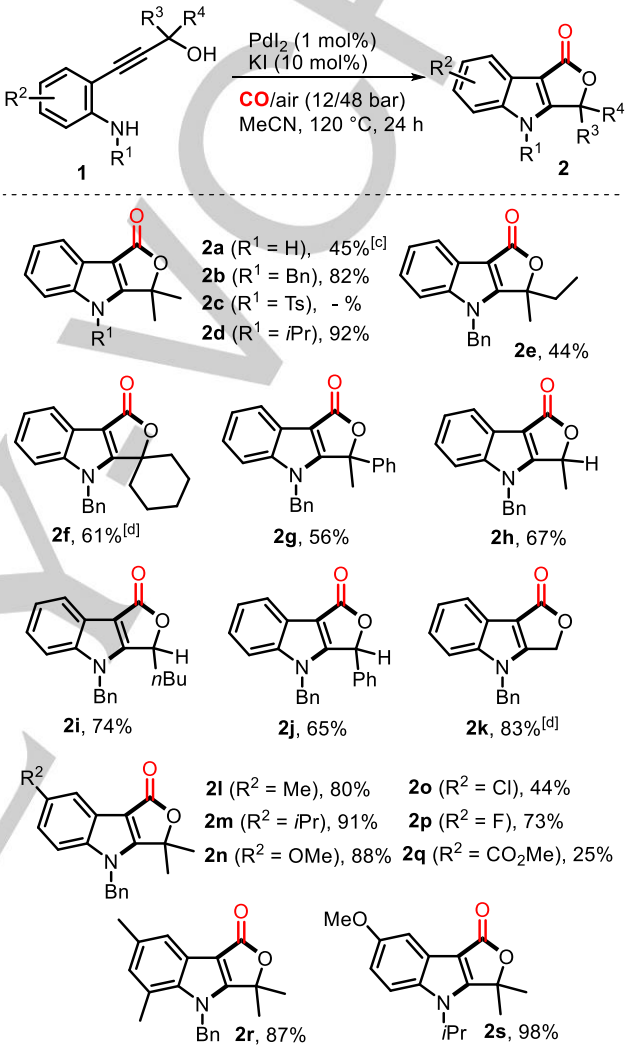
[a] Reaction conditions: **1** (1 mmol), PdI_2 (1-5 mol%), KI (Pd/KI molar ratio is 1/10), solvent (0.2 mmol of **1** / mL solvent), CO/air (reported pressure measured at 25 °C), 45 ml autoclave, 24 h. [b] Conversion of **1** was determined by GC analysis. [c] Yields were determined via ^{1}H NMR analysis with the internal standard method. [d] Isolated yield in brackets.

^{1}H NMR analysis on the reaction crude with an internal standard allowed to quantify the amount of product **2a** (R^1 = H)[5a] obtained in 26% yield and 2-vinyl indole **3a**[13a] formed in 6% yield (Table 1, entry 1). To improve conversion of **1a**, the temperature was raised at 100 °C (Table 1, entry 2). Yield of **2a** and **3a** reached 49% and 13%, respectively, and this remained the best result after the optimization study that included variation of palladium catalyst, solvent, substrate concentration and CO/air pressure. In particular, when the CO pressure was increased from 6 to 12 bar the yield of **2a** slightly decreased (39%, Table 1, entry 3) and dropped to 5% employing a 4:1 mixture of CO/air (24/6 bar, Table 1, entry 4), that turned out to be the best condition in many other alkoxycarbonilation processes.[7d] The relatively modest yield achieved in the desired product **2a** could be ascribed to side reaction of the primary amino group, including its oxidative carbonylation to give urea derivatives,[16] as confirmed by the formation of a complex mixture of heavy by-products (not investigated further).

To overcome this problem, we decided to test the reactivity of the corresponding substrates **1b** and **1c**, with the amino group protected with a benzyl (R^1 = Bn) and a tosyl (R^1 = Ts) group, respectively. While **1c** proved to be totally unreactive under various reaction conditions (probably due to the diminished nucleophilicity of the sulphonamide nitrogen), to our delight, the oxidative carbonylation of **1b** proceeded smoothly affording furo[3,4-*b*]indol-1-one **2b** in 76% yield, together with **3b** in 14% yield (Table 1, entry 5). The use of MeCN was crucial for the reaction outcome, as a highly coordinating solvent, such as NMP, gave very poor selectivity (Table 1, entry 6). On the other hand, when the carbonylation of **1b** was carried out in less polar solvents, such as toluene or 1,2-dimethoxyethane, the non-carbonylated product **3b** and **4b** were preferentially obtained (Table 1, entries 7 and 8). We then focused our attention again on the effect of CO/air pressure on product selectivity, and found that increasing both the CO and air pressure up to 12/48 bar respectively, a similar amount of **2b** was formed (Table1, entries 5 and 9). On the other hand, an excess of CO (CO/air = 4/1) caused the formation of several unidentified by-products (Table 1, entry 10). Finally, the palladium loading was also evaluated. Using 5 mol% of PdI_2 the yield of **2b** decreased in favor of **3b** (Table 1, entry 11). According to this, when a lower amount of palladium was employed (1 mol%, entry 12), the yield of **2b** reached 85% while **3b** was reduced (6%). The reaction temperature was raised at 120 °C to compensate the reduced reaction rate observed with 1 mol% of palladium. In all entries PdI_2/KI was kept at 1/10 molar ratio, since further modification of this parameter did not improve the yield of **2b**.

The optimized reaction conditions (Table 1, entry 12) were then employed in the oxidative carbonylation of other differently substituted substrates **1**, and the results are reported in Table 2. Since the benzyl group on the N gave the best results in the optimization study, most of the starting reagents were protected with Bn, also considering an easier removal with respect to other alkyl substituents. The best result was, however, obtained starting from aniline **1d**, substituted with an *iso*-propyl group, which provided the corresponding furoindolone **2d** in excellent yield (Table 2, 92%). As shown in Table 2, substituents in *α* position to hydroxyl group considerably affected the reaction outcome. When an ethyl group in place of a methyl one was used, the yield was significantly lower (Table 2, **2e**, 44%), while

Table 2. Scope of the PdI_2/KI-catalyzed synthesis of furo[3,4-b]indol-1-ones **2** by oxidative carbonylation of **1**.[a,b]

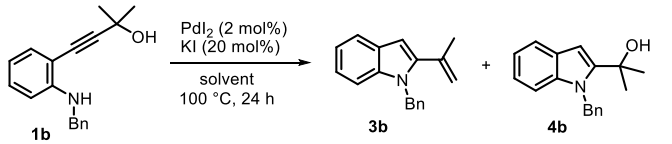


[a] Reaction conditions: **1** (1 mmol), CO (12 bar), air (48 bar), PdI_2 (1 mol%), KI (10 mol%), MeCN (4 mL), 45 ml autoclave, 120 °C, 24 h. [b] Isolated yield. [c] Reaction conditions of entry 2, Table 1. [d] 36h.

bulky groups, such as cyclohexyl or phenyl, led to satisfactory yields of the corresponding furoindolones **2f** and **2g** (Table 2, 61 and 56%, respectively). Good yield of **2** were obtained in the presence of secondary alcohol groups (Table 2, **2h-j**, 65-74%). The reaction also worked nicely with a substrate bearing a primary alcoholic group, as shown by the results obtained by **1k**, which, quite interestingly, led to a higher yield of the corresponding furoindolone **2k** (Table 2, 83%), although after a longer reaction time (36h). Then, the effect of substituents on the aromatic ring was evaluated. Electron donating groups (EDGs), such as Me, *i*Pr and OMe, gave the best results (Table 2, **2l-n**, 80-91%), while electron withdrawing groups (EWGs)

were less tolerated. In particular, substrates **1o** and **1p**, bearing a chloro or fluoro substituent *para* to the amino group, afforded **2o** and **2p** in 44% and 73% yield, respectively (Table 2). With a methoxycarbonyl group in the same position, substrate **1q** could be converted into the corresponding furoindolone **2q** in low yield (25%), and a nitro group gave only traces of the desired compound, thus confirming that a very strong electron withdrawing group is detrimental to the reaction success. A possible rationale for the observed behaviour can be related to the nucleophilic character of NR^1H group, which is appropriate in the presence of EDGs, leading to high yields of the corresponding furo[3,4-b]indol-1-one derivatives. EWGs are however less tolerated, since the corresponding NR^1H becomes less prone to attach the triple bond. Then, as expected, furonidolone **2r**, bearing two methyl substituents on the aromatic ring, was obtained in 87% yield, while **2s**, with an *iso*-propyl on nitrogen and a methoxy on the aromatic ring, was isolated almost quantitatively (Table 2).

Table 3. Formation of indoles **3b** and **4b** under non-carbonylative conditions.[a]

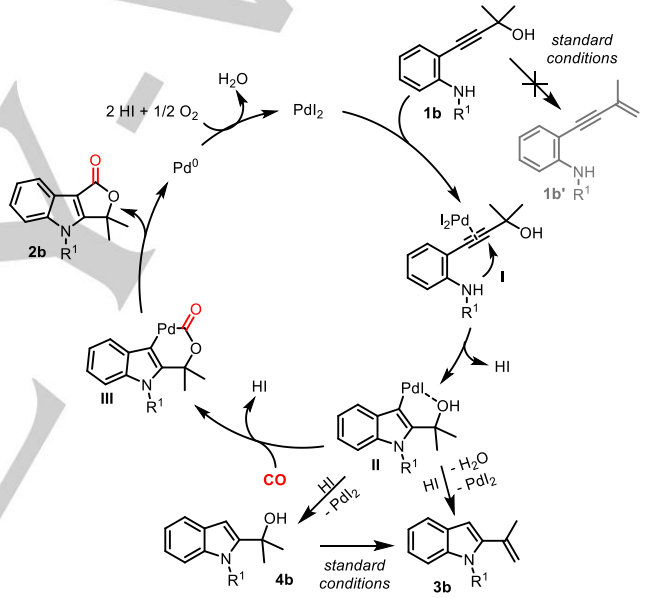


Entry	Solvent	Conv[b] (%)	Yield[c] (%)	Yield[c] (%)
		1b	**3b**	**4b**
1	MeCN	100	13	9
2	dioxane	68	27(24)[d]	23
3	toluene	96	15	60(56)[d]

[a] Reaction conditions: **1b** (0.5 mmol), PdI_2 (2 mol%), KI (20 mol%), solvent (0.2 mmol of **1** / mL solvent), 100 °C, 24 h. [b] Conversion of **1** was determined by GC analysis. [c] Yields were determined via ^1H NMR analysis with the internal standard method. [d] Isolated yield.

In all reactions, the main side-product turned out to be the vinyl indole derivative **3**, whose structure does not include the C=O group, so its formation could then occur in the absence of carbon monoxide. To verify this, substrate **1b** was caused to react in the presence of PdI_2 (2 mol%) and KI (20 mol%) in MeCN (0.2 mmol of **1b** / mL solvent) at 100 °C under inert atmosphere (Table 3, entry 1). Under these conditions, product **3b** was obtained in only 13% yield, and we noticed a not negligible amount of **4b** (9% yield) bearing the tertiary hydroxylic function. The synthetic value of this transformation improved working in dioxane (Table 3, entry 2). However, the highest yield in **4b** was reached in toluene (Table 3, entry 3), further confirming that the formation of **4b** is favored by non-polar solvents (see Table 1, entry 8). The selectivity is here dramatically influenced by the solvent, being a low polarity reaction medium the major requirement to avoid the dehydration of the alcohol moiety. Unfortunately, as we have seen, the use of apolar solvents is not compatible with the oxidative heterocyclization/cycloalkoxycarbonylation to furo[3,4-*b*]indol-1-ones (see Table 1).

On the basis of the above results and considerations and the existing knowledge on palladium-catalyzed indole synthesis from ethynilanilines,[2c,9g,13] we may propose the pathways shown in Scheme 2 for the formation of compounds **2**, **3** and **4**. The initial coordination of substrate **1b** with Pd(II) species generates the π-complex **I** (Scheme 2),[2c] where the decreased electron density at the triple bond promotes an intramolecular nucleophilic attack of the nitrogen atom across the acetylenic moiety to give the σ-indolylpalladium complex **II**.[17] The subsequent CO insertion likely affords palladacycle intermediate **III**;[18] however the formation of an intermediate isomer to **III** where CO is placed between Pd and the indolyl moiety cannot be ruled out. Finally, a reductive elimination step from **III** causes ring closure to indole-fused lactone **2**. The generated Pd(0) is reoxidated to PdI_2 by O_2 in the presence of 2 equivalents of HI (ensuing from the carbonylation process).[8] Vinyl indoles **3** and indoles **4** are probably formed from intermediate **II**, by palladium-catalyzed dehydration and/or protonolysis by HI. In both cases PdI_2 is directly regenerated, so the pathways leading to **3** and **4**



Scheme 2. Proposed reaction pathways for the PdI_2/KI-catalyzed synthesis of furo[3,4-*b*]indol-1-ones **2** and 2-vinyl indole **3**.

do not need molecular oxygen to restore the active catalyst. According to the experimental observations, the dehydration step would occur preferentially on intermediate **II** where palladium is in proper position for promoting the elimination of water. In fact, the starting reagent **1b** did not undergo dehydration to **1b'**. However, isolated compound **4b** was partially converted to **3b** under standard conditions (Scheme 2, see SI for details), demonstrating that it is a possible intermediate in the formation of vinyl indole **3b**.[19]

Conclusions

In summary, we have developed a one-step method for the direct synthesis of a variety of polycyclic furo[3,4-*b*]indol-1-ones via a novel palladium-catalyzed sequential indolization, carbonylation and lactonization process from suitably functionalized 2-alkynylanilines. This methodology is operationally very simple and leads to furo[3,4-*b*]indol-1-ones in fair to high yields using molecular oxygen as the sole oxidant. The described methodology demonstrates once again the potentiality of PdI_2/KI-catalyzed oxidative carbonylation reaction and, in particular, will stimulate the further studies of this important class of fused heterocycles.

Experimental Section

General procedure for the PdI_2/KI-catalyzed synthesis of 2: A 45 mL stainless steel autoclave was charged with substrate **1** (1 mmol), PdI_2 (3.6 mg, 1 mol%), KI (16 mg, 10 mol%) and dry MeCN (4 mL). The autoclave was sealed and pressurized with CO (12 bar) and air (48 bar). The reaction mixture was stirred at 120 °C for 24 h, after which the autoclave was cooled, degassed and opened. The solvent was evaporated, and the product **2** was purified by flash column chromatography on silica gel.

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Keywords: Carbonylation • Cyclization • Fused Heterocycles • Indoles • Palladium

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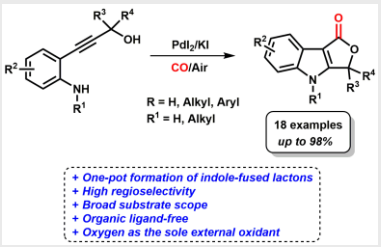
FULL PAPER

A novel and efficient catalytic approach to functionalized furo[3,4-*b*]indol-1-ones is reported. In a single transformation two fused heterocycles and three new bonds (C-N, C-C and C-O) are generated. The present carbonylative methodology gives direct access to structurally complex molecules from suitably functionalized 2-alkynylanilines.



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An unprecedented Pd-catalyzed carbonylative route to Fused Furo[3,4-*b*]indol-1-ones